

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

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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 Sciences  
Office of Biostatistics

## STATISTICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**NDA/BLA #:** NDA 208254  
**Supplement #:** 0001, 0006, and 0011  
**Drug Name:** Rhopressa™ (Netarsudil Ophthalmic Solution) 0.02%  
**Indication(s):** For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension  
**Applicant:** Aerie Pharmaceuticals  
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## 1 EXECUTIVE SUMMARY

This NDA seeks approval of Rhopressa™ (netarsudil ophthalmic solution) 0.02% dosed once daily (QD) in the affected eye(s) in the evening for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

The efficacy and safety of netarsudil ophthalmic solution 0.02% (also referred as Rhopressa throughout this review) QD was evaluated in three randomized, double-masked, and active-controlled non-inferiority pivotal clinical trials: AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304 (referred to as Studies 301, 302, and 304, respectively). These trials were similarly designed overall, but differed in terms of baseline IOP inclusion criteria, treatment dosing frequency and durations. Studies 301 and 302 enrolled subjects with baseline IOP < 27 mmHg and Study 304 enrolled subjects with baseline IOP < 30 mmHg. Two treatment arms (Rhopressa QD and timolol 0.5% twice-daily [BID]) were included in Studies 301 and 304 and 3 treatment arms (Rhopressa QD and BID; and timolol 0.5% BID) in Study 302. The treatment duration was 3 months in Study 301, 12 months in Study 302, and 6 months in Study 304.

For all three studies, the primary efficacy endpoints were the mean IOP in the study eye at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. The protocol-defined success criteria for non-inferiority of Rhopressa to timolol required that the upper limit of the 95% CIs around the difference in mean IOP values (Rhopressa QD - timolol) was within 1.5 mmHg at all time points through Month 3 and within 1.0 mmHg at a majority of the time points (at least 5 of 9 time points) through Month 3.

Study 301 failed to demonstrate non-inferiority of Rhopressa QD to timolol in the pre-defined primary analysis for all subjects in the per-protocol (PP) population; but non-inferiority was shown in a post hoc subgroup analysis for the subjects with maximum baseline IOP < 25 mmHg. Therefore, in Studies 302 and 304, the pre-specified primary analysis was based on the PP subjects who had maximum baseline IOP < 25 mmHg. Both Studies 302 and 304 demonstrated non-inferiority of Rhopressa QD to timolol in the primary analysis.

Mean IOP changes from baseline at post-baseline time points were protocol-defined secondary endpoints. Since the mean IOP changes from baseline form the basis for desired label claims and the efficacy conclusions are the same based on the results of these endpoints as those based on the primary efficacy endpoints, the statistical review focuses on the discussion of the results of mean IOP changes from baseline.

In Study 301, for all subjects, the IOP reduction was observed for all time points at all three study visits for Rhopressa QD, ranging from 3.2 to 5.0 mmHg (Table 1). For subjects with maximum baseline IOP < 25 mmHg, the Rhopressa and timolol groups had similar average IOP reductions from baseline, ranging from 3.7 to 5.1 mmHg and 3.2 to 4.7 mmHg, respectively. For subjects with maximum baseline IOP  $\geq$  25 mmHg, mean IOP reduction from baseline ranged from 2.2 to 4.9 mmHg in the Rhopressa group; and from 4.6 to 6.0 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all morning

time points, and on Days 43 and 90. The treatment differences were most noticeable at 8am and 10am on Days 43 and 90; and as high as 3.0 mmHg.

In Study 302, for all subjects, the IOP reduction was observed for all time points at all three study visits for Rhopressa QD, ranging from 3.7 to 4.5 mmHg (Table 2). For subjects with maximum baseline IOP < 25 mmHg, the Rhopressa and timolol groups had similar average IOP reductions from baseline, ranging from 3.3 to 4.6 mmHg and 3.7 to 5.1 mmHg, respectively. For subjects with maximum baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 3.4 to 4.9 mmHg in the Rhopressa group; and from 4.3 to 5.9 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all morning time points, and at Days 43 and 90. The treatment differences were also most noticeable at 8am and 10am on Days 43 and 90; and as high as 2.6 mmHg.

In Study 304, for all subjects, the IOP reduction was observed for all time points at all three study visits for Rhopressa, ranging from 3.9 to 4.8 mmHg (Table 3). For subjects with maximum baseline IOP < 25 mmHg, the Rhopressa and timolol groups had similar average IOP reductions from baseline, ranging from 3.9 to 4.7 mmHg and 3.8 to 5.2 mmHg, respectively. For subjects with maximum baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 3.9 to 5.0 mmHg in the Rhopressa group; and from 4.4 to 6.2 mmHg in the timolol group. Consistent with the findings in Study 301 and 302, timolol had higher IOP reduction effect compared with Rhopressa at all morning time points, and at Days 43 and 90. The treatment differences were also most noticeable at 8am and 10am on Days 43 and 90.

In conclusion, all three studies demonstrated that Rhopressa QD was efficacious in reducing elevated intraocular pressure; but Rhopressa QD was less efficacious compared to timolol 0.5% BID for subjects with higher maximum baseline IOP (≥ 25 mmHg). For the label of Rhopressa QD, the statistical reviewer recommended presenting the efficacy results of the mean IOP changes from baseline by two subgroups (baseline IOP < 25 mmHg and baseline IOP ≥ 25 mmHg).

**Table 1: Study 301 Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP ≥ 25 mmHg		
		Rhopressa QD	Timolol	Difference (95% CI)*	Rhopressa QD	Timolol	Difference (95% CI)*	Rhopressa QD	Timolol	Difference (95% CI)*
		Mean	Mean		Mean	Mean		Mean	Mean	
Baseline	08:00	23.4	23.4	0.1 (-0.3, 0.4)	22.4	22.5	-0.1 (-0.4, 0.2)	25.1	25.1	0.1 (-0.3, 0.5)
	10:00	22.3	21.9	0.4 (-0.1, 0.8)	21.3	21.1	0.2 (-0.2, 0.6)	23.9	23.6	0.3 (-0.3, 0.9)
	16:00	21.8	21.5	0.3 (-0.2, 0.8)	20.6	20.5	0.1 (-0.4, 0.6)	23.7	23.3	0.4 (-0.3, 1.2)
Day 15	08:00	-4.8	-5.0	0.3 (-0.2, 0.8)	-5.1	-4.7	-0.3 (-0.9, 0.3)	-4.3	-5.7	1.3 (0.4, 2.3)
	10:00	-5.0	-4.5	-0.5 (-1.0, 0.0)	-5.0	-4.2	-0.9 (-1.5, -0.3)	-4.9	-5.0	0.1 (-0.9, 1.2)
	16:00	-4.5	-3.9	-0.6 (-1.2, -0.1)	-4.4	-3.4	-0.9 (-1.6, -0.3)	-4.7	-4.6	-0.1 (-1.2, 0.9)
Day 43	08:00	-4.1	-5.1	1.1 (0.5, 1.7)	-4.5	-4.7	0.2 (-0.5, 0.9)	-3.3	-6.0	2.7 (1.5, 3.8)
	10:00	-4.1	-4.6	0.5	-4.3	-4.2	-0.2	-3.7	-5.3	1.6

				(-0.1, 1.1)			(-0.8, 0.5)			(0.4, 2.7)
	<b>16:00</b>	-3.8	-3.8	0.0 (-0.7, 0.6)	-4.0	-3.3	-0.7 (-1.4, 0.0)	-3.7	-4.8	1.2 (0.0, 2.3)
<b>Day 90</b>	<b>08:00</b>	-3.6	-4.9	1.3 (0.7, 1.9)	-4.2	-4.6	0.4 (-0.2, 1.1)	-2.6	-5.5	3.0 (1.8, 4.1)
	<b>10:00</b>	-3.3	-4.0	0.8 (0.1, 1.4)	-3.9	-3.7	-0.2 (-0.9, 0.5)	-2.2	-4.7	2.5 (1.4, 3.6)
	<b>16:00</b>	-3.2	-3.8	0.6 (0.0, 1.2)	-3.6	-3.2	-0.4 (-1.0, 0.3)	-2.6	-4.9	2.3 (1.2, 3.5)

\* The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

**Table 2: Study 302 Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP ≥ 25 mmHg		
		Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*	Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*	Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*
<b>Baseline</b>	<b>08:00</b>	23.5	23.5	0.1 (-0.3, 0.4)	22.5	22.5	0.0 (-0.2, 0.2)	25.1	25.2	0.0 (-0.4, 0.3)
	<b>10:00</b>	22.3	22.2	0.1 (-0.3, 0.5)	21.3	21.3	0.0 (-0.4, 0.4)	24.0	23.9	0.1 (-0.4, 0.7)
	<b>16:00</b>	21.6	21.6	-0.1 (-0.5, 0.4)	20.4	20.7	-0.3 (-0.7, 0.1)	23.5	23.3	0.1 (-0.6, 0.8)
<b>Day 15</b>	<b>08:00</b>	-4.5	-5.2	0.7 (0.2, 1.2)	-4.5	-4.9	0.4 (-0.2, 1.0)	-4.5	-5.9	1.4 (0.5, 2.3)
	<b>10:00</b>	-4.5	-4.7	0.2 (-0.3, 0.7)	-4.6	-4.4	-0.2 (-0.8, 0.4)	-4.5	-5.4	0.9 (-0.1, 1.9)
	<b>16:00</b>	-4.2	-4.0	-0.2 (-0.7, 0.3)	-3.9	-3.8	-0.1 (-0.6, 0.5)	-4.9	-4.3	-0.6 (-1.5, 0.3)
<b>Day 43</b>	<b>08:00</b>	-4.1	-5.4	1.2 (0.7, 1.8)	-4.6	-5.1	0.5 (-0.1, 1.1)	-3.4	-5.9	2.6 (1.5, 3.7)
	<b>10:00</b>	-4.2	-4.9	0.7 (0.2, 1.3)	-4.4	-4.7	0.3 (-0.3, 0.9)	-3.8	-5.3	1.5 (0.5, 2.6)
	<b>16:00</b>	-3.7	-4.3	0.7 (0.2, 1.2)	-3.5	-4.0	0.5 (-0.1, 1.1)	-3.9	-4.9	0.9 (0.0, 1.9)
<b>Day 90</b>	<b>08:00</b>	-4.0	-5.3	1.3 (0.7, 1.8)	-4.3	-5.1	0.8 (0.1, 1.5)	-3.4	-5.6	2.1 (1.1, 3.2)
	<b>10:00</b>	-4.0	-4.7	0.7 (0.1, 1.3)	-4.3	-4.4	0.1 (-0.5, 0.8)	-3.5	-5.3	1.7 (0.6, 2.8)
	<b>16:00</b>	-3.7	-3.9	0.2 (-0.4, 0.7)	-3.4	-3.7	0.3 (-0.4, 1.0)	-4.4	-4.3	-0.1 (-1.2, 1.0)

\* The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

**Table 3: Study 304 Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP ≥ 25 mmHg		
		Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*	Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*	Rhopressa QD Mean	Timolol Mean	Difference (95% CI)*
<b>Baseline</b>	<b>08:00</b>	23.9	23.9	0.0 (-0.3, 0.4)	22.4	22.4	0.0 (-0.3, 0.2)	26.3	26.0	0.3 (-0.2, 0.8)
	<b>10:00</b>	22.7	22.8	-0.1 (-0.5, 0.3)	21.1	21.3	-0.2 (-0.6, 0.2)	25.2	24.9	0.3 (-0.3, 0.8)
	<b>16:00</b>	22.2	22.0	0.1	20.7	20.7	0.0	24.5	24.0	0.5

				(-0.3, 0.6)			(-0.4, 0.4)			(-0.2, 1.1)
<b>Day 15</b>	<b>08:00</b>	-4.7	-5.3	0.6 (0.1, 1.1)	-4.7	-4.9	0.2 (-0.4, 0.8)	-4.7	-5.9	1.2 (0.3, 2.0)
	<b>10:00</b>	-4.8	-5.0	0.2 (-0.3, 0.7)	-4.5	-4.5	0.0 (-0.5, 0.5)	-5.0	-5.6	0.6 (-0.2, 1.5)
	<b>16:00</b>	-4.4	-4.2	-0.2 (-0.6, 0.3)	-4.4	-3.8	-0.6 (-1.1, -0.1)	-4.3	-4.9	0.6 (-0.2, 1.3)
<b>Day 43</b>	<b>08:00</b>	-4.5	-5.4	0.9 (0.4, 1.4)	-4.6	-4.8	0.3 (-0.3, 0.8)	-4.3	-6.2	1.9 (1.0, 2.8)
	<b>10:00</b>	-4.5	-4.8	0.3 (-0.1, 0.8)	-4.3	-4.3	-0.1 (-0.6, 0.5)	-4.7	-5.8	1.1 (0.2, 1.9)
	<b>16:00</b>	-4.2	-4.1	0.0 (-0.5, 0.4)	-4.1	-4.0	-0.1 (-0.6, 0.4)	-4.3	-4.4	0.2 (-0.6, 1.0)
<b>Day 90</b>	<b>08:00</b>	-4.5	-5.5	1.0 (0.5, 1.5)	-4.5	-5.2	0.6 (0.0, 1.2)	-4.5	-6.1	1.6 (0.6, 2.5)
	<b>10:00</b>	-4.2	-5.1	0.9 (0.4, 1.4)	-4.1	-4.5	0.4 (-0.2, 0.9)	-4.1	-5.9	1.8 (0.9, 2.7)
	<b>16:00</b>	-3.9	-4.3	0.3 (-0.1, 0.8)	-3.9	-3.9	0.0 (-0.6, 0.5)	-3.9	-5.0	1.1 (0.2, 1.9)

\* The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

## 2 INTRODUCTION

### 2.1 Overview

#### 2.1.1 Drug Class and Indication

Glaucoma is a complicated disease that damages the eye's optic nerve, which is vital to good vision. If left untreated, the damage to the optic nerve will lead to progressive, irreversible vision loss, and eventually blindness. Primary open-angle glaucoma (POAG) is the most common form of glaucoma. Of the several causes for glaucoma, elevated intraocular pressure (IOP) is the most important risk factor in most glaucoma. Therefore, reducing IOP is crucial in managing disease progression in patients with POAG or OHT. According to the applicant, this conclusion holds true not only for high-risk ocular hypertensive and glaucoma patients with elevated IOPs but also for glaucoma patients with IOPs in the normal range. Thus, the goal for treating patients should be to lower the IOP to the point that it prevents further damage to the optic nerve and achieve this without sacrificing safety or convenience.

The applicant discovered netarsudil, a new Rho kinase inhibitor, which showed in non-clinical studies to produce large reductions in IOP with a long duration of action. Therefore, the applicant initiated the clinical development plan for Rhopressa for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

#### 2.1.2 History of Drug Development

The applicant conducted all clinical studies for Rhopressa under IND 113064.

In the briefing package for the end-of-phase 2 (EOP2) meeting held on April 11, 2014, the applicant included an outline for two Phase 3 studies (Studies 301 and 302) evaluating only the once-daily dose regimen of Rhopressa. However, the Agency's advised the applicant to evaluate the twice-daily (BID) dosing of Rhopressa. The applicant complied with this suggestion and added one BID arm to Study 302. Note: the following are excerpts from the meeting minutes:

*"FDA stated that while they understand the design of AR-13324 and the data observed to date, they feel it important to evaluate AR-13324 0.02%, b.i.d. based upon observations with other classes (e.g., prostaglandin analogues where b.i.d. dosing is less effective than q.d. dosing). Should the Sponsor submit an NDA without clinical data as to b.i.d. dosing, FDA may make a decision that the product was not fully evaluated."*

Prior to the database lock of Study 302, the applicant found from the results of Study 301 that Rhopressa QD did not achieve non-inferiority to timolol for all subjects in the per-protocol (PP) population, but did achieve non-inferiority for a pre-specified efficacy endpoint for PP population subjects with maximum baseline IOP  $\leq 23$  mmHg as well as in a post hoc analysis in the PP population subjects with maximum baseline IOP  $< 25$  mmHg. Therefore, the applicant had a teleconference with the FDA on June 12, 2015. During that teleconference, the Agency accepted the applicant's proposal to change the primary efficacy analysis population for Study 302 to the PP subjects with maximum baseline IOP  $< 25$  mmHg.

This NDA submission is a re-submission of the original NDA. The applicant submitted the original NDA on August 30, 2016, and later withdrew it on October 27, 2016 due to manufacturing issues. The original NDA included the efficacy and safety data from two completed pivotal studies (Studies 301 and 302), and the protocol for Study 304 (dated in July 14, 2015). The re-submission, dated on February 28, 2017, included the 3-month interim efficacy and safety report of Study 304. On June 23, 2017, the applicant submitted the final complete clinical study report (CSR) for Study 304; the CSR stated that there were no protocol amendments and no changes to the planned analysis.

### 2.1.3 Studies Reviewed

The efficacy of Rhopressa was evaluated in three active-controlled pivotal clinical studies: Study 301 and Study 302, and Study 304.

**Table 4: Summary of Efficacy Studies to be assessed in the Statistical Review**

Study No	Design	Objective	Treatment Groups Randomized/Completed	Study Population
AR-13324-CS301	Multi-center, randomized, double-masked, parallel group, active-control	to assess the safety and ocular hypotensive efficacy of Rhopressa QD compared to timolol maleate ophthalmic solution, 0.5% BID in patients with elevated	Rhopressa QD / 202 Timolol BID / 209	Adult subjects and pediatric subjects (0 to 2 years of age) with OAG or OHT

	2-arm	intraocular pressure		
AR-13324-CS302	Multi-center, randomized, double-masked, parallel group, active-control 3-arm	to evaluate the safety and ocular hypotensive efficacy of Rhopressa QD and BID compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure	Rhopressa QD / 251 Rhopressa BID/ 254 Timolol BID / 251	Adult subjects and pediatric subjects (0 to 2 years of age) with OAG or OHT
AR-13324-CS304	Multi-center, randomized, double-masked, parallel group, active-control 2-arm	to assess the ocular hypotensive efficacy and safety of Rhopressa QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure.	Rhopressa QD / 351 Timolol BID / 357	Adult subjects with diagnosis of OAG or OHT in both eyes

Source: Statistical Reviewer's Summary.

## 2.2 Data Sources

The data sources for this review mainly came from the applicant's study reports for studies 301, 302, and 304. The study reports are available at the following locations:

Original submission: <\\cdsesub1\evsprod\NDA208254\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\ar-13324-cs301>

Original submission: <\\cdsesub1\evsprod\NDA208254\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\ar-13324-cs302>

Original submission (protocol for Study 304): <\\cdsesub1\evsprod\NDA208254\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\ar-13324-cs304>

In the resubmission dated 02/28/2017, the 3-month interim report for Study 304 was included in the following location:

<\\cdsesub1\evsprod\NDA208254\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\ar-13324-cs304>

Abbreviated versions of Studies 301 and 302 CSR were also submitted in this resubmission. The statistical reviewer mainly resorted to the original submission for detailed information of these two studies.

Final CSR for Study 304 was submitted on 6/23/2017:

<\\cdsesub1\evsprod\NDA208254\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\ar-13324-cs304-final>

The applicant submitted SAS datasets electronically; the datasets for the three studies are available respectively at:

Datasets for Studies 301 and 302 in the Original submission:

<\\cdsesub1\evsprod\NDA208254\0001\m5\datasets\ar-13324-cs301>

<\\cdsesub1\evsprod\NDA208254\0001\m5\datasets\ar-13324-cs302>

Datasets for Study 304's 3-month interim results:

<\\cdsesub1\evsprod\NDA208254\0007\m5\datasets\ar-13324-cs304>

And datasets for Study 304's final results:

<\\cdsesub1\evsprod\NDA208254\0011\m5\datasets\ar-13324-cs304-final>

The SAS program codes that were used to generate the results in the study reports are available respectively at:

<\\cdsesub1\evsprod\NDA208254\0001\m5\datasets\ar-13324-cs301\analysis\adam\programs>

<\\cdsesub1\evsprod\NDA208254\0001\m5\datasets\ar-13324-cs302\analysis\adam\programs>

<\\cdsesub1\evsprod\NDA208254\0007\m5\datasets\ar-13324-cs304\analysis\adam\programs>

[\\cdsesub1\evsprod\NDA208254\0011\m5\datasets\ar-13324-cs304-](\\cdsesub1\evsprod\NDA208254\0011\m5\datasets\ar-13324-cs304-final\analysis\adam\programs)

<final\analysis\adam\programs>

The IOP assessments were included in the “adeff1.xpt” dataset with variable names “AVAL”. The treatment variable, given both as numeric (TRTAN) and character (TRTA), was also included in both the above datasets. The adverse events were included in the “adae.xpt” dataset.

### **3 STATISTICAL EVALUATION**

#### **3.1 Data and Analysis Quality**

Overall, the submitted data were of good quality with definitions provided for each variable. Results of the primary and secondary efficacy endpoints can be reproduced by the statistical reviewer with minor data manipulation. The statistical reviewer's analyses were primarily based on the analysis datasets. The final statistical analysis plans (SAPs) for the three pivotal studies were submitted.

#### **3.2 Evaluation of Efficacy**

##### **3.2.1 Study Design and Endpoints**

The three efficacy studies 301, 302, and 304 were similar in design, except for the following key differences:

- The treatment duration:
  - Study 301 had a 3-month duration.
  - Study 302 had a 12-month duration with the first 3 months having the same design as Study 301; and the additional 9-month treatment period was mainly for safety evaluation.
  - Study 304 had a 6-month duration with the first 3 months having the same design as Study 301; and the additional 3-month treatment period in Study 304 was mainly for safety evaluation.
  
- Rhopressa dosing regimen:

- Both Studies 301 and 304 evaluated Rhopressa dosed QD in the evening (PM) compared to timolol 0.5% dosed BID in the morning (AM) and PM.
- Study 302 evaluated Rhopressa QD in the PM and Rhopressa BID in AM and PM compared to timolol in AM and PM.
- Enrolled Subjects (also see Table 6 for details):
  - Studies 301 and 302 enrolled subjects with > 20 mmHg and < 27 mmHg at 8am at the first and second qualification visits 2 to 7 days apart; and >17 mmHg and < 27 mmHg at 10am and 16pm at the second qualification visit.
  - While Study 304 enrolled adult subjects with a broader range of IOP at baseline (> 20 mmHg and < 30 mmHg at 8am at the first and second qualification visits 2 to 7 days apart; and >17 mmHg and < 30 mmHg at 10am and 16pm at the second qualification visit)
- Primary efficacy analysis population:
  - For Study 301, the primary analysis population was all subjects in the per-protocol (PP) population.
  - Before the database lock of Study 302, it was found in Study 301 that Rhopressa did not achieve non-inferiority to timolol for all subjects in the per-protocol (PP) population, but Rhopressa did achieve non-inferiority in a post hoc analysis in the PP population subjects with maximum baseline IOP < 25 mmHg. The applicant changed the primary efficacy analysis population for Study 302 to PP subjects with maximum baseline IOP < 25 mmHg before the study database lock.
  - For Study 304, the primary analysis population included subjects in the PP population with maximum baseline IOP < 25 mmHg from the study design stage.
- Pediatric subjects <18 years of age were eligible to enroll into both Studies 301 and 302; however, no subjects <18 years of age were enrolled in Study 301 and only 2 subjects <18 years of age were enrolled in Study 302. The subjects were 11 and 14 years old, respectively. Study 304 enrolled only adult subjects. Therefore, the applicant is requesting a full waiver from the requirements for pediatric information.

All the three studies were randomized, double-masked, active-controlled, and parallel-group studies assessing the safety and ocular hypotensive efficacy of Rhopressa compared to timolol in patients with elevated intraocular pressure. All three studies enrolled subjects with diagnosis of OAG or OHT. Prior to randomization, subjects who qualified for enrollment at screening but were using ocular hypertension medications were required to go through a minimum washout period. The minimum washout periods varied based on different medication class.

**Table 5: Ocular Hypertensive Medication Washout Period**

<b>Medication Class</b>	<b>Minimum Washout Period</b>
Prostaglandins	4 weeks
β-adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and	2 weeks

apraclonidine)	
Muscarinic agonists (eg, pilocarpine), carbonic anhydrase inhibitors (topical or oral)	5 Days

Source: Table 2 of Study 301 Report.

After washout, subjects were required to meet minimum IOP criteria while off ocular hypotensive medication for two different qualification visits within one week. The IOP enrollment requirement was based on the following entry criteria. Please also see Appendix 1 for key inclusion and exclusion criteria.

**Table 6: IOP Entry Criteria (Studies 301, 302, and 304)**

Study	Qual. 1	Qual. 2	Eye
<b>301</b>	>20 and < 27 mmHg at 8:00 h	>20 and < 27 mmHg at 8:00 h >17 and < 27 mmHg at 10:00 h >17 and < 27 mmHg at 16:00 h	Same eye at all qualification time points
<b>302</b>	>20 and < 27 mmHg at 8:00 h	>20 and < 27 mmHg at 8:00 h >17 and < 27 mmHg at 10:00 h >17 and < 27 mmHg at 16:00 h	Same eye at all qualification time points
<b>304</b>	>20 and < 30 mmHg at 8:00 h	>20 and < 30 mmHg at 8:00 h >17 and < 30 mmHg at 10:00 h >17 and < 30 mmHg at 16:00 h	Same eye at all qualification time points

Qual. 1 = Qualification Visit 1; Qual. 2 = Qualification Visit 2; Qualification Visit 2 was within 2 to 7 days after Qualification Visit 1.

Source: Protocol for AR-13324-CS301; Protocol for AR-13324-CS302; and Protocol for AR-13324-CS304.

After the start of study medication on Day 1, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) for safety and efficacy evaluation. For Study 302, subjects also had office visits at Day 180 (Month 6), Day 270 (Month 9), and Day 365 (Month 12). For Study 304, subjects had office visits at Day 120 (Month 4), Day 150 (Month 5), and Day 180 (Month 6). All treatments were dosed to both eyes during the treatment period. For all three studies, a visit variance of  $\pm 3$  days was to be allowed for the Week 2 and Week 6 study visits while subsequent study visits had an allowed visit variance of  $\pm 5$  days. The study visits, efficacy assessment time points, and overall study duration of the three trials is presented in the following table. Please also refer to Appendix 1 for the schedule of assessments for the three studies.

**Table 7: Study Duration and Visits (Studies 301, 302, and 304)**

Study	Screening	Efficacy Assessment up to Month 3	Efficacy Assessment After Month 3
<b>301</b>	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Not Applicable
<b>302</b>	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Month 6 (08:00 h) Month 9 (08:00 h) Month 12 (08:00 h)
<b>304</b>	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Month 4 (08:00, 10:00, 16:00 h) Month 5 (08:00, 10:00, 16:00 h) Month 6 (08:00, 10:00, 16:00 h)

Qual. 1 = Qualification Visit 1; Qual. 2 = Qualification Visit 2;

Source: Protocol for AR-13324-CS301; Protocol for AR-13324-CS302; and Protocol for AR-13324-CS304.

For all three studies, the primary efficacy outcome was the mean IOP in the study eye at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. If the subject qualified in only one eye, then this eye was designated the study eye. If the subject qualified in two eyes, then the study eye was the eye with the higher IOP at 08:00 hours on Visit 3. If both eyes have the same IOP at 08:00 hours on Visit 3, then the right eye was the study eye. According to the applicant, two consecutive IOP measurements of each eye were measured. If the 2 measurements differed by more than 2 mmHg, a third measurement was taken. IOP was analyzed as the mean of 2 measurements or as the median of 3 measurements (called mean IOP by the applicant).

The sample size estimations of the three studies were based on the following assumptions respectively.

- Study 301

- 0.05 two-sided level of significance at each of the 9 time points
- A correlation between time points of 0.60 or less
- Standard deviation of 3.0 mmHg
- 90% power
- Zero treatment difference between Rhopressa QD and timolol
- The upper limit of the 95% confidence interval (CI) was within 1.5 mmHg around the treatment difference between Rhopressa and timolol
- About 85% of enrolled subjects completed through Month 3 without a major protocol deviation

Based on the above assumption, the estimated sample size was approximately 200 subjects per arm.

- Study 302

- 0.05 two-sided level of significance at each of the 9 time points
- A correlation between time points of 0.60 or less
- Standard deviation of 2.75 mmHg
- 85% power
- Zero treatment difference between Rhopressa BID and timolol
- The upper limit of the 95% confidence interval (CI) was within 1.5 mmHg around the treatment difference between Rhopressa and timolol
- About 80% of enrolled subjects completed through Month 3 without a major protocol deviation; and approximately 65% of these patients had baseline IOP < 25 mmHg

Based on the above assumption, the estimated sample size was approximately 252 subjects per arm.

- Study 304

- 0.05 two-sided level of significance at each of the 9 time points
- A correlation between time points of 0.60 or less
- Standard deviation of 2.75 mmHg
- 90% power
- Zero treatment difference between Rhopressa BID and timolol

- The upper limit of the 95% confidence interval (CI) was within 1.5 mmHg around the treatment difference between Rhopressa and timolol
- About 80% of enrolled subjects completed through Month 3 without a major protocol deviation; and approximately 50% of these patients had baseline IOP < 25 mmHg

Based on the above assumption, the estimated sample size was approximately 350 subjects per arm.

### 3.2.2 Statistical Methodologies

All three studies (301, 302, and 304) intended to demonstrate the non-inferiority of Rhopressa to timolol in terms of IOP measurements at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits). According to the protocol-defined and Agency-agreed clinical criteria for efficacy, one study was considered a success and clinical non-inferiority of Rhopressa can be concluded if the upper limit of the 95% CIs around the difference in mean IOP values (Rhopressa - timolol) was within 1.5 mmHg at all time points through Month 3 and within 1.0 mmHg at a majority of the time points (at least 5 of 9 time points) through Month 3. The statistical reviewer considered the 1.5 mmHg non-inferiority margin acceptable based on historical data for timolol.

For all three studies, there were four different analysis populations (also known as analysis sets) defined by the applicant:

- **Randomized Population**, which included all subjects who were randomized to treatment. The baseline variables and demographic characteristics were presented based on this population.
- **Intent-to-Treat (ITT) population**, which included all randomized subjects who received at least one dose of study medication. The ITT population was analyzed as randomized and used for sensitivity efficacy analyses.
- **Per-Protocol (PP) Population**, which was a subset of the ITT population and included subjects who did not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. The primary efficacy analyses for this study were based on PP population. According to the applicant, the PP population summarized subjects as treated for purpose of analysis.
- **Safety Population**, which included all randomized subjects who received at least one dose of study treatment. The safety population was analyzed as treated and used for the safety analyses.

The primary analysis of mean IOP was conducted using two-sample t-test individually for each comparison at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits). Treatment difference at each time point and the corresponding 95% CI were calculated. For Study 301, the primary analyses were conducted with observed data for the PP population in the study eye. For Studies 302 and 304, the primary efficacy analyses were conducted with observed data for the PP population having maximum baseline IOP (at 08:00, 10:00, and 16:00

hours) <25 mmHg in the study eye. These analyses were agreed upon with the Agency before the database unlocked.

To evaluate the robustness of the primary analysis results, the applicant conducted various sensitivity and supportive analyses of the primary efficacy variables using both the PP population and ITT population. These analyses included different imputation methods for missing data:

- Last observation carried forward (LOCF) for missing observations
- Baseline observation carried forward (BOCF) for missing observations
- Multiple imputations using Monte Carlo Markov Chain (MCMC) method for missing observations

And different analysis models for the observed data:

- ANCOVA with IOP at the given visit and time point as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the PP population.
- Mixed model repeated measures (MMRM) with individual IOP at each time point using baseline as the covariate; treatment, visit, time point, treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point as the fixed effect factors; and subject as the random effect, repeated measure. An unstructured covariance structure was used to model the within-subject, between-visit, and time point variances.

Similar analyses as the primary efficacy analyses were completed for the following secondary efficacy variable:

- Change from baseline IOP measures at each time point and visit

In addition, different analyses of the primary endpoint and the mean IOP change from baseline were conducted by the statistical reviewer. The statistical reviewer also summarized and explored the median of both endpoints. The following table summarized the different analyses approaches conducted by the applicant and the statistical reviewer.

**Table 8: Summary of Analysis Methods**

	Two-Sample t-test <sup>1</sup>	One-Sample t-test <sup>2</sup>	ANCOVA <sup>3</sup>	MMRM ANCOVA*	Median
<b>Primary Endpoint</b>					
Mean IOP at each time point at Week 2, Week 6, and Month 3	A/S		A/S	A/S	S
<b>Secondary Endpoint</b>					
Mean IOP change from baseline at each time point at Week 2, Week 6, and Month 3	A/S	A	S	S	S

ANCOVA = Analysis of Covariant; MMRM = Mixed Model Repeated Measures

A/S: Analyses performed by the applicant for the overall population and for the subgroup of subjects with baseline IOP < 25 mmHg; and by the statistical reviewer for the subgroup of subjects with baseline IOP > 25 mmHg; A: Analyses performed by the applicant; S: Analyses performed by the statistical reviewer.

Note: All Analyses were performed on both ITT and PP population; and based on observed data, LOCF, and BOCF for missing data imputation

<sup>1</sup> Two-sample t-test comparing actual mean IOP value at each time point between Rhopressa and timolol

<sup>2</sup> One-sample t-test comparing the mean change from baseline with the null hypothesized difference of zero within each treatment group.

<sup>3</sup> ANCOVA model including treatment as the main effect and baseline as covariate.

\* MMRM analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment by visit, treatment by time point, visit by time point, and treatment by visit by time point as model terms. An unstructured covariance structure was used to model the within-subject, between-visit, and time point variances.

For Study 302, since it tested two difference doses of Rhopressa vs. Timolol BID, the primary analysis was conducted using a hierarchical strategy to preserve the overall Type I error rate: first test Rhopressa QD to timolol; if QD demonstrates clinical non-inferiority, test Rhopressa BID to timolol. This sequential testing procedure to control overall Type I error rate is acceptable from statistical perspective.

**Regarding the primary endpoint of mean IOP vs. the sedentary endpoint of mean IOP change from baseline**

The statistical review focused on the results of mean IOP changes from baseline based on the ANCOVA adjusted analyses in the subsequent sections and proposed to present these results in the clinical studies section in the label for the following reasons:

- (1) At the subject level, the mean IOP change from baseline can be derived from the mean IOP and vice versa.
- (2) At the population level, the treatment differences are the same for both endpoints.
- (3) The 95% confidence intervals for the treatment differences are the same for both endpoints if the confidence intervals are obtained based on the ANCOVA adjusted for baseline IOP.
- (4) In Studies 301, 302, and 304, the 95% confidence intervals for the treatment differences are similar for both endpoints regardless of the analysis methods.
- (5) The mean IOP changes from baseline form the basis for desired label claims.

**3.2.3 Patient Disposition, Demographic and Baseline Characteristics**

**3.2.3.1 Study 301**

Four hundred and eleven (411) subjects were randomized into the study, including 202 in the Rhopressa group and 209 in the Timolol group. Forty-four (44, 10.7%) subjects discontinued the study early. More subjects in Rhopressa arm discontinued the study early (31 [15.3%]) than subjects in timolol group (13 [6.2%]). The most frequent reason for discontinuation was AE. There were more subjects in Rhopressa arm discontinued the study due to AEs (20 [9.9%]) than subjects in timolol group (4 [1.9%]).

**Table 9: Study 301 Summary of Subjects' Disposition**

	<b>Rhopressa n (%)</b>	<b>Timolol n (%)</b>	<b>Overall n (%)</b>
<b>Number of Subjects Randomized</b>	202	209	411
<b>Completed the Study</b>	171 (84.7)	196 (93.8)	367 (89.3)
<b>Discontinued the Study Early</b>	31 (15.3)	13 (6.2)	44 (10.7)

<b>Reasons for Early Discontinuation</b>			
Adverse Event	20 (9.9)	4 (1.9)	24 (5.8)
Withdrawal of Consents	3 (1.5)	2 (1.0)	5 (1.2)
Non-Compliant	0	1 (0.5)	1 (0.2)
Lost to Follow-up	0	1 (0.5)	1 (0.2)
Lack of efficacy	3 (1.5)	0	3 (0.7)
Investigator Decision	2 (1.0)	0	2 (0.5)
Protocol Violation	3 (1.5)	5 (2.4)	8 (1.9)

Source: Table 5 of Study 301 Report.

All 411 randomized subjects were included in both the safety and the ITT population. The PP population had 370 subjects. Among these 370 subjects, 237 (64%) subjects had maximum baseline IOP < 25 mmHg.

**Table 10: Study 301 Summary of Study Population**

	<b>Rhopressa n (%)</b>	<b>Timolol n (%)</b>	<b>Overall n (%)</b>
<b>ITT</b>	<b>202</b>	<b>209</b>	<b>411</b>
Maximum Baseline IOP < 25 mmHg	125 (62%)	138 (66%)	263 (64%)
Maximum Baseline IOP ≥ 25 mmHg	77 (38%)	71 (34%)	148 (36%)
<b>PP</b>	<b>182</b>	<b>188</b>	<b>370</b>
Maximum Baseline IOP < 25 mmHg	113 (62%)	124 (66%)	237 (64%)
Maximum Baseline IOP ≥ 25 mmHg	69 (38%)	64 (34%)	133 (36%)

Source: Table 6 of Study 301 Report and statistical reviewer's calculation.

As presented in the following table, in general, demographic and baseline characteristics were comparable between the treatment groups.

**Table 11: Study 301 Demographic and Baseline Characteristics (ITT)**

Characteristics	<b>Rhopressa (N=202)</b>	<b>Timolol (N=209)</b>	<b>Total (N=410)</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
<b>Study Eye Diagnosis</b>			
Open Angle Glaucoma (OAG)	134 (66.3)	136 (65.1)	270 (65.7)
Ocular Hypertension (OHT)	68 (33.7)	73 (34.9)	141 (34.3)
<b>Gender</b>			
Male	88 (43.6)	73 (34.9)	161 (39.2)
Female	114 (56.4)	136 (65.1)	250 (60.8)
<b>Age</b>			
Mean (Std)	65.8 (11.7)	64.2 (11.3)	65.0 (11.5)
Min, Max	20, 96	26, 90	20, 96
Median	67.0	65.0	66.0
< 65	78 (38.6)	96 (45.9)	174 (42.3)
≥ 65	124 (61.4)	113 (54.1)	237 (57.7)
<b>Race</b>			

Characteristics	Rhopressa (N=202)	Timolol (N=209)	Total (N=410)
	n (%)	n (%)	n (%)
Asian	2 (1.0)	4 (1.9)	6 (1.5)
Black/African American	43 (21.3)	51 (24.4)	94 (22.9)
White	157 (77.7)	153 (73.2)	310 (75.4)
Other	0	1 (0.5)	1 (0.2)
<b>Ethnicity</b>			
Hispanic or Latino	27 (13.4)	28 (13.4)	55 (13.4)
Non-Hispanic or Latino	175 (86.6)	181 (86.6)	310 (86.6)
<b>Iris Color of Study Eye</b>			
Blue/Grey/Green	71 (35.1)	54 (25.8)	125 (30.4)
Brown/Black	107 (53.0)	141 (67.5)	248 (60.3)
Hazel	24 (11.9)	14 (6.7)	38 (9.2)

Source: Tables 7 of Study 301 report.

### 3.2.3.2 Study 302

Seven hundred and fifty-six (756) subjects were randomized into the study, including 251 in the Rhopressa QD group, 254 in the Rhopressa BID group, and 251 in the Timolol group. One hundred and sixty-one (161, 21.3%) subjects discontinued the study prior to Month 3; and 320 (42.3%) subjects discontinued the study prior to Month 12. More subjects in both Rhopressa arms discontinued the 12-month study early (105 [41.8%] for QD, and 168 [66.1%] for BID) than subjects in timolol group (47 [18.7%]). The most frequent reason for discontinuation was AE. By Month 12, there were much more subjects in both Rhopressa arms discontinued the study due to AEs (71 [28.3%] for QD, and 132 [52.2%] for BID) than subjects in timolol group (15 [6.0%]).

**Table 12: Study 302 Summary of Subjects' Disposition**

	Rhopressa QD n (%)	Rhopressa BID n (%)	Timolol n (%)	Overall n (%)
<b>Number of Subjects Randomized</b>	251	254	251	756
<b>Study Completion</b>				
Completed Month 3	205 (81.7)	153 (60.2)	237 (94.4)	595 (78.7)
Discontinued Prior to Month 3	46 (18.3)	191 (39.8)	14 (5.6)	161 (21.3)
Completed Month 12	146 (58.2)	86 (33.9)	204 (81.3)	436 (57.7)
Discontinued Prior to Month 12	105 (41.8)	168 (66.1)	47 (18.7)	320 (42.3)
<b>Discontinued Prior to Month 3</b>				
<b>Reasons for Early Discontinuation</b>				
Adverse Event	31 (12.4)	77 (30.3)	2 (0.8)	110 (14.6)
Withdrawal of Consents	2 (0.8)	11 (4.3)	2 (0.8)	15 (19.8)
Non-Compliant	2 (0.8)	1 (0.4)	0	3 (0.4)
Lost to Follow-up	0	1 (0.4)	0	1 (0.1)
Lack of efficacy	4 (1.6)	3 (1.2)	1 (0.4)	8 (1.1)

Disallowed Concurrent Medication	1 (0.4)	1 (0.4)	0	2 (0.3)
Investigator Decision	0	0	0	0
Protocol Violation	4 (1.6)	4 (1.6)	9 (3.6)	17 (2.2)
Death	0	0	0	0
Other	2 (0.8)	3 (1.2)	0	5 (0.7)
<b>Discontinued Prior to Month 12</b>	<b>105 (41.8)</b>	<b>168 (66.1)</b>	<b>47 (18.7)</b>	<b>320 (42.3)</b>
<b>Reasons for Early Discontinuation</b>				
Adverse Event	71 (28.3)	132 (52.0)	15 (6.0)	218 (28.8)
Withdrawal of Consents	9 (3.6)	13 (5.1)	9 (3.6)	31 (4.1)
Non-Compliant	3 (1.2)	1 (0.4)	3 (1.2)	4 (0.5)
Lost to Follow-up	1 (0.4)	3 (1.2)	0	4 (0.5)
Lack of efficacy	10 (4.0)	4 (1.6)	2 (0.8)	16 (2.1)
Disallowed Concurrent Medication	2 (0.8)	2 (0.8)	5 (2.0)	9 (1.2)
Investigator Decision	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Protocol Violation	4 (1.6)	6 (2.4)	10 (4.0)	20 (2.6)
Death	2 (0.8)	0	0	2 (0.3)
Other	2 (0.8)	5 (2.0)	1 (0.4)	8 (1.1)

Source: Tables 14.1.2.2 and 7 of Study 302 Report.

All 756 randomized subjects except one subject were included in both the safety and the ITT population. The PP population had 632 subjects. Among these 632 subjects, 403 (64%) had maximum baseline IOP < 25 mmHg.

**Table 13: Study 302 Summary of Study Population**

	<b>Rhopressa QD</b>	<b>Rhopressa BID</b>	<b>Timolol</b>	<b>Overall</b>
<b>Safety</b>	<b>251</b>	<b>253</b>	<b>251</b>	<b>755</b>
<b>ITT</b>	<b>251</b>	<b>253</b>	<b>251</b>	<b>755</b>
Maximum Baseline IOP < 25 mmHg	155 (62%)	159 (63%)	163 (65%)	477 (63%)
Maximum Baseline IOP ≥ 25 mmHg	96 (38%)	94 (37%)	88 (35%)	278 (37%)
<b>PP</b>	<b>206</b>	<b>209</b>	<b>217</b>	<b>632</b>
Maximum Baseline IOP < 25 mmHg	129 (63%)	132 (63%)	142 (65%)	403 (64%)
Maximum Baseline IOP ≥ 25 mmHg	77 (37%)	77 (37%)	75 (35%)	229 (36%)

Source: Table 7 and Table 8 of Study 302 Report.

As presented in the following table, demographic and baseline characteristics were comparable among the treatment groups.

**Table 14: Study 302 Demographic and Baseline Characteristics (ITT)**

Characteristics	<b>Rhopressa QD</b>	<b>Rhopressa BID</b>	<b>Timolol</b>	<b>Total</b>
	<b>(N=251)</b>	<b>(N=254)</b>	<b>(N=251)</b>	<b>(N=756)</b>
	<b>n (%)</b>		<b>n (%)</b>	<b>n (%)</b>
<b>Study Eye Diagnosis</b>				
Open Angle Glaucoma (OAG)	167 (66.5)	158 (62.2)	171 (68.1)	496 (65.6)
Ocular Hypertension (OHT)	84 (33.5)	96 (37.8)	80 (31.9)	260 (34.4)

Characteristics	Rhopressa QD (N=251)	Rhopressa BID (N=254)	Timolol (N=251)	Total (N=756)
	n (%)		n (%)	n (%)
<b>Gender</b>				
Male	103 (41.0)	89 (35.0)	101 (40.2)	293 (38.8)
Female	148 (59.0)	165 (65.0)	150 (59.8)	463 (61.2)
<b>Age</b>				
Mean (Std)	65.3 (11.5)	64.1 (12.5)	63.0 (11.8)	64.1 (12.0)
Min, Max	14, 86	18, 92	11, 88	11, 92
Median	67.0	65.0	64.0	65.0
< 65	111 (44.2)	126 (49.6)	131 (52.2)	268 (48.7)
≥ 65	140 (55.8)	128 (50.4)	120 (47.8)	388 (51.3)
<b>Race</b>				
Asian	2 (0.8)	6 (2.4)	6 (2.4)	14 (1.9)
Black/African American	69 (27.5)	69 (27.2)	76 (30.3)	214 (28.3)
White	178 (70.9)	177 (69.7)	166 (66.1)	521 (68.9)
Other	2 (0.8)	2 (0.8)	3 (1.2)	7 (0.9)
<b>Ethnicity</b>				
Hispanic or Latino	41 (16.3)	43 (16.9)	42 (16.7)	126 (16.7)
Non-Hispanic or Latino	210 (83.7)	211 (83.1)	209 (83.3)	630 (83.3)
<b>Iris Color of Study Eye</b>				
Blue/Grey/Green	60 (23.9)	57 (22.4)	69 (27.5)	186 (24.6)
Brown/Black	155 (61.8)	169 (66.5)	165 (65.7)	489 (64.7)
Hazel	35 (13.9)	28 (11.0)	17 (6.8)	80 (10.6)
Other	1 (0.4)	0	0	1 (0.1)

Source: Tables 14.1.1.2 of Study 302 report.

### 3.2.3.3 Study 304

Seven hundred and eight (708) subjects were randomized into the study, including 351 in the Rhopressa group and 357 in the Timolol group. Eight-three (83, 11.7%) subjects discontinued the study prior to Month 3; and 151 (21.3%) subjects discontinued the study by Month 6. More subjects in Rhopressa arm discontinued the 6-month study early (108 [30.8%]) than subjects in timolol group (43 [12.0%]). The most frequent reason for discontinuation was AE. By Month 6, there were more subjects in Rhopressa arm discontinued the study due to AEs (68 [19.4%]) than subjects in timolol group (8 [2.2%]).

**Table 15: Study 304 Summary of Subjects' Disposition**

	Rhopressa n (%)	Timolol n (%)	Overall n (%)
<b>Number of Subjects Randomized</b>	351	357	708
<b>Study Completion</b>			
Completed Month 3	290 (82.6)	335 (93.8)	625 (88.3)
Discontinued Prior to Month 3	61 (17.4)	22 (6.2)	83 (11.7)

Completed Month 6	243 (69.2)	314 (88.0)	557 (78.8)
Discontinued Prior to Month 6	108 (30.8)	43 (12.0)	151 (21.3)
<b>Discontinued Prior to Month 3</b>			
<b>Reasons for Early Discontinuation</b>			
Adverse Event	39 (11.1)	6 (1.7)	45 (6.4)
Withdrawal of Consents	7 (2.0)	7 (2.0)	14 (2.0)
Non-Compliant	1 (0.3)	1 (0.3)	2 (0.3)
Lost to Follow-up	0	0	0
Lack of efficacy	5 (1.4)	0	5 (0.7)
Disallowed Concurrent Medication	1 (0.3)	2 (0.6)	3 (0.4)
Investigator Decision	0	2 (0.6)	2 (0.3)
Protocol Violation	4 (1.1)	3 (0.8)	7 (1.0)
Death	1 (0.3)	0	1 (0.1)
Other	3 (0.9)	1 (0.3)	4 (0.6)
<b>Discontinued Prior to Month 6</b>			
<b>Reasons for Early Discontinuation</b>			
Adverse Event	68 (19.4)	8 (2.2)	76 (10.7)
Withdrawal of Consents	12 (3.4)	16 (4.5)	28 (4.0)
Non-Compliant	1 (0.3)	2 (0.6)	3 (0.4)
Lost to Follow-up	1 (0.3)	3 (0.8)	4 (0.6)
Lack of efficacy	12 (3.4)	1 (0.3)	13 (1.8)
Disallowed Concurrent Medication	1 (0.3)	3 (0.8)	4 (0.6)
Investigator Decision	2 (0.6)	4 (1.1)	6 (0.8)
Protocol Violation	5 (1.4)	4 (1.1)	9 (1.3)
Death	1 (0.3)	0	1 (0.1)
Other	5 (1.4)	2 (0.6)	7 (1.0)

Source: Table 5 of the 3-month interim CSR and Table 5 of the full CSR of Study 304.

All 708 randomized subjects were included in both the safety and the ITT population. The PP population had 623 subjects. Among these 623 subjects, 373 (60%) had maximum baseline IOP < 25 mmHg.

**Table 16: Study 304 Summary of Study Population**

	<b>Rhopressa</b>	<b>Timolol</b>	<b>Overall</b>
<b>Safety</b>	<b>351</b>	<b>357</b>	<b>708</b>
<b>ITT</b>	<b>351</b>	<b>357</b>	<b>708</b>
Maximum Baseline IOP < 25 mmHg	214 (61%)	209 (59%)	423 (60%)
Maximum Baseline IOP ≥ 25 mmHg	137 (39%)	148 (41%)	285 (40%)
<b>PP</b>	<b>306</b>	<b>317</b>	<b>623</b>
Maximum Baseline IOP < 25 mmHg	186 (61%)	187 (59%)	373 (60%)
Maximum Baseline IOP ≥ 25 mmHg	120 (39%)	130 (41%)	250 (40%)

Source: Tables 5 and 6 of Study 304 Report.

As presented in the following table, demographic and baseline characteristics were comparable between the treatment groups.

**Table 17: Study 304 Demographic and Baseline Characteristics (ITT)**

Characteristics	Rhopressa (N=351)	Timolol (N=357)	Total (N=708)
	n (%)	n (%)	n (%)
<b>Study Eye Diagnosis</b>			
Open Angle Glaucoma (OAG)	223 (63.5)	244 (68.3)	467 (66.0)
Ocular Hypertension (OHT)	128 (36.5)	112 (31.4)	240 (33.9)
<b>Gender</b>			
Male	143 (40.7)	120 (33.6)	263 (37.1)
Female	208 (59.3)	237 (66.4)	445 (62.9)
<b>Age</b>			
Mean (Std)	64.1 (11.6)	64.5 (11.0)	64.3 (11.3)
Min, Max	18, 89	25, 91	18, 91
Median	65.0	66.0	65.5
< 65	165 (47.0)	164 (45.9)	329 (46.5)
≥ 65	186 (53.0)	193 (54.1)	379 (53.5)
<b>Race</b>			
Asian	7 (2.0)	6 (1.7)	13 (1.8)
Black/African American	84 (23.9)	75 (21.0)	159 (22.5)
White	259 (73.8)	274 (76.8)	533 (75.3)
Other	1 (0.3)	2 (0.6)	3 (0.4)
<b>Ethnicity</b>			
Hispanic or Latino	89 (25.4)	87 (24.4)	176 (24.9)
Non-Hispanic or Latino	262 (74.6)	270 (75.6)	532 (75.1)
<b>Iris Color of Study Eye</b>			
Blue/Grey/Green	73 (20.8)	90 (25.2)	163 (23.0)
Brown/Black	241 (68.7)	227 (63.6)	468 (66.1)
Hazel	36 (10.3)	40 (11.2)	76 (10.7)
Other	1 (0.3)	0	1 (0.1)

Source: Tables 14.1.1.2 of Study 304 report.

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Study 301

For the overall PP population, the two treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 21.8 to 23.4 mmHg for the Rhopressa QD group and 21.5 to 23.4 mmHg for the timolol group. IOP reductions were observed in both groups; mean IOP reduction from baseline ranged from 3.2 to 5.0 in the Rhopressa group and from 3.8 to 5.0 in the timolol group. The upper 95% confidence limit for the treatment differences was 1.7 mmHg at 8AM on Day 43 and 1.9 mmHg at 8AM on Day 90, exceeding the non-inferiority margin of 1.5 mmHg and favoring timolol.

For subjects with baseline IOP <25 mmHg, the two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.6 to 5.1 mmHg in the Rhopressa group; and from 3.2 to 4.7 mmHg in the timolol group. The criteria for noninferiority were met for Rhopressa subjects in this subgroup, with the upper limit of the 95% CIs for the treatment differences (Rhopressa – timolol) within 1.5 mmHg at all 9 time points.

For subjects with baseline IOP ≥ 25 mmHg, mean IOP reduction from baseline ranged from 2.2 to 4.9 mmHg in the Rhopressa group; and from 4.6 to 6.0 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all morning time points, and on Days 43 and 90. The treatment difference was 2.7 mmHg at 8AM on Day 43 (with the upper limit of the 95% CI as high as 3.8 mmHg) and 3.0 mmHg at 8AM on Day 90 (with the upper limit of the 95% CI as high as 4.1 mmHg).

**Table 18: Study 301 Mean IOP Change from Baseline in Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP ≥ 25 mmHg		
		Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>
		Mean	Mean		Mean	Mean		Mean	Mean	
<b>Baseline</b>	<b>08:00</b>	23.4	23.4	0.1 (-0.3, 0.4)	22.4	22.5	-0.1 (-0.4, 0.2)	25.1	25.0	0.1 (-0.3, 0.5)
	<b>10:00</b>	22.3	21.9	0.4 (-0.1, 0.8)	21.3	21.1	0.2 (-0.2, 0.6)	23.9	23.6	0.3 (-0.3, 0.9)
	<b>16:00</b>	21.8	21.5	0.3 (-0.2, 0.8)	20.6	20.5	0.1 (-0.4, 0.6)	23.7	23.3	0.4 (-0.3, 1.2)
<b>Day 15</b>	<b>08:00</b>	-4.8	-5.0	0.3 (-0.2, 0.8)	-5.1	-4.7	-0.3 (-0.9, 0.3)	-4.3	-5.7	1.3 (0.4, 2.3)
	<b>10:00</b>	-5.0	-4.5	-0.5 (-1.0, 0.0)	-5.0	-4.2	-0.9 (-1.5, -0.3)	-4.9	-5.0	0.1 (-0.9, 1.2)
	<b>16:00</b>	-4.5	-3.9	-0.6 (-1.2, -0.1)	-4.4	-3.4	-0.9 (-1.6, -0.3)	-4.7	-4.6	-0.1 (-1.2, 0.9)
<b>Day 43</b>	<b>08:00</b>	-4.1	-5.1	1.1 (0.5, 1.7)*	-4.5	-4.7	0.2 (-0.5, 0.9)	-3.3	-6.0	2.7 (1.5, 3.8)
	<b>10:00</b>	-4.1	-4.6	0.5 (-0.1, 1.1)	-4.3	-4.2	-0.2 (-0.8, 0.5)	-3.7	-5.3	1.6 (0.4, 2.7)
	<b>16:00</b>	-3.8	-3.8	0.0 (-0.7, 0.6)	-4.0	-3.3	-0.7 (-1.4, 0.0)	-3.7	-4.8	1.2 (0.0, 2.3)
<b>Day 90</b>	<b>08:00</b>	-3.6	-4.9	1.3 (0.7, 1.9)*	-4.2	-4.6	0.4 (-0.2, 1.1)	-2.6	-5.5	3.0 (1.8, 4.1)
	<b>10:00</b>	-3.3	-4.0	0.8 (0.1, 1.4)	-3.9	-3.7	-0.2 (-0.9, 0.5)	-2.2	-4.7	2.5 (1.4, 3.6)
	<b>16:00</b>	-3.2	-3.8	0.6 (0.0, 1.2)	-3.6	-3.2	-0.4 (-1.0, 0.3)	-2.6	-4.9	2.3 (1.2, 3.5)

<sup>1</sup> The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

\* The upper limit is above the non-inferiority margin of 1.5 mmHg.

Source: Statistical Reviewer’s analysis based on the randomized subjects who did not have major protocol violations.

The analyses of the mean IOP endpoints yielded the same efficacy conclusion as the analyses of the mean IOP change from baseline. The detailed discussion of mean IOP results was provided in Appendix 2. A graphical presentation of the mean IOP was provided in Figure 1.

### 3.2.4.2 Study 302

Based on the above post hoc findings of Study 301, the applicant changed the primary efficacy analyses population of then-ongoing Study 302 to be the subgroup of PP subjects who had maximum baseline IOP < 25 mmHg at all time points before unblinding Study 302.

Mean IOP reduction for Rhopressa BID group was numerically lower (better) than mean IOP for Rhopressa QD group at all post-baseline time points. However, Rhopressa BID group had much more discontinuation due to AE comparing with Rhopressa QD group (see 3.2.3.2). The applicant concluded that although Rhopressa dosed BID provided slightly larger IOP reductions, but had a less favorable safety profile as reflected in a high discontinuation rate during the 12-month study (see also Section 3.2.3.2). The statistical reviewer concurred with the applicant's conclusion and focused on Rhopressa QD dose for Study 302. Please refer to Appendix 2 for the detailed efficacy results of Rhopressa BID.

For the overall PP population, the two treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 21.6 to 23.5 mmHg for the Rhopressa QD group and the same for the timolol group. IOP reductions were observed in both treatment groups; mean IOP reduction from baseline ranged from 3.7 to 4.5 in the Rhopressa group and from 3.9 to 5.4 in the timolol group. The upper 95% confidence limit for the treatment differences was as high as 1.8 mmHg at 8AM on both Days 43 and 90, exceeding the non-inferiority margin of 1.5 mmHg and favoring timolol.

For the primary efficacy analyses population of PP subjects who had maximum baseline IOP < 25 mmHg at all baseline measurement time points, the mean baseline IOP was in the range 21.3 to 22.5 mmHg for the Rhopressa QD group, and 21.3 to 22.5 mmHg for the timolol group. The two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.4 to 4.6 mmHg in the netarsudil group; and from 3.7 to 5.1 mmHg in the timolol group. The upper 95% confidence limit for the treatment differences was within 1.5 mmHg at all nine time points.

For subjects with baseline IOP  $\geq$  25 mmHg, mean IOP reduction from baseline ranged from 3.4 to 4.9 mmHg in the netarsudil group; and from 4.3 to 5.6 mmHg in the timolol group. Compared with timolol, the netarsudil group had a smaller mean IOP reduction at all morning time points, and on Days 43 and 90. The treatment difference was 2.6 mmHg at 8AM on Day 43 (with the upper limit of the 95% CI as high as 3.7 mmHg) and 2.1 mmHg at 8AM on Day 90 (with the upper limit of the 95% CI as high as 3.2 mmHg).

**Table 19: Study 302 Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP $\geq$ 25 mmHg		
		Rhopressa QD	Timolol	Difference (95% CI) <sup>a</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>a</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>a</sup>
		Mean	Mean		Mean	Mean		Mean	Mean	
<b>Baseline</b>	<b>08:00</b>	23.5	23.5	0.1	22.5	22.5	0.0	25.1	25.2	0.0

				(-0.3, 0.4)			(-0.2, 0.2)			(-0.4, 0.3)
	<b>10:00</b>	22.3	22.2	0.1 (-0.3, 0.5)	21.3	21.3	0.0 (-0.4, 0.4)	24.0	23.9	0.1 (-0.4, 0.7)
	<b>16:00</b>	21.6	21.6	-0.1 (-0.5, 0.4)	20.4	20.7	-0.3 (-0.7, 0.1)	23.5	23.3	0.1 (-0.6, 0.8)
<b>Day 15</b>	<b>08:00</b>	-4.5	-5.2	0.7 (0.2, 1.2)	-4.5	-4.9	0.4 (-0.2, 1.0)	-4.5	-5.9	1.4 (0.5, 2.3)*
	<b>10:00</b>	-4.5	-4.7	0.2 (-0.3, 0.7)	-4.6	-4.4	-0.2 (-0.8, 0.4)	-4.5	-5.4	0.9 (-0.1, 1.9)*
	<b>16:00</b>	-4.2	-4.0	-0.2 (-0.7, 0.3)	-3.9	-3.8	-0.1 (-0.6, 0.5)	-4.9	-4.3	-0.6 (-1.5, 0.3)
<b>Day 43</b>	<b>08:00</b>	-4.1	-5.4	1.2 (0.7, 1.8)*	-4.6	-5.1	0.5 (-0.1, 1.1)	-3.4	-5.9	2.6 (1.5, 3.7)*
	<b>10:00</b>	-4.2	-4.9	0.7 (0.2, 1.3)	-4.4	-4.7	0.3 (-0.3, 0.9)	-3.8	-5.3	1.5 (0.5, 2.6)*
	<b>16:00</b>	-3.7	-4.3	0.7 (0.2, 1.2)	-3.5	-4.0	0.5 (-0.1, 1.1)	-3.9	-4.9	0.9 (0.0, 1.9)*
<b>Day 90</b>	<b>08:00</b>	-4.0	-5.3	1.3 (0.7, 1.8)*	-4.3	-5.1	0.8 (0.1, 1.5)	-3.4	-5.6	2.1 (1.1, 3.2)*
	<b>10:00</b>	-4.0	-4.7	0.7 (0.1, 1.3)	-4.3	-4.4	0.1 (-0.5, 0.8)	-3.5	-5.3	1.7 (0.6, 2.8)
	<b>16:00</b>	-3.7	-3.9	0.2 (-0.4, 0.7)	-3.4	-3.7	0.3 (-0.4, 1.0)	-4.4	-4.3	-0.1 (-1.2, 1.0)

<sup>1</sup> The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

\* The upper limit is above the non-inferiority margin of 1.5 mmHg.

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

The analyses of the mean IOP endpoints yielded the same efficacy conclusion as the analyses of the mean IOP change from baseline. The detailed discussion of mean IOP results was provided in Appendix 2. A graphical presentation of the mean IOP was provided in Figure 1.

### 3.2.4.3 Study 304

For the overall PP population, the two treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 22.2 to 23.9 mmHg for the Rhopressa QD group and in the range of 22.0 to 23.9 mmHg for the timolol group. IOP reductions were observed in both treatment groups; mean IOP reduction from baseline ranged from 3.9 to 4.8 in the Rhopressa group and from 4.1 to 5.3 in the timolol group. The upper 95% confidence limit for the treatment differences was within 1.5 mmHg at all nine time points.

For the primary efficacy analyses population of PP subjects who had maximum baseline IOP < 25 mmHg at all time points, the mean baseline IOP was in the range of 20.7 to 22.4 mmHg for the Rhopressa QD group, 20.7 to 22.4 for the timolol group. The two treatment groups had similar mean IOP reductions; mean IOP reduction from baseline ranged from 3.9 to 4.7 mmHg in the netarsudil group; and from 3.8 to 5.2 mmHg in the timolol group. The upper 95% confidence limit for the treatment differences was within 1.5 mmHg at all nine time points.

For subjects with baseline IOP  $\geq$  25 mmHg, mean IOP reduction from baseline ranged from 3.9 to 5.0 mmHg in the Rhopressa group; and from 4.9 to 6.2 mmHg in the timolol group. Compared with timolol, the Rhopressa group had a smaller mean IOP reduction at all time points and especially obvious on the morning time points on Days 43 and 90. The treatment difference was

1.9 mmHg at 8AM on Day 43 (with the upper limit of the 95% CI as high as 2.8 mmHg) and 1.8 mmHg at 10AM on Day 90 (with the upper limit of the 95% CI as high as 2.7 mmHg).

**Table 20: Study 304 Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**

		Overall			Baseline IOP < 25 mmHg			Baseline IOP ≥ 25 mmHg		
		Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>	Rhopressa QD	Timolol	Difference (95% CI) <sup>1</sup>
		Mean	Mean		Mean	Mean		Mean		
<b>Baseline</b>	<b>08:00</b>	23.9	23.9	0.0 (-0.3, 0.4)	22.4	22.4	0.0 (-0.3, 0.2)	26.3	26.0	0.3 (-0.2, 0.8)
	<b>10:00</b>	22.7	22.8	-0.1 (-0.5, 0.3)	21.1	21.3	-0.2 (-0.6, 0.2)	25.2	24.9	0.3 (-0.3, 0.8)
	<b>16:00</b>	22.2	22.0	0.1 (-0.3, 0.6)	20.7	20.7	0.0 (-0.4, 0.4)	24.5	24.0	0.5 (-0.2, 1.1)
<b>Day 15</b>	<b>08:00</b>	-4.7	-5.3	0.6 (0.1, 1.1)	-4.7	-4.9	0.2 (-0.4, 0.8)	-4.7	-5.9	1.2 (0.3, 2.0)*
	<b>10:00</b>	-4.8	-5.0	0.2 (-0.3, 0.7)	-4.5	-4.5	0.0 (-0.5, 0.5)	-5.0	-5.6	0.6 (-0.2, 1.5)
	<b>16:00</b>	-4.4	-4.2	-0.2 (-0.6, 0.3)	-4.4	-3.8	-0.6 (-1.1, -0.1)	-4.3	-4.9	0.6 (-0.2, 1.3)
<b>Day 43</b>	<b>08:00</b>	-4.5	-5.4	0.9 (0.4, 1.4)	-4.6	-4.8	0.3 (-0.3, 0.8)	-4.3	-6.2	1.9 (1.0, 2.8)*
	<b>10:00</b>	-4.5	-4.8	0.3 (-0.1, 0.8)	-4.3	-4.3	-0.1 (-0.6, 0.5)	-4.7	-5.8	1.1 (0.2, 1.9)*
	<b>16:00</b>	-4.2	-4.1	0.0 (-0.5, 0.4)	-4.1	-4.0	-0.1 (-0.6, 0.4)	-4.3	-4.4	0.2 (-0.6, 1.0)
<b>Day 90</b>	<b>08:00</b>	-4.5	-5.5	1.0 (0.5, 1.5)	-4.5	-5.2	0.6 (0.0, 1.2)	-4.5	-6.1	1.6 (0.6, 2.5)*
	<b>10:00</b>	-4.2	-5.1	0.9 (0.4, 1.4)	-4.1	-4.5	0.4 (-0.2, 0.9)	-4.1	-5.9	1.8 (0.9, 2.7)*
	<b>16:00</b>	-3.9	-4.3	0.3 (-0.1, 0.8)	-3.9	-3.9	0.0 (-0.6, 0.5)	-3.9	-5.0	1.1 (0.2, 1.9)*

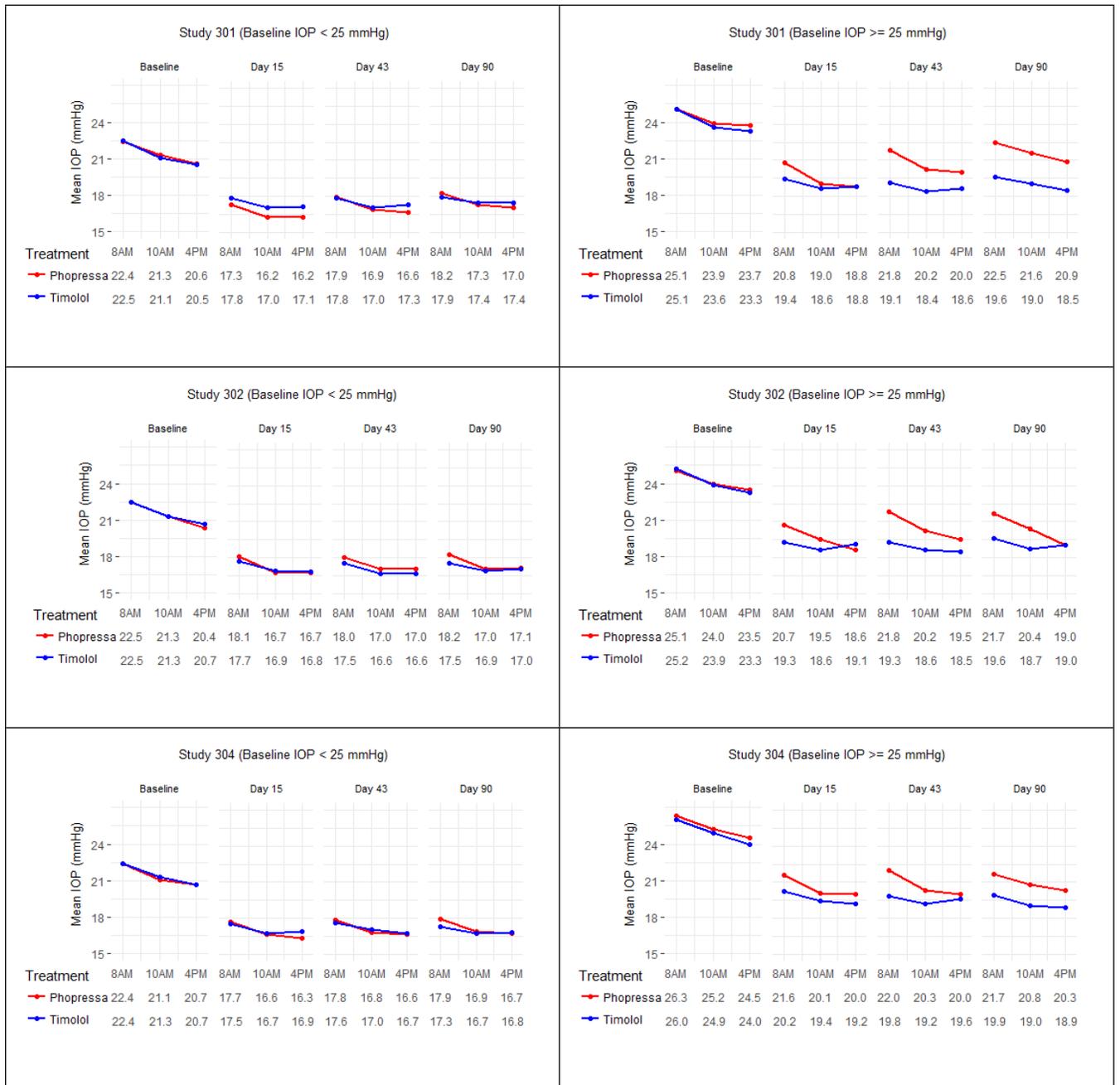
<sup>1</sup> The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

\* The upper limit is above the non-inferiority margin of 1.5 mmHg.

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

The analyses of the mean IOP endpoints yielded the same efficacy conclusion the analyses of the mean IOP change from baseline. The detailed discussion of mean IOP results was provided in Appendix 2. A graphical presentation of the mean IOP was provided in Figure 1.

**Figure 1: Mean IOP of Study Eye (mmHg) by Visit and Time (Rhopressa QD vs. Timolol BID)**



### 3.2.4.4 Sensitivity and Supportive Analyses

As discussed previously, in all three studies, about 15% to 18% subjects in the Rhopressa QD group and about 6% in timolol group discontinued the study prior to Month 3. Among these discontinued subjects, discontinuation due to other reasons were comparable between the two groups and the percentage was relatively low ( $\leq 2\%$  for each reason). However, all studies showed significantly higher discontinuation rates due to AE in the Rhopressa group compared to the timolol group.

**Table 21: Summary of Subjects Disposition**

	<b>Rhopressa QD n/N (%)</b>	<b>Timolol BID n/N (%)</b>
<b>Study 301</b>		
<b>ITT</b>	202	209
<b>Completed the Study</b>	171 (84.7)	196 (93.8)
<b>Discontinued Prior to Month 3</b>	31 (15.3)	13 (6.2)
Discontinued Prior to Month 3 Due to AE	20 (9.9)	4 (1.9)
<b>Study 302</b>		
<b>ITT</b>	251	251
<b>Completed Month 3</b>	205 (81.7)	237 (94.4)
<b>Discontinued Prior to Month 3</b>	46 (18.3)	14 (5.6)
Discontinued Prior to Month 3 Due to AE	31 (12.4)	2 (0.8)
<b>Completed Month 12</b>	146 (58.2)	204 (81.3)
<b>Discontinued Prior to Month 12</b>	105 (41.8%)	47 (18.7)
Discontinued Prior to Month 12 Due to AE	71 (28.3)	15 (6.0)
<b>Study 304</b>		
<b>ITT</b>	351	357
<b>Completed Month 3</b>	290 (82.6)	335 (93.8)
<b>Discontinued Prior to Month 3</b>	61 (17.4)	22 (6.2)
Discontinued Prior to Month 3 Due to AE	39 (11.1)	6 (1.7)
<b>Completed Month 6</b>	243 (69.2)	314 (88.0)
<b>Discontinued Prior to Month 6</b>	108 (30.8)	43 (12.0)
Discontinued Prior to Month 12 Due to AE	68 (19.4)	8 (2.2)

Source: Statistical Reviewer's summary based on Table 5 of Study 301 Report, Tables 14.1.2.2 and 7 of Study 302 Report, and Tables 5 and 6 of Study 304 Report.

The statistical reviewer summarized the efficacy results for those subjects who discontinued prior to Month 3. As presented in the following table, prior to discontinuation, the IOP lowering effect of Rhopressa for these subjects who discontinued due to AE was consistent with the treatment effect for those subjects who did not discontinued.

**Table 22: Mean IOP Change from Baseline (mmHg) in Study Eye by Visit and Time for Rhopressa-Treated Subjects Who Discontinued Due to AE Prior to Month 3 (Overall)**

	<b>Study 301</b>		<b>Study 302</b>		<b>Study 304</b>	
	<b>Rhopressa QD</b>		<b>Rhopressa QD</b>		<b>Rhopressa QD</b>	
<b>Baseline</b>	N	Mean	N	Mean	N	Mean
<b>08:00</b>	20	23.68	31	23.83	39	24.53
<b>10:00</b>	20	22.20	31	22.73	39	23.68

<b>16:00</b>	20	21.83	31	21.94	39	22.03
<b>Day 15</b>						
<b>08:00</b>	19	-5.0	29	-5.4	35	-5.2
<b>10:00</b>	16	-5.9	24	-5.2	31	-5.4
<b>16:00</b>	16	-4.3	26	-4.4	31	-5.8
<b>Day 43</b>						
<b>08:00</b>	11	-4.8	19	-4.1	25	-4.7
<b>10:00</b>	11	-4.4	16	-4.5	24	-4.9
<b>16:00</b>	11	-4.6	16	-3.9	24	-5.5
<b>Day 90</b>						
<b>08:00</b>	0	n/a	7	-3.4	4	-3.9
<b>10:00</b>	0	n/a	3	-4.0	1	-2.5
<b>16:00</b>	0	n/a	1	-6.0	0	n/a

Source: Statistical Reviewer's Summary based on all randomized subjects who received study medication.

As described in Table 8, the applicant and the statistical reviewer conducted various sensitivity and supportive analyses for the primary efficacy endpoints for both ITT and PP populations to investigate the robustness of the results of the primary efficacy analysis. Other than the BOCF analysis, all the other analyses results were consistent with the primary efficacy results. Note: Detailed results were presented in Appendix 3 for some of these analyses.

Although the BOCF analysis results failed to demonstrate non-inferiority of Rhopressa to timolol for subjects with baseline IOP < 25 mmHg in Study 302 at one time point (8AM on Day 90), it is noted that IOP reductions were observed and consistent in Rhopressa group in all three studies for this analysis; mean IOP reduction from baseline ranged from about 3 to 5 mmHg in the Rhopressa group (Table 23).

**Table 23: BOCF Analyses Results of Mean IOP Change from Baseline (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg)**

Study	Treatment	Day	IOP			Treatment Difference (95% CI) <sup>1</sup>		
			Time			Time		
			8:00 Mean	10:00 Mean	16:00 Mean	8:00	10:00	16:00
301	Rhopressa	BL	22.4	21.3	20.6	-0.11	0.21	0.10
	Timolol		22.5	21.1	20.5	(-0.39, 0.18)	(-0.21, 0.64)	(-0.36, 0.56)
	Rhopressa	15	-4.9	-4.8	-4.1	-0.2	-0.7	-0.8
	Timolol		-4.7	-4.1	-3.4	(-0.8, 0.5)	(-1.3, 0.0)	(-1.4, -0.1)
	Rhopressa	43	-4.2	-4.0	-3.8	0.4	0.1	-0.6
	Timolol		-4.6	-4.1	-3.2	(-0.3, 1.1)	(-0.6, 0.7)	(-1.3, 0.1)
Rhopressa	90	-3.7	-3.4	-3.2	0.8	0.2	-0.1	
Timolol		-4.4	-3.6	-3.1	(0.1, 1.4)	(-0.5, 0.9)	(-0.7, 0.6)	
302	Rhopressa	BL	22.5	21.3	20.4	0.00	0.02	-0.28
	Timolol		22.5	21.3	20.7	(-0.25, 0.25)	(-0.37, 0.41)	(-0.71, 0.14)
	Rhopressa	15	-4.4	-4.5	-3.8	0.4	-0.2	0.0
	Timolol		-4.8	-4.3	-3.8	(-0.2, 1.0)	(-0.7, 0.4)	(-0.6, 0.6)
	Rhopressa	43	-4.3	-4.1	-3.3	0.7	0.5	0.7
	Timolol		-5.1	-4.6	-4.0	(0.1, 1.3)	(-0.1, 1.1)	(0.1, 1.3)
Rhopressa	90	-3.9	-3.8	-3.0	1.2	0.6	0.6	
Timolol		-5.0	-4.3	-3.6	(0.5, 1.8)*	(-0.1, 1.2)	(0.0, 1.3)	

302	Rhopressa	BL	22.4	21.1	20.7	-0.05	-0.21	0.01
	Timolol		22.4	21.3	20.7	(-0.27, 0.18)	(-0.55, 0.14)	(-0.37, 0.38)
	Rhopressa	15	-4.7	-4.4	-4.2	0.2	0.0	-0.5
	Timolol		-4.9	-4.4	-3.7	(-0.4, 0.7)	(-0.5, 0.6)	(-1.0, 0.0)
	Rhopressa	43	-4.3	-4.1	-3.9	0.4	0.1	0.1
	Timolol		-4.8	-4.2	-3.9	(-0.1, 1.0)	(-0.5, 0.6)	(-0.5, 0.6)
Rhopressa	90	-4.1	-3.7	-3.4	0.9	0.7	0.3	
Timolol		-5.0	-4.4	-3.7	(0.3, 1.5)	(0.1, 1.2)	(-0.3, 0.9)	

BL = Baseline

<sup>1</sup> The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

\* The upper limit is above the non-inferiority margin of 1.5 mmHg.

Source: Statistical reviewer's analysis based on all randomized subjects who had no major protocol violation.

**Table 24: BOCF Analyses Results of Mean IOP Change from Baseline (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline > 25 mmHg)**

Study	Treatment	Day	IOP			Treatment Difference (95% CI) <sup>1</sup>		
			Time			Time		
			8:00 Mean	10:00 Mean	16:00 Mean	8:00	10:00	16:00
301	Rhopressa	BL	25.1	23.9	23.7	0.1	0.3	0.4
	Timolol		25.0	23.6	23.3	(-0.3, 0.5)	(-0.3, 0.9)	(-0.3, 1.2)
	Rhopressa	15	-4.3	-4.9	-4.7	1.3	0.1	-0.1
	Timolol		-5.7	-5.0	-4.6	(0.4, 2.3)	(-0.9, 1.2)	(-1.2, 0.9)
	Rhopressa	43	-3.1	-3.5	-3.4	2.8	1.7	1.3
	Timolol		-5.9	-5.2	-4.8	(1.6, 3.9)	(0.6, 2.8)	(0.2, 2.5)
Rhopressa	90	-2.2	-1.8	-2.2	3.2	2.8	2.5	
Timolol		-5.4	-4.6	-4.8	(2.2, 4.3)	(1.7, 3.8)	(1.4, 3.6)	
302	Rhopressa	BL	25.1	24.0	23.5	0.0	0.1	0.1
	Timolol		25.2	23.9	23.3	(-0.4, 0.3)	(-0.4, 0.7)	(-0.6, 0.8)
	Rhopressa	15	-4.3	-4.2	-4.7	1.5	1.1	-0.4
	Timolol		-5.9	-5.3	-4.3	(0.6, 2.4)	(0.1, 2.1)	(-1.3, 0.5)
	Rhopressa	43	-3.1	-3.3	-3.4	2.7	2.0	1.4
	Timolol		-5.8	-5.3	-4.8	(1.7, 3.8)	(1.0, 3.0)	(0.5, 2.3)
Rhopressa	90	-2.7	-2.6	-3.2	2.8	2.6	1.0	
Timolol		-5.5	-5.2	-4.2	(1.8, 3.8)	(1.5, 3.6)	(0.0, 2.0)	
302	Rhopressa	BL	26.3	25.2	24.5	0.3	0.3	0.5
	Timolol		26.0	24.9	24.0	(-0.2, 0.8)	(-0.3, 0.8)	(-0.2, 1.1)
	Rhopressa	15	-4.6	-4.8	-4.2	1.2	0.7	0.7
	Timolol		-5.8	-5.6	-4.9	(0.4, 2.1)	(-0.1, 1.6)	(-0.1, 1.5)
	Rhopressa	43	-4.0	-4.3	-3.9	2.1	1.4	0.5
	Timolol		-6.0	-5.6	-4.3	(1.2, 3.0)	(0.5, 2.2)	(-0.4, 1.3)
Rhopressa	90	-3.5	-3.2	-3.1	2.1	2.3	1.5	
Timolol		-5.7	-5.5	-4.6	(1.2, 3.1)	(1.4, 3.2)	(0.6, 2.3)	

BL = Baseline

<sup>1</sup> The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical reviewer's analysis based on all randomized subjects who had no major protocol violation.

### 3.2.4.5 Long-Term Efficacy Results

The long-term efficacy results post 90 days were presented in the following two tables for Studies 302 and 304 respectively.

In Study 302, for subjects with baseline IOP < 25 mmHg, the mean IOP reduction from baseline ranged from 3.7 to 4.6 mmHg for Rhopressa QD group and from 4.7 to 5.0 mmHg for timolol group at 8AM on Month 6, 9, and 12 visits. For subjects with baseline IOP ≥ 25 mmHg, the mean IOP reduction from baseline ranged from 3.2 to 3.6 mmHg for Rhopressa QD group and from 4.7 to 5.2 mmHg for timolol. These results were consistent with the efficacy results observed in the first 3 months; and Rhopressa appeared to maintain about 3.5 to 4.5 mmHg IOP reduction treatment effect till 12-month of treatment.

**Table 25: Study 302 Mean IOP Change from Baseline (mmHg) in Study Eye by Study Visit (Month 6 to 12)**

	Maximum Baseline IOP < 25 mmHg					Maximum Baseline IOP ≥ 25 mmHg				
	Rhopressa QD		Timolol		Difference (95% CI) *	Rhopressa QD		Timolol		Difference (95% CI) *
	N	Mean	N	Mean		N	Mean	N	Mean	
<b>Baseline</b>										
<b>08:00</b>	129	22.5	142	22.5	0.0 (-0.3, 0.3)	77	25.1	75	25.2	-0.0 (-0.4, 0.3)
<b>10:00</b>	129	21.3	142	21.3	0.0 (-0.4, 0.4)	77	24.0	75	23.9	0.1 (-0.4, 0.7)
<b>16:00</b>	129	20.4	142	20.7	-0.3 (-0.7, 0.1)	77	23.5	75	23.3	0.1 (-0.6, 0.8)
<b>Month 6</b>										
<b>08:00</b>	105	-4.6	135	-4.7	0.1 (-0.7, 0.8)	52	-3.4	67	-5.4	2.0 (0.9, 3.2)
<b>Month 9</b>										
<b>08:00</b>	91	-4.3	125	-5.0	0.7 (-0.1, 1.5)	41	-3.6	65	-5.2	1.5 (0.4, 2.7)
<b>Month 12</b>										
<b>08:00</b>	86	-3.7	124	-5.0	1.3 (0.4, 2.2)	40	-3.2	62	-4.7	1.6 (0.3, 2.9)

\* The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

In Study 304, for subjects with baseline IOP < 25 mmHg, the mean IOP change from baseline ranged from 3.8 to 4.8 mmHg for Rhopressa QD group and from 3.6 to 5.2 mmHg for timolol group on Month 4, 5, and 6 visits. For subjects with baseline IOP ≥ 25 mmHg, the mean IOP reduction from baseline ranged from 3.6 to 4.6 mmHg for Rhopressa QD group and from 4.4 to 6.3 mmHg for timolol. These results were consistent with the efficacy results observed in the first 3 months; and Rhopressa appeared to maintain about 3.5 to 4.5 mmHg IOP reduction treatment effect till 6-month of treatment.

**Table 26: Study 304 Mean IOP Change from Baseline (mmHg) in Study Eye by Study Visit (Month 4 to 6)**

Day Time	Maximum Baseline IOP < 25 mmHg				Difference (95% CI) *	Maximum Baseline IOP ≥ 25 mmHg				
	Netarsudil QD		Timolol			Netarsudil QD		Timolol		Difference (95% CI) *
	N	Mean	N	Mean		N	Mean	N	Mean	
<b>Baseline</b>										

<b>08:00</b>	186	22.4	187	22.4	-0.1 (-0.3, 0.2)	120	26.3	130	26.0	0.3 (-0.2, 0.9)
<b>10:00</b>	186	21.1	187	21.3	-0.2 (-0.6, 0.1)	120	25.2	130	24.9	0.3 (-0.3, 0.8)
<b>16:00</b>	186	20.7	187	20.7	0.0 (-0.4, 0.4)	120	24.5	130	24.0	0.5 (-0.2, 1.1)
<b>Month 4</b>										
<b>08:00</b>	158	-4.5	177	-5.1	0.5 (-0.1, 1.1)	86	-4.6	114	-6.2	1.7 (0.7, 2.6)
<b>10:00</b>	158	-4.0	177	-4.4	0.4 (-0.2, 1.0)	85	-4.6	114	-6.0	1.4 (0.5, 2.3)
<b>16:00</b>	158	-3.8	177	-3.9	0.1 (-0.5, 0.6)	85	-3.8	113	-4.8	1.0 (0.1, 1.9)
<b>Month 5</b>										
<b>08:00</b>	153	-4.7	174	-5.2	0.4 (-0.2, 1.1)	79	-4.2	114	-6.3	2.1 (1.1, 3.1)
<b>10:00</b>	155	-4.4	174	-4.2	-0.1 (-0.7, 0.5)	78	-4.3	113	-6.0	1.7 (0.6, 2.7)
<b>16:00</b>	153	-4.0	174	-4.1	0.1 (-0.4, 0.7)	76	-3.8	113	-4.8	1.0 (0.0, 2.0)
<b>Month 6</b>										
<b>08:00</b>	147	-4.8	174	-5.1	0.3 (-0.2, 0.9)	77	-3.6	112	-5.9	2.3 (1.2, 3.4)
<b>10:00</b>	146	-4.2	174	-4.2	0.0 (-0.6, 0.6)	77	-3.9	112	-5.9	2.0 (0.9, 3.1)
<b>16:00</b>	146	-4.0	174	-3.6	-0.4 (-1.0, 0.1)	77	-3.8	112	-4.4	0.7 (-0.4, 1.7)

\* The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP

Source: Statistical Reviewer's analysis based on the randomized subjects who did not have major protocol violations.

### 3.3 Evaluation of Safety

For each of the three studies (301, 302, and 304), more subjects in the Rhopressa groups discontinued the study early due to AEs than subjects in the timolol group. In Study 302, the Rhopressa BID group had more subjects who discontinued the study due to AEs than the Rhopressa QD group. The most frequent adverse events that lead to discontinuations were: conjunctival hyperaemia, and cornea verticillata.

**Table 27: Study 301 Safety Analysis: Adverse Events Associated with Discontinuations  $\geq 1.0\%$  of Subjects in Either Treatment Group by Month 3 (Safety Population)**

System Organ Class Preferred Term	Rhopressa QD (N=208) n (%)	Timolol (N=208) n (%)
<b>Any TEAEs Resulting in Test Agent Discontinuation</b>	22 (10.8)	4 (1.9)
<b>Eye Disorders</b>	15 (7.4)	0
Conjunctivitis Allergic	2 (1.0)	0
Eyelids Pruritus	2 (1.0)	0
Lacrimation Increased	2 (1.0)	0

Source: Table 14.3.3.4 of Study 301 Report.

**Table 28: Study 302 Safety Analysis: Adverse Events Associated with Discontinuations  $\geq 5.0\%$  of Subjects in Any Treatment Group by Month 12 (Safety Population)**

System Organ Class Preferred Term	Rhopressa QD (N=251) n (%)	Rhopressa BID (N=253) n (%)	Timolol (N=251) n (%)
<b>Any TEAEs Resulting in Test Agent Discontinuation</b>	76 (30.3)	136 (53.8)	16 (6.4)
<b>Eye Disorders</b>	65 (25.9)	121 (47.8)	5 (2.0)
Conjunctival Hyperaemia	31 (12.4)	60 (23.7)	0
Cornea Verticillata	13 (5.2)	24 (9.5)	0
Vision Blurred	8 (3.2)	21 (8.3)	2 (0.8)

Source: Table 14.3.3.4 of Study 302 Report.

**Table 29: Study 304 Safety Analysis: Adverse Events Associated with Discontinuations  $\geq$  5.0% of Subjects in Any Treatment Group by Month 6 (Safety Population)**

<b>System Organ Class</b>	<b>Rhopressa QD (N=251) n (%)</b>	<b>Timolol (N=251) n (%)</b>
<b>Preferred Term</b>		
<b>Any TEAEs Resulting in Test Agent Discontinuation</b>	71 (20.2)	11 (3.1)
<b>Eye Disorders</b>	53 (15.1)	1 (0.3)
Conjunctival Hyperaemia	14 (4.0)	0
Cornea Verticillata	14 (4.0)	0

Source: Table 14.3.3.4 of Study 302 Report.

A total of three deaths were reported in in the Rhopressa QD group: 2 due to myocardial infarctions (Study 302) and 1 due to cardiac arrest (Study 304). These deaths were assessed not related to Rhopressa treatment by study investigators.

The following tables presented the treatment-emergent adverse events for the three studies. The most frequent AEs reported for Rhopressa-treated subjects were conjunctival hyperemia, cornea verticillata, and conjunctival hemorrhage.

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

**Table 30: Study 301 Treatment-Emergent Adverse Events Reported for 2.0% or More of Subjects in Either Treatment Group (Safety Population)**

	<b>Rhopressa QD (N=203)</b>	<b>Timolol (N=208)</b>
<b>Ocular Treatment-Emergent Adverse Events</b>		
<b>Eye Disorders</b>		
Conjunctival hyperemia	108 (53.2)	17 (8.2)
Conjunctival hemorrhage	27 (13.3)	1 (0.5)
Erythema of eyelid	12 (5.9)	0
Vision blurred	11 (5.4)	1 (0.5)
Corneal deposits	11 (5.4)	0
Visual acuity reduced	8 (3.9)	3 (1.4)
Conjunctival vascular disorder	8 (3.9)	1 (0.5)
Eye irritation	8 (3.9)	1 (0.5)
Lacrimation increased	8 (3.9)	0
Conjunctivitis allergic	6 (3.0)	0
Blepharitis	4 (2.0)	2 (1.0)
Eyelid edema	4 (2.0)	2 (1.0)
Punctate keratitis	4 (2.0)	1 (0.5)
Conjunctival edema	4 (2.0)	0
Eye pruritus	4 (2.0)	0
Photophobia	4 (2.0)	0
<b>General Disorders and Administration Site Conditions</b>		
Instillation site pain	30 (14.8)	42 (20.2)
Instillation site erythema	24 (11.8)	4 (1.9)
Instillation site discomfort	10 (4.9)	9 (4.3)
<b>Investigations</b>		
Vital dye staining cornea present	17 (8.4)	19 (9.1)

Source: Tables 11 of Study 301 Report.

**Table 31: Study 302 Treatment-Emergent Adverse Events Reported for 2.0% or More of Subjects in Any of the Treatment Groups (Safety Population, at 12 months)**

	Rhopressa QD (N=251)	Rhopressa BID (N=253)	Timolol (N=251)
<b>Ocular Treatment-Emergent Adverse Events</b>			
<b>Eye Disorders</b>			
Conjunctival hyperemia	152 (60.6)	168 (66.4)	35 (13.9)
Cornea Verticillata	64 (25.5)	64 (25.3)	2 (0.8)
Conjunctival hemorrhage	49 (19.5)	49 (19.4)	2 (0.8)
Vision blurred	27 (10.8)	44 (17.4)	7 (2.8)
Lacrimation Increased	19 (7.6)	25 (9.9)	0
Visual acuity reduced	22 (8.8)	22 (8.7)	6 (2.4)
Eye Pruritus	14 (5.6)	20 (7.9)	3 (1.2)
Conjunctival edema	8 (3.2)	19 (7.5)	0
Erythema of Eyelid	14 (5.6)	12 (4.7)	2 (0.8)
Eye Irritation	11 (4.4)	13 (5.1)	8 (3.2)
Conjunctival hemorrhage	49 (19.5)	49 (19.4)	2 (0.8)
Punctate keratitis	12 (4.8)	12 (4.7)	5 (2.0)
Eyelid oedema	11 (4.4)	12 (4.7)	3 (1.2)
Eye pain	10 (4.0)	11 (4.3)	8 (3.2)
Foreign Body Sensation in Eyes	7 (2.8)	14 (5.5)	1 (0.4)
Conjunctivitis allergic	6 (2.4)	11 (4.3)	17 (3.4)
Photophobia	5 (2.0)	8 (3.2)	1 (0.4)
Blepharitis	4 (1.6)	8 (3.2)	1 (0.4)
Corneal Opacity	1 (0.4)	11 (4.3)	0
Eye Discharge	4 (1.6)	8 (3.2)	3 (1.2)
Dry Eye	6 (2.4)	4 (1.6)	6 (2.4)
Cataract	3 (1.2)	2 (0.8)	5 (2.0)
<b>General Disorders and Administration Site Conditions</b>			
Instillation site pain	45 (17.9)	45 (17.8)	41 (16.3)
Instillation site erythema	14 (5.6)	32 (12.6)	5 (2.0)
Instillation site discomfort	9 (3.6)	7 (2.8)	5 (2.0)
<b>Infections and Infestations</b>			
Conjunctivitis	6 (2.4)	8 (3.2)	3 (1.2)
Upper Respiratory Tract Infection	5 (2.0)	9 (3.6)	7 (2.8)
Nasopharyngitis	5 (2.0)	2 (0.8)	3 (1.2)
Urinary Tract Infection	2 (0.8)	5 (2.0)	4 (1.6)
<b>Investigations</b>			
Vital dye staining cornea present	14 (5.6)	17 (6.7)	14 (5.6)
<b>Nervous System Disorders</b>			
Headache	6 (2.4)	10 (4.0)	9 (3.6)
<b>Skin and Subcutaneous Tissue Disorders</b>			
Dermatitis Allergic	2 (0.8)	6 (2.4)	0

Source: Tables 14.3.3.1 of Study 302 Report.

**Table 32: Study 304 Treatment-Emergent Adverse Events Reported for 2.0% or More of Subjects in Either Treatment Group (Safety Population, at 6 months)**

	Rhopressa QD	Timolol

	(N=351)	(N=357)
<b>Ocular Treatment-Emergent Adverse Events</b>		
<b>Eye Disorders</b>		
Conjunctival hyperemia	242 (68.9)	94 (26.3)
Cornea Verticillata	86 (24.5)	0
Conjunctival hemorrhage	56 (16.0)	11 (3.1)
Lacrimation increased	26 (7.4)	5 (1.4)
Erythema of eyelid	26 (7.4)	2 (0.6)
Vision blurred	22 (6.3)	4 (1.1)
Punctate keratitis	11 (3.1)	8 (2.2)
Visual acuity reduced	14 (4.0)	4 (1.1)
Eye pruritus	13 (3.7)	4 (1.1)
Foreign Body Sensation in Eyes	12 (3.4)	4 (1.1)
Eye irritation	12 (3.4)	3 (0.8)
Dry Eye	9 (2.6)	4 (1.1)
Eye pain	5 (1.4)	8 (2.2)
Eyelids Pruritus	12 (3.4)	1 (0.3)
Conjunctival edema	11 (3.1)	1 (0.3)
Eyelid edema	10 (2.8)	1 (0.3)
Eye Discharge	8 (2.3)	2 (0.6)
Blepharitis	7 (2.0)	2 (0.6)
Conjunctivitis allergic	9 (2.6)	0
<b>General Disorders and Administration Site Conditions</b>		
Instillation site pain	83 (23.6)	92 (25.8)
Instillation site erythema	36 (10.3)	4 (1.1)
Instillation site discomfort	4 (1.1)	7 (2.0)
<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection	10 (2.8)	14 (3.9)
<b>Investigations</b>		
Vital dye staining cornea present	34 (9.7)	24 (6.7)
Intraocular Pressure Increased	7 (2.0)	1 (0.3)

Source: Tables 14.3.3.1 of Study 304 Report.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses based on gender, race, and age were performed (see results in Appendix 4). In Study 304, Rhopressa QD had much higher mean IOP compared to timolol in non-white subjects. Other than this subgroup for Study 304, the results were similar to those seen for the overall population for each demographic subgroup. The results for the non-white race subgroup should be interpreted with caution due to the small sample sizes. Analyses by geographic region were not conducted since all clinical sites were in the United States.

## 5 SUMMARY AND CONCLUSIONS

## 5.1 Statistical Issues

There are no major statistical issues identified for the three pivotal studies submitted.

The primary efficacy analysis was based on the observed data without imputation for missing values that were mainly caused by study discontinuation due to AEs. Various sensitivity analyses, including the analyses using LOCF, BOCF to impute the missing values, were conducted to examine the robustness of the primary analysis results. These sensitivity analyses were conducted on both PP and ITT populations. Except for the BOCF analysis, all analysis results were supportive of the primary efficacy results, demonstrating non-inferiority of Rhopressa to timolol for subjects with baseline IOP < 25 mmHg (Table 33).

The BOCF analysis treated all dropout patients as having no IOP reduction for post-dropout time points. This analysis yielded less favorable results for Rhopressa than the other analyses because compared to timolol, approximately 8-12% more Rhopressa-treated subjects discontinued study due to AEs (Tables 9, 12, 15). The BOCF analysis failed to demonstrate non-inferiority of Rhopressa to timolol for subjects with baseline IOP < 25 mmHg in Study 302 at one time point (8AM on Day 90, see Table 23). Nevertheless, for subjects with baseline IOP < 25 mmHg, in the BOCF analysis Rhopressa treatment yielded clinically meaningful mean IOP reduction from baseline, ranging from approximately 3 to 5 mmHg in the three studies (Table 23). For subjects with baseline IOP ≥ 25 mmHg, the mean IOP reduction ranged from approximately 2 to 5 mmHg in the BOCF analysis (Table 24).

**Table 33: Status of Non-inferiority\* of Rhopressa QD to Timolol BID**

	Study	Baseline IOP		
		< 25 mmHg	<27 mmHg	< 30 mmHg
PP (Observed)	301	Yes	No	n/a
	302	Yes	No	n/a
	304	Yes	Yes	Yes
ITT (Observed)	301	Yes	No	n/a
	302	Yes	No	n/a
	304	Yes	Yes	Yes
PP (LOCF)	301	Yes	No	n/a
	302	Yes	No	n/a
	304	Yes	Yes	No
ITT (LOCF)	301	Yes	No	n/a
	302	Yes	No	n/a
	304	Yes	Yes	No
PP (BOCF)	301	Yes	No	n/a
	302	No	No	n/a
	304	Yes	Yes	No
ITT (BOCF)	301	Yes	No	n/a
	302	No	No	n/a
	304	Yes	Yes	No

Yes: The non-inferiority criteria was met. No: The non-inferiority criteria was not met.

\* Based on the ANCOVA adjusted for baseline IOP for the mean IOP changes from baseline.

## 5.2 Collective Evidence

In all three studies, for all subjects, Rhopressa QD demonstrated IOP reduction effect; the mean IOP reduction from baseline ranging from 3 to 5 mmHg for Rhopressa-treated subjects.

For subjects with maximum baseline IOP < 25 mmHg, overall Rhopressa and the active comparator timolol had similar mean IOP reductions at Days 15, 43, and 90. However, for subjects with maximum baseline IOP  $\geq$  25 mmHg, compared with timolol, Rhopressa QD resulted in smaller mean IOP reductions at almost all time points after Day 15. The treatment difference was most noticeable at 8am and 10am.

## 5.3 Conclusions and Recommendations

Based on these results, the statistical reviewer concluded that all three studies demonstrated that Rhopressa QD was efficacious in reducing elevated intraocular pressure; but Rhopressa QD was less efficacious compared to the active comparator, timolol ophthalmic solution 0.5% BID for subjects with higher maximum baseline IOP ( $\geq$  25 mmHg).

## 5.4 Labeling Recommendations

In the NDA resubmission, the applicant's proposed label had the following text for the clinical studies section. Of note: this text is the same as the one included in the original NDA.

***"14. CLINICAL STUDIES***

(b) (4)

After the advisory committee meeting held on October 13, 2017, the applicant submitted an updated label (<\\cdsesub1\evsprod\NDA208254\0021\m1\us\114-labeling\draft\labeling>) with the following text for the clinical studies section:

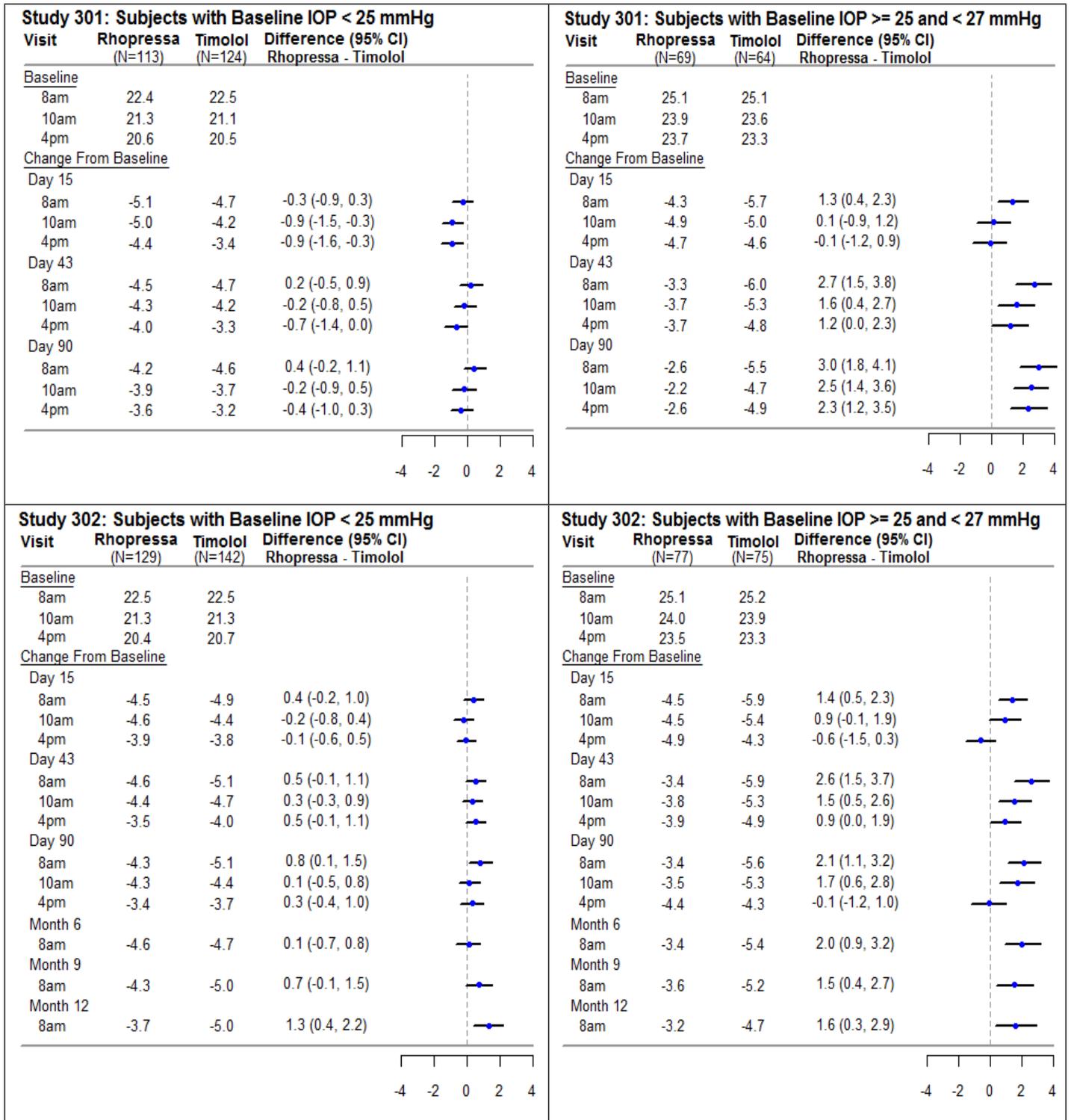
(b) (4)

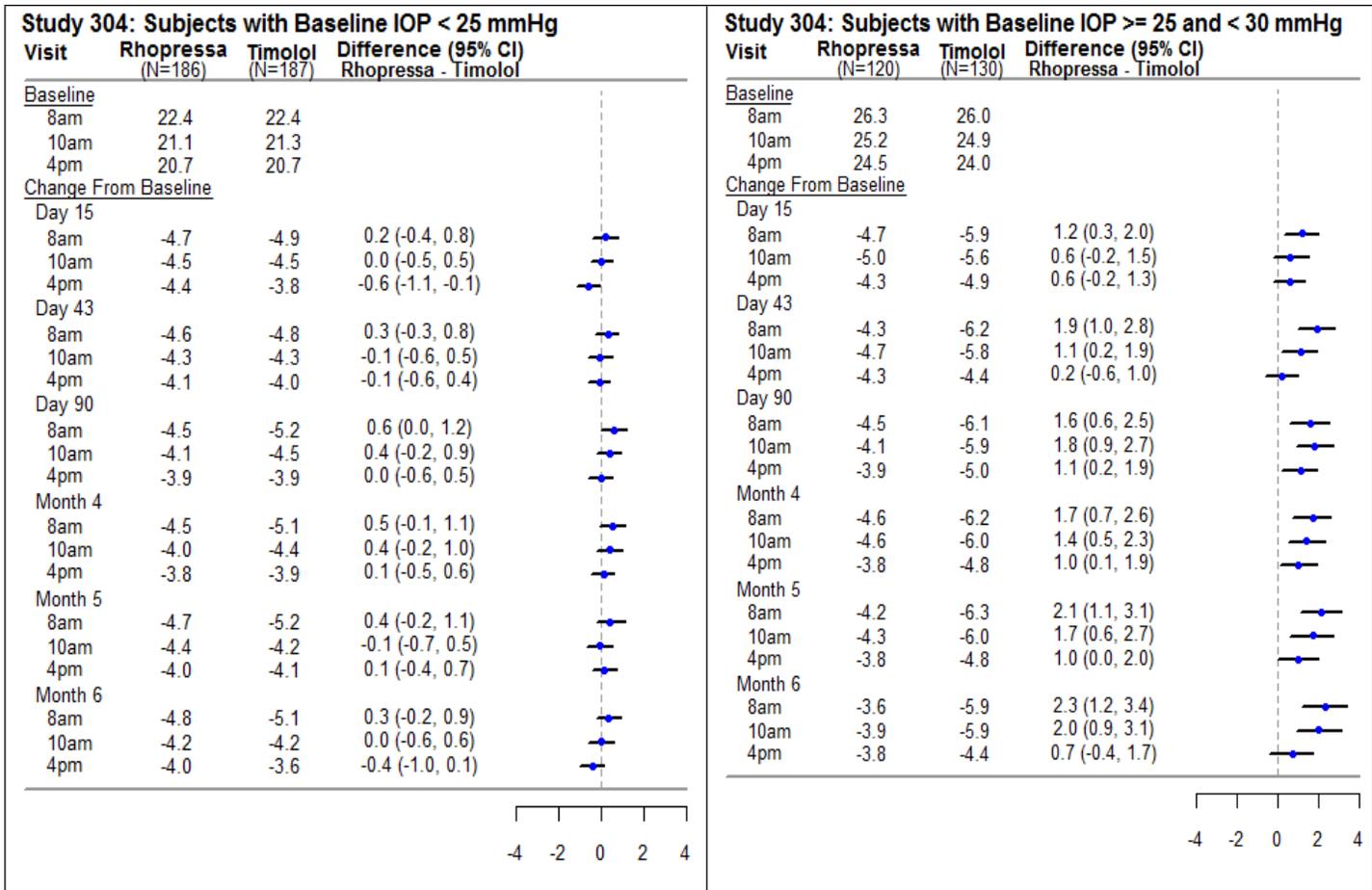
The applicant's proposal did not include any details on the designs and efficacy results for Studies 301, 302 and 304. Since Rhopressa is the first drug in a new class and had resulted in smaller IOP reduction compared to timolol in patients with higher baseline IOP ( $\geq 25$  mmHg), the statistical review team recommends including some details in the label that will help health care providers better understand the treatment effect of Rhopressa. The following is the statistical review team's proposed text for the clinical studies section. Of note, Table 1 includes the long-term efficacy data to show that Rhopressa treatment effect is durable past 90 days; this table can be replaced with Table 2 to include only the efficacy data up to 90 days if the clinical team considers the first table too busy.

*RHOPRESSA 0.02% was evaluated in three randomized and controlled clinical trials (Studies 301, 302, and 304) in patients with open-angle glaucoma or ocular hypertension. Studies 301 and 302 enrolled subjects with baseline IOP lower than 27 mmHg and Study 304 enrolled subjects with baseline IOP lower than 30 mmHg. The treatment duration was 3 months in Study 301, 12 months in Study 302, and 6 months in Study 304.*

*The three studies demonstrated up to 5 mmHg reductions in IOP for subjects treated with RHOPRESSA 0.02% once daily in the evening. For patients with baseline IOP < 25 mmHg, the IOP reductions with RHOPRESSA 0.02% dosed daily were similar to those with timolol 0.5% dosed daily (see Table 1). For patients with baseline IOP equal to or above 25 mmHg, however, RHOPRESSA 0.02% resulted in smaller mean IOP reductions at the morning time points than timolol 0.5% for study visits after Day 15; the difference in mean IOP reduction between the two treatment groups was as high as 3 mmHg, favoring timolol.*

**Table 1: Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time**





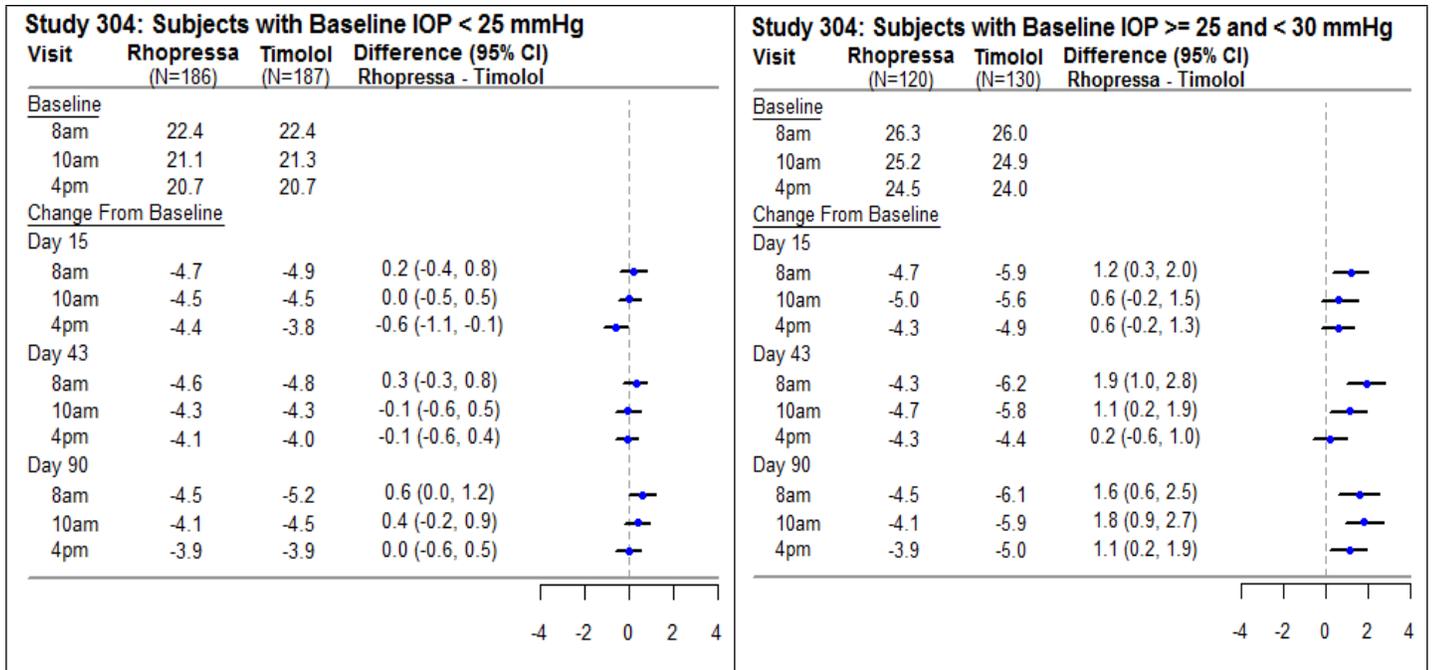
This table was produced based on the observed data from all randomized subjects who did not have major protocol violations. The treatment differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP.

**Table 2: Mean IOP Change from Baseline of Study Eye (mmHg) by Visit and Time**

Study 301: Subjects with Baseline IOP < 25 mmHg				Study 301: Subjects with Baseline IOP ≥ 25 and < 27 mmHg			
Visit	Rhopressa (N=113)	Timolol (N=124)	Difference (95% CI) Rhopressa - Timolol	Visit	Rhopressa (N=69)	Timolol (N=64)	Difference (95% CI) Rhopressa - Timolol
<b>Baseline</b>				<b>Baseline</b>			
8am	22.4	22.5		8am	25.1	25.1	
10am	21.3	21.1		10am	23.9	23.6	
4pm	20.6	20.5		4pm	23.7	23.3	
<b>Change From Baseline</b>				<b>Change From Baseline</b>			
<b>Day 15</b>				<b>Day 15</b>			
8am	-5.1	-4.7	-0.3 (-0.9, 0.3)	8am	-4.3	-5.7	1.3 (0.4, 2.3)
10am	-5.0	-4.2	-0.9 (-1.5, -0.3)	10am	-4.9	-5.0	0.1 (-0.9, 1.2)
4pm	-4.4	-3.4	-0.9 (-1.6, -0.3)	4pm	-4.7	-4.6	-0.1 (-1.2, 0.9)
<b>Day 43</b>				<b>Day 43</b>			
8am	-4.5	-4.7	0.2 (-0.5, 0.9)	8am	-3.3	-6.0	2.7 (1.5, 3.8)
10am	-4.3	-4.2	-0.2 (-0.8, 0.5)	10am	-3.7	-5.3	1.6 (0.4, 2.7)
4pm	-4.0	-3.3	-0.7 (-1.4, 0.0)	4pm	-3.7	-4.8	1.2 (0.0, 2.3)
<b>Day 90</b>				<b>Day 90</b>			
8am	-4.2	-4.6	0.4 (-0.2, 1.1)	8am	-2.6	-5.5	3.0 (1.8, 4.1)
10am	-3.9	-3.7	-0.2 (-0.9, 0.5)	10am	-2.2	-4.7	2.5 (1.4, 3.6)
4pm	-3.6	-3.2	-0.4 (-1.0, 0.3)	4pm	-2.6	-4.9	2.3 (1.2, 3.5)

Study 302: Subjects with Baseline IOP < 25 mmHg				Study 302: Subjects with Baseline IOP ≥ 25 and < 27 mmHg			
Visit	Rhopressa (N=129)	Timolol (N=142)	Difference (95% CI) Rhopressa - Timolol	Visit	Rhopressa (N=77)	Timolol (N=75)	Difference (95% CI) Rhopressa - Timolol
<b>Baseline</b>				<b>Baseline</b>			
8am	22.5	22.5		8am	25.1	25.2	
10am	21.3	21.3		10am	24.0	23.9	
4pm	20.4	20.7		4pm	23.5	23.3	
<b>Change From Baseline</b>				<b>Change From Baseline</b>			
<b>Day 15</b>				<b>Day 15</b>			
8am	-4.5	-4.9	0.4 (-0.2, 1.0)	8am	-4.5	-5.9	1.4 (0.5, 2.3)
10am	-4.6	-4.4	-0.2 (-0.8, 0.4)	10am	-4.5	-5.4	0.9 (-0.1, 1.9)
4pm	-3.9	-3.8	-0.1 (-0.6, 0.5)	4pm	-4.9	-4.3	-0.6 (-1.5, 0.3)
<b>Day 43</b>				<b>Day 43</b>			
8am	-4.6	-5.1	0.5 (-0.1, 1.1)	8am	-3.4	-5.9	2.6 (1.5, 3.7)
10am	-4.4	-4.7	0.3 (-0.3, 0.9)	10am	-3.8	-5.3	1.5 (0.5, 2.6)
4pm	-3.5	-4.0	0.5 (-0.1, 1.1)	4pm	-3.9	-4.9	0.9 (0.0, 1.9)
<b>Day 90</b>				<b>Day 90</b>			
8am	-4.3	-5.1	0.8 (0.1, 1.5)	8am	-3.4	-5.6	2.1 (1.1, 3.2)
10am	-4.3	-4.4	0.1 (-0.5, 0.8)	10am	-3.5	-5.3	1.7 (0.6, 2.8)
4pm	-3.4	-3.7	0.3 (-0.4, 1.0)	4pm	-4.4	-4.3	-0.1 (-1.2, 1.0)



This table was produced based on the observed data from all randomized subjects who did not have major protocol violations. The treatment Differences and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP.

## Appendix 1: Inclusion and Exclusion Criteria and Schedule of Assessment

For all three studies 301, 302, and 304, the following were applicant-defined key inclusion and exclusion criteria.

### Key Inclusion Criteria for Adults (all three studies):

- 18 years of age or greater
- Diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT). For entry into this study, this diagnosis must have been in BOTH eyes. It could be OAG in 1 eye and OHT in the fellow eye.
- Unmedicated (post-washout) IOP > 20 mmHg and < 27 mmHg in the study eye at 2 qualification visits (08:00 hours), 2 to 7 days apart. At the second qualification visit, IOP > 17 mmHg and < 27 mmHg at 10:00 and 16:00 hours (in the same eye).
- Corrected visual acuity in each eye +1.0 logMAR or better by Early Treatment of Diabetic Retinopathy Study (ETDRS) in each eye (equivalent to 20/200).
- Able and willing to give signed informed consent and follow instructions.

### **Key Exclusion Criteria for Adults (all three studies):**

- Glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: Previous laser peripheral iridotomy was NOT acceptable. Intraocular pressure  $\geq 27$  mmHg (unmedicated) in both eyes or use of more than 2 ocular hypotensive medications within 30 days of screening. **Note: fixed dose combinations count as two medications.**
- Known hypersensitivity to any component of the formulations to be used (benzalkonium chloride, etc.), to topical anesthetics or  $\beta$ -adrenoceptor antagonists.
- Previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (e.g., radial keratotomy, PRK, LASIK, corneal cross-linking, etc.).
- Refractive surgery in either eye.
- Ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening.
- Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or zoster keratitis at screening in either eye.
- Ocular medication in either eye of any kind within 30 days of screening, with the exception of a) ocular hypotensive medications (which must have been washed out according to the provided schedule), b) lid scrubs (which may have been used prior to, but not after screening) or c) lubricating drops for dry eye (which may have been used throughout the study).
- Clinically significant ocular disease in either eye that might have interfered with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month was not judged safe.
- Central corneal thickness in either eye up to 620  $\mu\text{m}$  at screening.
- Any abnormality in either eye preventing reliable applanation tonometry.

### **Diagnosis and Main Criteria for Inclusion of Pediatric Subjects 0 to 2 Years of Age Studies 301 and 302):**

#### **Key Inclusion Criteria**

- 0 to 2 years of age
- Diagnosis of glaucoma due to elevated IOP.
- No contraindications to the conduct of the trial as determined by the Investigator.
- Subjects may have been aphakic or had undergone goniotomy, but required further IOP lowering according to the Investigator. Subjects must not have been on another IOP-lowering medication for at least 30 days prior to entry into the study. If they were on another medication and the Investigator determined that it was safe to do so, the subject could be washed out from the prior medication and screened for entry into the trial.
- Able to provide signed informed assent from parent or guardian and to follow instructions.

## Key Exclusion Criteria

- Any condition or concern by the Investigator that participating in the trial would have been a safety risk for the subject, need for multiple examinations under anesthesia, or ocular/systemic pathologies or co-morbidities that enhanced the risk to the subject.

Schedule of assessments for the three studies are presented in the following table.

**Table 34: Study 301 Schedule of Assessments**

Day (D)/Week (W)/Month (M)	Screening	Qual. #1	Qual. #2			Treatment								
			D1			W2 (Day 15)			W6 (Day 43)			M3 (Day 90) (EXIT)		
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0	6.1	6.2
Hour	--	08:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00
Informed Consent	X													
Inclusion/Exclusion	X	X	X	X	X									
Washout <sup>1</sup>	X													
Demography	X													
Medical/Ophthalmic History	X	X	X											
Concomitant Medications	X	X	X			X			X			X		
Heart Rate/Blood Pressure	X	X	X			X			X			X		
Urine Pregnancy test <sup>2</sup>	X											X		
Clinical Labs (Chemistry/Hematology)	X													X
Symptoms/Adverse Events (AEs) <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test <sup>4</sup>						X			X			X		
Visual Acuity (ETDRS)	X	X	X			X			X			X		
Pupil Size			X									X		
Intraocular Pressure (IOP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy <sup>5</sup> / Pachymetry <sup>6</sup>	G/P													
Visual Field <sup>7</sup>	X											X		
Ophthalmoscopy (Dilated)	X													X
Eye-Drop Instillation Evaluation	X													
Study Dose (Self-administered)						X			X			X		
Study Medication Dispensed					X			X			X			
Study Medication Collected						X <sup>7</sup>			X <sup>7</sup>			X <sup>7</sup>		
Study Completed														X

Abbreviations: ETDRS = Early Treatment of Diabetic Retinopathy Study; Qual = Qualification

### Table 3 Notes:

**Qualifying IOP:** At Qualification #1 and/or #2, individuals who did NOT meet the requirements for minimum qualifying IOPs (IOP > 20 mmHg) could return for up to 2 additional qualification visits within 1 week of failing the first. Subjects who had IOP ≥ 27 mmHg (in both eyes) at Qualification #1 or #2 were not allowed to return.

**Early Discontinuation:** Visit 6 Procedures were to be completed.

**Dosing:** Investigational staff were to instruct subjects (or parent/guardian or caregiver) to administer their masked medication at home in both eyes between 07:30 and 08:30 hours (7:30 am and 8:30 am) and between 20:00 and 22:00 hours (8 pm and 10 pm) except during site visits. During site visits subjects brought medication to the office and self-administered the AM dose 30 minutes AFTER the first IOP measurement.

**Visit requirements:** IOP measurements at all visits were to be made within (±) one half hour of the protocol-specified times of 08:00, 10:00, and 16:00 hours with the exception of the screening visit.

**Visit window:** Allowable visit variation on post-qualification visits was ± 3 days.

### Table 3 Footnotes:

<sup>1</sup> Subjects currently using ocular hypotensive medications must have undergone a minimum washout period.

<sup>2</sup> Urine pregnancy test for women of childbearing potential.

<sup>3</sup> Symptoms: Subjects were queried at each visit "How are you feeling?" and treatment-emergent AEs were documented on the AE case report form (CRF). Additional symptoms reported after screening and before randomization were documented on the medical history CRF.

<sup>4</sup> Comfort test: At 08:00 hours for on study drug visits, subjects were queried "Did you experience any discomfort when placing the drops in your eyes?"

<sup>5</sup> Gonioscopy and entry visual field evaluation up to 3 months prior to randomization was acceptable. Visual field must have met the requirement for automated threshold visual field (e.g., 30-2 or 24-2 Humphrey) and reliability.

<sup>6</sup> Pachymetry within 1 week of screening was acceptable.

<sup>7</sup> Used kit(s) dispensed during the previous visit were collected at 08:00 hours (after the AM dosing).

Source: Table 3 of Study 301 Report.

**Table 35: Study 302 Schedule of Assessments**

Day/Week/Month	Screening	Qual. #1	Qual. #2			Treatment											
	--	--	D1			W2 (Day 15)			W6 (Day 43)			M3 (Day 90)			M6/M9	M12 (D365)	
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0	6.1	6.2	7/8	9 (Exit)	
Hour	--	08:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00	08:00	08:00	
Informed Consent	X																
Inclusion/Exclusion	X	X	X	X	X												
Washout <sup>1</sup>	X																
Demography	X																
Medical/Ophthalmic Hx	X	X	X														
Concomitant Rx	X	X	X			X			X			X			X	X	
HR/BP	X	X	X			X			X			X			X	X	
Urine Pregnancy test <sup>2</sup>	X											X			X	X	
Clinical Labs (chem/hem)	X												X			X	
Symptoms/AEs <sup>3</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comfort Test <sup>4</sup>						X			X			X			X	X	
Visual Acuity (ETDRS)	X	X	X			X			X			X			X	X	
Pupil size			X									X			M6	X	
IOP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Gonioscopy <sup>5</sup> / Pachymetry <sup>6</sup>	G/P																
Visual field <sup>5</sup>	X											X				X	
Ophthalmoscopy (dilated)	X													X	M6	X	
Specular microscopy			X									X					
Eye-Drop Instillation Eval	X																
Study Dose (pt self-admin)						X			X			X			X		
Study meds dispensed					X			X			X			X	X		
Study meds collected					X			X			X			X	X	X	
Study completed																X	

At Qualification #1 and/or # 2, individuals who did NOT meet the requirements for minimum qualifying IOPs (IOP >20 mmHg) could return for up to 2 additional qualification visits within 1 week of failing the first. Those that were ≥ 27 mmHg (in both eyes) at Qualification #1 or #2 were not allowed to return.

HR/BP = heart rate/blood pressure; G = gonioscopy, P = pachymetry. Early Discontinuation: Visit 9 Procedures to be completed

Dosing: Investigational staff were to instruct patients (or parent/guardian) to administer their masked medication at home in both eyes between 07:30 – 08:30 hours (7:30am and 8:30am) and 20:00 – 22:00 hours (8pm and 10pm) except during site visits. During site visits subjects were to bring medication to the office and self-administer the AM dose 30 minutes AFTER the first IOP measurement.

Visit requirements: IOP measurements at all visits were to be made within (+/-) one half hour of the protocol specified times of 08:00, 10:00 and 16:00 hours with the exception of the screening visit.

Visit window: Allowable visit variation on post-qualification visits with the first 3 months was ± 3 days. Subsequent visits have ± 5 day variance.

- Subjects currently using ocular hypotensive medications must undergo a minimum washout period.
- Urine pregnancy test for women of childbearing potential
- Symptoms: Patients were queried at each visit "How are you feeling?" and treatment emergent AE's were documented on the AE form. Additional symptoms reported after screening and before randomization were documented on the medical history form
- Comfort test: At 08:00 hours for on study drug visits, patients were queried "Did you experience any discomfort when placing the drops in your eyes?"
- Gonioscopy and entry visual field evaluation up to three months prior to randomization was acceptable. Visual field must meet the requirement for automated threshold visual field (e.g., 30-2 or 24-2 Humphrey) and reliability.
- Pachymetry within one week of screening was acceptable.
- Collect used kit(s) dispensed during the previous visit at 08:00 hours (after the AM dosing).

Source: Table 9.5.1.3 of Study 302 Report.

**Table 36: Study 304 Schedule of Assessments**

Day (D)/Week (W)/Month (M)	Screening	Qual #1	Qual. #2 D1			Post D1 Treatment Period Assessments											
						W2 (Day 15±3)			W6 (Day 43±3)			M3 (Day 90±3), M4 (Day 120±3), M5 (Day 150±3)			M6 (Day 180±7)		
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0-8.0	6.1- 8.1	6.2-8.2	9.0	9.1	9.2
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16	08	10	16
Informed Consent	X																
Inclusion/Exclusion	X	X	X	X	X												
Washout <sup>1</sup>	X																
Demography	X																
Medical/Ophthalmic History	X	X	X														
Concomitant Medications	X	X	X			X			X			X			X		
HR/BP	X	X	X			X			X			X			X		
Urine Pregnancy Test <sup>2</sup>	X														X		
Clinical Labs (Chem/Hem)	X <sup>3</sup>																X
Symptoms/AEs <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test <sup>5</sup>						X			X			X			X		
Visual Acuity (ETDRS)	X	X	X			X			X			X			X		
Pupil size			X									M3			X		
IOP	X	X <sup>6</sup>	X <sup>6</sup>	X <sup>6</sup>	X <sup>6</sup>	X	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy /Pachymetry <sup>8</sup>	G/P																
Visual Field <sup>7</sup>	X											M3			X		
Ophthalmoscopy (dilated)	X													M3			X
Eye-Drop Instillation Evaluation	X																
Study Dose (Self-admin)						X			X			X			X		
Study Medications Dispensed					X			X			X			X			
Study Medications Collected						X <sup>10</sup>			X <sup>10</sup>			X <sup>10</sup>			X <sup>10</sup>		
Study Completed																	X

Abbreviations: D=Day; W = Week; M = Month; HR/BP = heart rate/blood pressure; Chem/Hem = Chemistry/Hematology; AE = adverse event; ETDRS = Early Treatment of Diabetic Retinopathy Study; IOP = Intraocular pressure; G = gonioscopy; P = pachymetry; Self-admin = Self-administered

Early Discontinuation: Visit 9.0 procedures are to be completed plus a dilated ophthalmoscopy examination.

Dosing: Investigational staff will instruct subjects to administer their masked medication at home in both eyes between 07:30 and 08:30 hours and 20:00 – 22:00 hours except during site visit days. During site visits, subject will bring medication to the office and self administer the AM dose 30 minutes AFTER the first IOP measurement.

Visit Requirements: IOP measurements at all visits are to be made within ±30 minutes of the protocol specified times of 08:00, 10:00 and 16:00 hours with the exception of the screening visit.

IOP Requirements: At Qualification Visit #1 and/or #2, individuals who do NOT meet the requirements for minimum qualifying IOPs (IOP >20 mmHg and <30 mmHg) may return for up to 2 additional qualification visits within 1 week of failing the first. Those that are >30 mmHg (in both eyes) at Qualification Visit #1 or #2 are not allowed to return.

- 1 Subjects currently using ocular hypotensive medications must undergo a minimum washout period (Table 2 for details).
- 2 Urine pregnancy test for women of childbearing potential is required.
- 3 For subjects who are unable or unwilling to have blood drawn for clinical labs at Visit 1 (Screening), the blood sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).
- 4 Ocular symptoms: Subjects will be queried at each visit “How are you feeling?” and TEAEs beginning at Visit 4 (Qualification Visit #2) will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form. AEs will be recorded for every study visit (ie, at 08:00, 10:00, and 16:00 hours) as needed.
- 5 Comfort test: At 08:00 hour for study drug visits, subjects will be queried “Did you experience any discomfort when placing the drops in your eyes?”
- 6 Individuals returning at an unscheduled visit within 1 week are required to only remeasure IOP in both eyes.
- 7 Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
- 8 Pachymetry within one week of Screening is acceptable.
- 9 Entry visual field evaluation up to 3 months prior to randomization is acceptable. Visual field collection must meet the requirement for automated threshold visual field assessment (eg, 30-2 or 24-2 Humphrey) and reliability.
- 10 Collect used kit(s) dispensed during the previous visit.

Source: Table 3 of Study 304 Report.

## Appendix 2: Mean IOP Analysis

### 1. Study 301

For the overall PP population, the two treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 21.8 to 23.4 mmHg for the Rhopressa QD group and 21.5 to 23.4 mmHg for the timolol group. During the 3-month treatment period, mean IOP ranged from 17.24 to 19.81 mmHg in the Rhopressa QD group and from 17.44 to 18.47 mmHg in the timolol group. Differences in mean IOP between Rhopressa and timolol for the 9 time points ranged from -0.45 to +1.33 mmHg. The upper 95% confidence limit for the differences in mean IOP was as high as 2.03 mmHg, favoring timolol. Therefore, noninferiority of Rhopressa dosed QD to timolol dosed BID was not demonstrated in the overall PP population.

**Table 37: Study 301 Mean IOP (mmHg) in Study Eye by Visit and Time (PP Observed, All)**

	Rhopressa		Timolol		Difference (95% CI) <sup>1</sup>
	N	Mean	N	Mean	
<b>Baseline</b>					
<b>08:00</b>	182	23.42	188	23.37	0.06 (-0.29, 0.41)
<b>10:00</b>	182	22.28	188	21.92	0.36 (-0.07, 0.79)
<b>16:00</b>	182	21.78	188	21.45	0.33 (-0.15, 0.82)
<b>Day 15</b>					
<b>08:00</b>	177	18.68	187	18.33	0.35 (-0.27, 0.96)
<b>10:00</b>	176	17.29	186	17.55	-0.26 (-0.87, 0.36)
<b>16:00</b>	176	17.24	186	17.70	-0.45 (-1.08, 0.17)
<b>Day 43</b>					
<b>08:00</b>	170	19.35	184	18.24	1.11 (0.42, 1.80)
<b>10:00</b>	170	18.14	184	17.44	0.70 (0.04, 1.36)
<b>16:00</b>	170	17.86	183	17.71	0.15 (-0.52, 0.83)
<b>Day 90</b>					
<b>08:00</b>	157	19.81	181	18.47	1.33 (0.64, 2.03)
<b>10:00</b>	158	18.92	181	17.96	0.96 (0.26, 1.66*)
<b>16:00</b>	158	18.48	181	17.74	0.74 (0.07, 1.42)

<sup>1</sup> Treatment difference and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5%. are based on 2-sample t-tests  
Source: Tables 8 of Study 301 report based on the randomized subjects who did not have major protocol violations.

Post hoc analyses were conducted by the applicant on the PP subgroup of 237 subjects who had maximum baseline IOP < 25 mmHg (113 Rhopressa-treated subjects and 124 timolol-treated subjects) at all time points. The mean baseline IOP was in the range 20.62 to 22.39 mmHg for the Rhopressa subgroup and 20.52 to 22.50 mmHg for the timolol subgroup. During the 3-month treatment period, mean IOP ranged from 16.18 to 18.22 mmHg in the Rhopressa QD group and from 16.96 to 17.91 mmHg in the timolol group. Differences in mean IOP between Rhopressa and timolol ranged from -0.91 to +0.31 mmHg for the 9 time points. The criteria for noninferiority were met for Rhopressa subjects in this subgroup, with the upper limit of the 95% CIs for the differences (Rhopressa – timolol) in mean IOP within 1.5 mmHg at all 9 time points.

The statistical reviewer further examined subjects who had maximum baseline IOP ≥ 25 mmHg at one or more time points. During the 3-month treatment period, for this subgroup, mean IOP

ranged from 18.82 to 22.52 mmHg in the Rhopressa QD group and from 18.37 to 19.56 mmHg in the timolol group. Differences in mean IOP between Rhopressa and timolol for the 9 time points over the 3-month efficacy assessment period ranged from 0.07 to 2.96 mmHg. For these subjects, the upper 95% confidence limit for the differences in mean IOP was as high 4.08 mmHg.

**Table 38: Study 301 Mean IOP (mmHg) in Study Eye by Visit and Time (PP Observed)**

	Baseline < 25 mmHg					Baseline ≥ 25 mmHg				
	Rhopressa		Timolol		Difference (95% CI) <sup>1</sup>	Rhopressa		Timolol		Difference (95% CI) <sup>1</sup>
	N	Mean	N	Mean		N	Mean	N	Mean	
<b>Baseline</b>										
<b>08:00</b>	113	22.39	124	22.50	-0.11 (-0.39, 0.18)	69	25.11	64	25.05	0.06 (-0.34, 0.47)
<b>10:00</b>	113	21.28	124	21.07	0.21 (-0.21, 0.64)	69	23.92	64	23.58	0.34 (-0.25, 0.94)
<b>16:00</b>	113	20.62	124	20.52	0.10 (-0.36, 0.56)	69	23.68	64	23.25	0.43 (-0.31, 1.17)
<b>Day 15</b>										
<b>08:00</b>	108	17.34	123	17.78	-0.44 (-1.10, 0.22)	69	20.78	64	19.41	1.37 (0.36, 2.39)
<b>10:00</b>	107	16.18	122	16.98	-0.81 (-1.44, -0.17)	69	19.01	64	18.62	0.40 (-0.71, 1.50)
<b>16:00</b>	107	16.22	122	17.14	-0.92 (-1.58, -0.26)	69	18.82	64	18.75	0.07 (-1.05, 1.19)
<b>Day 43</b>										
<b>08:00</b>	105	17.85	121	17.81	0.05 (-0.68, 0.77)	65	21.78	63	19.09	2.69 (1.53, 3.85)
<b>10:00</b>	105	16.88	121	16.96	-0.08 (-0.74, 0.58)	65	20.17	63	18.37	1.80 (0.59, 3.00)
<b>16:00</b>	105	16.57	120	17.26	-0.69 (-1.40, 0.02)	65	19.95	63	18.56	1.39 (0.18, 2.60)
<b>Day 90</b>										
<b>08:00</b>	99	18.22	119	17.91	0.31 (-0.40, 1.02)	58	22.52	62	19.56	2.96 (1.84, 4.08)
<b>10:00</b>	99	17.34	119	17.43	-0.09 (-0.82, 0.63)	59	21.58	62	18.98	2.59 (1.49, 3.70)
<b>16:00</b>	99	17.02	119	17.37	-0.35 (-1.03, 0.34)	59	20.93	62	18.46	2.47 (1.33, 3.62)

<sup>1</sup> Treatment difference and two-sided CIs for comparing Rhopressa QD vs Timolol 0.5% are based on 2-sample t-tests  
Source: Table 9 of Study 301 report and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis based on the randomized subjects who did not have major protocol violations.

## 2. Study 302

For the primary efficacy analyses population of PP subjects who had maximum baseline IOP < 25 mmHg at all baseline measurement time points, the mean baseline IOP was in the range 21.3 to 22.5 mmHg for the Rhopressa QD group, 21.3 to 22.6 for the Rhopressa BID group, and 21.3 to 22.5 mmHg for the timolol group. For the three treatment groups:

- Noninferiority of Rhopressa QD to timolol was demonstrated. During the 3-month efficacy assessment period, mean IOP ranged from 16.95 to 18.24 mmHg in the Rhopressa QD group and from 16.60 to 17.69 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol for the 9 time points over the 3-month efficacy assessment period ranged from -0.21 to +0.77 mmHg. The upper 95% confidence limit for the differences in mean IOP between Rhopressa BID and timolol was within 1.5 mmHg at all of the 9 time points.
- Noninferiority of Rhopressa dosed BID to timolol was also demonstrated. During the 3-month efficacy assessment period, mean IOP ranged from 15.65 to 17.58 mmHg in the

Rhopressa BID group. Differences in mean IOP between Rhopressa BID and timolol ranged from -1.18 to +0.11 mmHg. The upper 95% confidence limit for the differences in mean IOP between Rhopressa BID and timolol was within 1.5 mmHg at all of the 9 time points.

**Table 39: Study 302 Mean IOP (mmHg) in Study Eye by Visit and Time (PP, Baseline < 25 mmHg, Observed)**

Day and Time	Mean IOP						QD vs. Timolol BID	BID vs. Timolol BID
	Rhopressa QD		Rhopressa BID		Timolol		Difference (95% CI) <sup>1</sup>	Difference (95% CI) <sup>1</sup>
<b>Baseline</b>								
<b>08:00</b>	129	22.54	132	22.55	142	22.54	0.00 (-0.25, 0.25)	0.01 (-0.24, 0.26)
<b>10:00</b>	129	21.29	132	21.27	142	21.27	0.02 (-0.37, 0.41)	-0.01 (-0.40, 0.38)
<b>16:00</b>	129	20.43	132	20.56	142	20.71	-0.28 (-0.71, 0.14)	-0.15 (-0.58, 0.29)
<b>Day 15</b>								
<b>08:00</b>	127	18.06	122	17.21	142	17.69	0.37 (-0.26, 0.99)	-0.48 (-1.19, 0.22)
<b>10:00</b>	126	16.72	120	16.35	141	16.93	-0.21 (-0.82, 0.41)	-0.57 (-1.24, 0.09)
<b>16:00</b>	126	16.68	118	15.65	141	16.83	-0.15 (-0.75, 0.46)	-1.18 (-1.82, 0.54)
<b>Day 43</b>								
<b>08:00</b>	122	17.95	111	17.64	141	17.46	0.49 (-0.13, 1.12)	0.17 (-0.51, 0.86)
<b>10:00</b>	120	16.95	106	16.28	141	16.63	0.32 (-0.31, 0.95)	-0.34 (-1.02, 0.33)
<b>16:00</b>	120	17.00	106	15.75	141	16.60	0.40 (-0.22, 1.02)	-0.85 (-1.53, -0.17)
<b>Day 90</b>								
<b>08:00</b>	116	18.24	91	17.58	140	17.47	0.77 (0.03, 1.50)	0.11 (-0.64, 0.86)
<b>10:00</b>	114	17.03	88	16.94	140	16.92	0.10 (-0.59, 0.80)	0.02 (-0.72, 0.77)
<b>16:00</b>	114	17.13	88	16.51	139	16.95	0.18 (-0.55, 0.91)	-0.44 (-1.16, 0.27)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%. Source: Tables 13 and 14 of Study 302 report based on the randomized subjects who did not have major protocol violations.

The statistical reviewer examined subjects who had maximum baseline IOP  $\geq$  25 mmHg at one or more time points. For this subgroup:

- During the 3-month efficacy assessment period, mean IOP ranged from 18.55 to 21.80 mmHg in the Rhopressa QD group and from 18.49 to 19.62 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol ranged from -0.50 to +2.55 mmHg. The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 2 of the 9 time points and as high as 3.67 mmHg.
- During the 3-month efficacy assessment period, mean IOP ranged from 17.44 to 20.77 mmHg in the Rhopressa BID group. Differences in mean IOP between Rhopressa BID and timolol ranged from -1.60 to +1.09 mmHg. The upper 95% confidence limit for the differences in mean IOP was as high as 2.27 mmHg.

**Table 40: Study 302 Mean IOP (mmHg) in Study Eye by Visit and Time (PP Observed, Baseline  $\geq$  25 mmHg)**

Day and Time	Mean IOP						QD vs. Timolol BID	BID vs. Timolol BID
	Rhopressa QD		Rhopressa BID		Timolol		Difference (95% CI) <sup>1</sup>	Difference (95% CI) <sup>1</sup>
<b>Baseline</b>								
<b>08:00</b>	77	25.14	77	25.13	75	25.18	-0.04 (-0.37, 0.30)	-0.05 (-0.39, 0.29)
<b>10:00</b>	77	24.02	77	23.97	75	23.89	0.13 (-0.44, 0.71)	0.08 (-0.48, 0.64)

<b>16:00</b>	77	23.46	77	23.07	75	23.33	0.13 (-0.56, 0.83)	-0.26 (-0.97, 0.46)
<b>Day 15</b>								
<b>08:00</b>	74	20.66	69	19.95	75	19.31	1.35 (0.44, 2.26)	0.64 (-0.38, 1.67)
<b>10:00</b>	73	19.49	65	17.93	74	18.56	0.93 (-0.08, 1.93)	-0.63 (-1.67, 0.41)
<b>16:00</b>	74	18.55	66	17.44	74	19.05	-0.50 (-1.48, 0.48)	-1.60 (-2.63, -0.58)
<b>Day 43</b>								
<b>08:00</b>	71	21.80	58	20.34	74	19.26	2.55 (1.41, 3.67)	1.09 (0.12, 2.06)
<b>10:00</b>	67	20.18	56	18.62	74	18.61	1.57 (0.50, 2.64)	0.01 (-1.00, 1.00)
<b>16:00</b>	67	19.46	56	18.15	74	18.49	0.97 (0.01, 1.93)	-0.34 (-1.40, 0.71)
<b>Day 90</b>								
<b>08:00</b>	61	21.69	47	20.77	74	19.62	2.07 (0.98, 3.16)	1.14 (0.02, 2.27)
<b>10:00</b>	59	20.41	43	19.57	73	18.67	1.74 (0.60, 2.87)	0.90 (-0.35, 2.15)
<b>16:00</b>	56	18.96	43	18.26	73	19.03	-0.08 (-1.22, 1.07)	-0.78 (-2.06, 0.50)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical Reviewer's Calculation based on the randomized subjects who did not have major protocol violations.

The applicant also analyzed all PP subjects. For all PP subjects, noninferiority of Rhopressa QD to timolol was not demonstrated. During the 3-month efficacy assessment period, mean IOP ranged from 17.37 to 19.43 mmHg in the Rhopressa QD group and from 17.25 to 18.25 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol ranged from -0.22 to +1.29 mmHg. The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 7 of the 9 time points and was as high as 1.93 mmHg at 8AM on Day 43.

**Table 41: Study 302 Mean IOP (mmHg) in Study Eye by Visit and Time (PP Observed, All)**

Day and Time	Mean IOP						QD vs. Timolol	BID vs. Timolol
	Rhopressa QD		Rhopressa BID		Timolol		Difference (95% CI) <sup>1</sup>	Difference (95% CI) <sup>1</sup>
<b>Baseline</b>								
<b>08:00</b>	206	23.51	209	23.50	217	23.45	0.06 (-0.25, 0.37)	0.05 (-0.27, 0.36)
<b>10:00</b>	206	22.31	209	22.26	217	22.18	0.14 (-0.27, 0.54)	0.08 (-0.32, 0.48)
<b>16:00</b>	206	21.56	209	21.49	217	21.61	-0.05 (-0.50, 0.40)	-0.13 (-0.57, 0.32)
<b>Day 15</b>								
<b>08:00</b>	201	19.01	191	18.20	217	18.25	0.76 (0.21, 1.31)	-0.05 (-0.67, 0.56)
<b>10:00</b>	199	17.74	185	16.91	215	17.49	0.25 (-0.33, 0.82)	-0.58 (-1.17, 0.00)
<b>16:00</b>	200	17.37	183	16.28	215	17.59	-0.22 (-0.78, 0.34)	-1.31 (-1.89, -0.73)
<b>Day 43</b>								
<b>08:00</b>	193	19.37	169	18.57	215	18.08	1.29 (0.66, 1.93)	0.49 (-0.11, 1.08)
<b>10:00</b>	187	18.10	162	17.09	215	17.31	0.79 (0.19, 1.40)	-0.22 (-0.82, 0.38)
<b>16:00</b>	187	17.88	162	16.58	215	17.25	0.63 (0.07, 1.19)	-0.67 (-1.28, -0.06)
<b>Day 90</b>								
<b>08:00</b>	177	19.43	138	18.66	214	18.21	1.21 (0.54, 1.89)	0.45 (-0.24, 1.14)
<b>10:00</b>	173	18.18	131	17.81	213	17.52	0.66 (0.01, 1.31)	0.28 (-0.40, 0.97)
<b>16:00</b>	170	17.73	131	17.08	212	17.67	0.06 (-0.58, 0.70)	-0.59 (-1.25, 0.08)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Tables 14.2.1.5.1 of Study 302 report based on the randomized subjects who did not have major protocol violations.

### 3. Study 304

For the primary efficacy analyses population of PP subjects who had maximum baseline IOP < 25 mmHg at all time points, the mean baseline IOP was in the range of 20.7 to 22.4 mmHg for the Rhopressa QD group, 20.7 to 22.4 for the timolol group. During the 3-month efficacy assessment period, mean IOP ranged from 16.32 to 17.85 mmHg in the Rhopressa QD group and from 16.68 to 17.58 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol for the 9 time points over the 3-month efficacy assessment period ranged from -0.59 to +0.59 mmHg. Noninferiority of Rhopressa dosed QD to timolol was demonstrated. The upper 95% confidence limit for the differences in mean IOP between Rhopressa and timolol was within 1.5 mmHg.

The statistical reviewer conducted additional analysis for the subgroup of subjects who had maximum baseline IOP ≥ 25 mmHg at one or more time points. The findings were consistent with what's observed in Studies 301 and 302; noninferiority of Rhopressa to timolol was not demonstrated in this subgroup. During the 3-month efficacy assessment period, mean IOP ranged from 20.01 to 21.99 mmHg in the Rhopressa QD group and from 18.94 to 20.15 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol for the 9 time points ranged from 0.41 to +2.14 mmHg. The upper 95% confidence limit for the differences in mean IOP between Rhopressa and timolol was as high as 3.12 at 8AM on Day 43.

**Table 42: Study 304 Mean IOP (mmHg) in Study Eye by Visit and Time (PP Observed)**

Day Time	Baseline < 25 mmHg					Baseline ≥ 25 mmHg				
	Rhopressa		Timolol		Difference (95% CI)	Rhopressa		Timolol		Difference (95% CI) <sup>1</sup>
	N	Mean	N	Mean		N	Mean	N	Mean	
<b>Baseline</b>										
<b>08:00</b>	186	22.40	187	22.44	-0.05 (-0.27, 0.18)	120	26.30	130	25.96	0.34 (-0.16, 0.85)
<b>10:00</b>	186	21.06	187	21.28	-0.21 (-0.55, 0.14)	120	25.18	130	24.91	0.26 (-0.29, 0.81)
<b>16:00</b>	186	20.69	187	20.68	0.01 (-0.37, 0.38)	120	24.48	130	23.99	0.49 (-0.16, 1.13)
<b>Day 15</b>										
<b>08:00</b>	184	17.68	184	17.49	0.19 (-0.41, 0.79)	118	21.57	129	20.15	1.42 (0.51, 2.34)
<b>10:00</b>	181	16.55	184	16.70	-0.15 (-0.72, 0.42)	116	20.09	129	19.35	0.75 (-0.15, 1.64)
<b>16:00</b>	181	16.32	184	16.91	-0.59 (-1.15, -0.04)	116	20.01	129	19.17	0.83 (-0.00, 1.67)
<b>Day 43</b>										
<b>08:00</b>	177	17.84	184	17.58	0.26 (-0.32, 0.85)	112	21.99	127	19.84	2.14 (1.16, 3.12)
<b>10:00</b>	177	16.75	183	16.97	-0.22 (-0.81, 0.37)	109	20.33	127	19.19	1.15 (0.30, 1.99)
<b>16:00</b>	176	16.57	182	16.67	-0.10 (-0.66, 0.46)	109	20.03	127	19.63	0.41 (-0.47, 1.29)
<b>Day 90</b>										
<b>08:00</b>	167	17.85	180	17.27	0.59 (0.01, 1.17)	94	21.71	121	19.91	1.79 (0.74, 2.85)
<b>10:00</b>	166	16.90	180	16.68	0.22 (-0.36, 0.80)	93	20.80	120	18.95	1.85 (0.89, 2.81)
<b>16:00</b>	165	16.73	180	16.78	-0.05 (-0.66, 0.56)	93	20.31	120	18.94	1.37 (0.46, 2.28)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Table 14.1.1.2 of Study 304 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis based on the randomized subjects who did not have major protocol violations.

The applicant also analyzed all PP subjects. For all PP subjects, noninferiority of Rhopressa QD to timolol was not demonstrated. During the 3-month efficacy assessment period, mean IOP ranged from 17.76 to 19.45 mmHg in the Rhopressa QD group and from 17.59 to 18.50 mmHg in the timolol group. Differences in mean IOP between Rhopressa QD and timolol ranged from -

0.08 to +0.95 mmHg. The upper 95% confidence limit for the differences in mean IOP was slightly higher than 1.5 mmHg at two time points (1.53 mmHg at 8AM on Day 43 and 1.51 mmHg at 8AM on Day 90).

**Table 43: Study 304 Mean IOP (mmHg) in Study Eye by Visit and Time (Overall)**

	Rhopressa		Timolol		Difference (95% CI) <sup>1</sup>
	N	Mean	N	Mean	
<b>Baseline</b>					
<b>08:00</b>	306	23.93	317	23.89	0.04 (-0.34, 0.41)
<b>10:00</b>	306	22.67	317	22.77	-0.09 (-0.52, 0.33)
<b>16:00</b>	306	22.17	317	22.04	0.13 (-0.31, 0.57)
<b>Day 15</b>					
<b>08:00</b>	302	19.20	313	18.58	0.61 (0.04, 1.19)
<b>10:00</b>	297	17.93	313	17.79	0.14 (-0.41, 0.70)
<b>16:00</b>	297	17.76	313	17.85	-0.08 (-0.61, 0.45)
<b>Day 43</b>					
<b>08:00</b>	289	19.45	311	18.50	0.95 (0.36, 1.53)
<b>10:00</b>	286	18.12	310	17.88	0.24 (-0.31, 0.78)
<b>16:00</b>	285	17.89	309	17.88	0.01 (-0.54, 0.56)
<b>Day 90</b>					
<b>08:00</b>	261	19.24	301	18.33	0.91 (0.31, 1.51)
<b>10:00</b>	259	18.30	300	17.59	0.71 (0.14, 1.28)
<b>16:00</b>	258	18.02	300	17.65	0.38 (-0.19, 0.94)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.  
Source: Table 14.2.1.2.1 of Study 304 report based on the randomized subjects who did not have major protocol violations.

## Appendix 3: Supportive Analyses Results

### ITT Population

**Table 44: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg; ITT Observed)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
		n	IOP	n	IOP	n	IOP				
301	Rhopressa	15	120	17.35	119	16.32	119	16.42	-0.34 (-0.95, 0.28)	-0.56 (-1.17, 0.53)	-0.59 (-1.22, 0.04)
	Timolol		136	17.69	135	16.88	135	17.01			
	Rhopressa	43	117	17.84	115	16.87	116	16.64	0.13 (-0.56, 0.82)	-0.07 (-0.69, 0.56)	-0.56 (-1.22, 0.10)
	Timolol		134	17.71	134	16.94	133	17.20			
	Rhopressa	90	107	18.25	107	17.42	106	17.03	0.42 (-0.26, 1.09)	0.10 (-0.60, 0.80)	-0.28 (-0.92, 0.37)
	Timolol		129	17.84	129	17.32	129	17.31			
302	Rhopressa	15	152	17.84	151	16.66	152	16.69	0.25 (-0.33, 0.83)	-0.22 (-0.80, 0.35)	-0.09 (-0.67, 0.48)
	Timolol		162	17.59	161	16.89	161	16.79			
	Rhopressa	43	144	17.80	141	16.85	140	16.91	0.46 (-0.12, 1.04)	0.36 (-0.23, 0.96)	0.41 (-0.17, 0.99)
	Timolol		159	17.34	158	16.49	158	16.50			

	Rhoptressa	90	135	18.17	132	16.99	131	17.05	0.81	0.14	0.17
	Timolol		157	17.36	153	16.85	152	16.89	(0.12, 1.50)	(-0.52, 0.80)	(-0.52, 0.85)
304	Rhoptressa	15	212	17.58	208	16.49	207	16.22	0.09	-0.19	-0.64
	Timolol		204	17.49	204	16.68	204	16.86	(-0.47, 0.66)	(-0.74, 0.36)	(-1.17, -0.11)
	Rhoptressa	43	203	17.82	203	16.84	202	16.62	0.33	0.00	0.00
	Timolol		204	17.49	203	16.84	202	16.62	(-0.21, 0.88)	(-0.57, 0.56)	(-0.55, 0.55)
	Rhoptressa	90	189	17.94	187	16.93	186	16.86	0.67	0.27	0.12
	Timolol		197	17.28	197	16.66	197	16.73	(0.11, 1.22)	(-0.29, 0.84)	(-0.46, 0.71)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhoptressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on statistical reviewer's calculation, Tables 14.2.1.5.1 of Study 302 report; and Table 14.2.1.1.9 of Study 304 report.

**Table 45: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhoptressa QD vs. Timolol BID; Baseline  $\geq$  25 mmHg; ITT Observed)**

Study	Treatment	Day	IOP Time						Treatment Difference (95% CI) <sup>1</sup>		
			8:00		10:00		16:00		8:00	10:00	16:00
			n	IOP	n	IOP	n	IOP			
301	Rhoptressa	15	77	20.86	77	19.14	77	18.96	1.42	0.52	0.20
	Timolol		70	19.44	71	18.62	70	18.76			
	Rhoptressa	43	73	21.73	73	20.19	73	20.12	2.60	1.76	1.44
	Timolol		69	19.12	69	18.43	69	18.67			
	Rhoptressa	90	64	22.46	65	21.59	65	21.00	2.86	2.49	2.37
	Timolol		67	19.61	67	19.10	67	18.63			
302	Rhoptressa	15	92	20.62	90	19.37	91	18.64	1.18	0.75	-0.33
	Timolol		87	19.44	86	18.62	86	18.98			
	Rhoptressa	43	87	21.72	82	20.10	83	19.39	2.37	1.40	0.80
	Timolol		85	19.35	85	18.71	85	18.58			
	Rhoptressa	90	75	21.91	73	20.63	70	19.26	2.24	1.94	0.22
	Timolol		85	19.67	84	18.69	84	19.04			
304	Rhoptressa	15	133	21.47	130	19.88	130	19.66	1.48	0.58	0.53
	Timolol		147	19.99	147	19.30	147	19.14			
	Rhoptressa	43	125	21.85	122	20.18	122	19.87	2.06	1.09	0.40
	Timolol		144	19.79	143	19.10	143	19.47			
	Rhoptressa	90	103	21.70	101	20.71	101	20.41	1.85	1.73	1.47
	Timolol		137	19.85	136	18.97	136	18.94			

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhoptressa QD vs Timolol 0.5%.

Source: Statistical reviewer's Calculation.

**Table 46: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhoptressa QD vs. Timolol BID; Overall; ITT Observed)**

Study	Treatment	Day	IOP Time						Treatment Difference (95% CI) <sup>1</sup>		
			8:00		10:00		16:00		8:00	10:00	16:00
			n	IOP	n	IOP	n	IOP			
301	Rhoptressa	15	197	18.72	196	17.42	196	17.42	0.44	-0.05	-0.19
	Timolol		206	18.28	206	17.48	205	17.61			
	Rhoptressa	43	190	19.33	188	18.16	189	17.98	1.15	0.72	0.28
	Timolol		203	18.18	203	17.44	202	17.71			

	Rhopressa	90	171	19.83	172	19.00	171	18.54	1.39	1.07	0.78
	Timolol		196	18.44	196	17.93	196	17.76	(0.72, 2.05)	(0.39, 1.74)	(0.13, 1.43)
302	Rhopressa	15	244	18.89	241	17.67	243	17.42	0.65	0.18	-0.13
	Timolol		249	18.24	247	17.49	247	17.55	(0.14, 1.16)	(-0.35, 0.72)	(-0.65, 0.39)
	Rhopressa	43	231	19.28	223	18.05	223	17.83	1.24	0.78	0.60
	Timolol		244	18.04	243	17.26	243	17.23	(0.65, 1.83)	(0.20, 1.36)	(0.07, 1.13)
	Rhopressa	90	210	19.50	205	18.29	201	17.82	1.33	0.79	0.17
	Timolol		242	18.17	237	17.50	236	17.65	(0.69, 1.97)	(0.16, 1.41)	(-0.45, 0.78)
304	Rhopressa	15	345	19.08	338	17.79	337	17.55	0.54	0.02	-0.27
	Timolol		351	18.54	351	17.78	351	17.81	(0.00, 1.09)	(-0.51, 0.54)	(-0.77, 0.23)
	Rhopressa	43	328	19.36	325	18.10	324	17.85	0.92	0.32	0.04
	Timolol		348	18.44	346	17.78	345	17.80	(0.37, 1.46)	(-0.19, 0.83)	(-0.48, 0.56)
	Rhopressa	90	292	19.27	288	18.26	288	18.10	0.94	0.65	0.47
	Timolol		334	18.33	333	17.61	333	17.63	(0.38, 1.50)	(0.11, 1.19)	(-0.07, 1.01)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on Table 14.2.1.5 of Study 301 report, Tables 14.2.1.5.2 of Study 302 report; and Tables 14.2.1.3.6 of Study 304 report.

## LOCF Results

**Table 47: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg; PP LOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
		n	IOP	n	IOP	n	IOP				
301	Rhopressa	15	113	17.56	113	16.44	113	16.44	-0.24	-0.60	-0.73
	Timolol		124	17.80	124	17.04	124	17.17	(-0.91, 0.42)	(-1.25, 0.05)	(-1.38, -0.07)
	Rhopressa	43	113	18.20	113	17.12	113	16.78	0.34	0.09	-0.52
	Timolol		124	17.85	124	17.03	124	17.30	(-0.40, 1.08)	(-0.57, 0.76)	(-1.21, 0.16)
	Rhopressa	90	113	18.51	113	17.48	113	17.16	0.55	0.02	-0.25
	Timolol		124	17.96	124	17.46	124	17.41	(-0.14, 1.23)	(-0.68, 0.71)	(-0.90, 0.40)
302	Rhopressa	15	129	18.11	129	16.80	129	16.72	0.42	-0.15	-0.14
	Timolol		142	17.69	142	16.95	142	16.86	(-0.20, 1.04)	(-0.76, 0.46)	(-0.74, 0.46)
	Rhopressa	43	129	18.01	129	17.01	129	17.01	0.55	0.36	0.38
	Timolol		142	17.46	142	16.65	142	16.63	(-0.06, 1.15)	(-0.26, 0.97)	(-0.22, 0.98)
	Rhopressa	90	129	18.24	129	17.16	129	17.17	0.81	0.26	0.24
	Timolol		142	17.43	142	16.90	142	16.93	(0.11, 1.51)	(-0.42, 0.93)	(-0.44, 0.92)
304	Rhopressa	15	186	17.71	186	16.67	186	16.44	0.15	-0.11	-0.53
	Timolol		187	17.56	187	16.78	187	16.97	(-0.45, 0.75)	(-0.68, 0.47)	(-1.09, 0.03)
	Rhopressa	43	186	17.95	186	16.89	186	16.75	0.29	-0.15	0.02
	Timolol		187	17.66	187	17.04	187	16.73	(-0.28, 0.87)	(-0.74, 0.43)	(-0.54, 0.58)
	Rhopressa	90	186	17.97	186	17.02	186	16.92	0.63	0.28	0.09
	Timolol		187	17.34	187	16.74	187	16.82	(0.05, 1.21)	(-0.29, 0.85)	(-0.51, 0.69)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on statistical reviewer's calculation, Table 14.2.1.2.1 of Study 302 report; and Table 14.2.1.1.2 of Study 304 report.

**Table 48: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Overall Population; PP LOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
n	IOP	n	IOP	n	IOP						
301	Rhopressa	15	182	18.78	182	17.42	182	17.34	0.43	-0.16	-0.36
	Timolol		188	18.35	188	17.58	188	17.71	(-0.18, 1.04)	(-0.77, 0.45)	(-0.98, 0.25)
	Rhopressa	43	182	19.49	182	18.20	182	17.97	1.22	0.70	0.23
	Timolol		188	18.28	188	17.50	188	17.74	(0.54, 1.89)	(0.06, 1.34)	(-0.43, 0.89)
	Rhopressa	90	182	19.95	182	18.93	182	18.62	1.42	0.92	0.82
	Timolol		188	18.53	188	18.00	188	17.80	(0.76, 2.09)	(0.26, 1.59)	(0.17, 1.48)
302	Rhopressa	15	206	19.12	206	17.90	206	17.47	0.87	0.38	-0.16
	Timolol		217	18.25	217	17.52	217	17.63	(0.32, 1.42)	(-0.20, 0.95)	(-0.72, 0.40)
	Rhopressa	43	206	19.42	206	18.28	206	18.00	1.34	0.94	0.71
	Timolol		217	18.08	217	17.34	217	17.29	(0.72, 1.95)	(0.34, 1.54)	(0.16, 1.26)
	Rhopressa	90	206	19.68	206	18.50	206	18.04	1.50	0.96	0.37
	Timolol		217	18.18	217	17.54	217	17.68	(0.84, 2.16)	(0.33, 1.59)	(-0.24, 0.97)
304	Rhopressa	15	306	19.25	306	18.07	306	17.92	0.61	0.22	0.02
	Timolol		317	18.64	317	17.85	317	17.90	(0.04, 1.19)	(-0.33, 0.78)	(-0.52, 0.55)
	Rhopressa	43	306	19.58	306	18.39	306	18.16	0.98	0.42	0.21
	Timolol		317	18.60	317	17.96	317	17.95	(0.40, 1.56)	(-0.13, 0.97)	(-0.34, 0.76)
	Rhopressa	90	306	19.65	306	18.69	306	18.35	1.20	0.97	0.57
	Timolol		317	18.44	317	17.72	317	17.78	(0.60, 1.81)	(0.40, 1.53)	(0.02, 1.12)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on Table 14.2.1.2 of Study 301 report, Table 14.2.1.2.2 of Study 302 report; and Table 14.2.1.1.8 of Study 304 report.

**Table 49: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg; ITT LOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
n	IOP	n	IOP	n	IOP						
301	Rhopressa	15	125	17.55	125	16.55	125	16.61	-0.17	-0.39	-0.46
	Timolol		138	17.72	138	16.95	138	17.07	(-0.79, 0.45)	(-1.02, 0.23)	(-1.09, 0.18)
	Rhopressa	43	125	18.16	125	17.12	125	16.83	0.40	-0.11	-0.44
	Timolol		138	17.76	138	17.02	138	17.26	(-0.30, 1.09)	(-0.52, 0.73)	(-1.08, 0.21)
	Rhopressa	90	125	18.50	125	17.58	125	17.17	0.67	0.24	-0.18
	Timolol		138	17.83	138	17.34	138	17.34	(0.00, 1.33)	(-0.43, 0.91)	(-0.79, 0.44)
302	Rhopressa	15	155	17.91	155	16.75	155	16.73	0.30	-0.17	-0.10
	Timolol		163	17.61	163	16.92	163	16.83	(-0.28, 0.88)	(-0.74, 0.41)	(-0.67, 0.47)
	Rhopressa	43	155	17.85	155	16.93	155	16.96	0.47	0.39	0.40
	Timolol		163	17.38	163	16.54	163	16.56	(-0.09, 1.04)	(-0.18, 0.97)	(-0.16, 0.97)
	Rhopressa	90	155	18.16	155	17.15	155	17.11	0.80	0.38	0.31
	Timolol		163	17.36	163	16.77	163	16.79	(0.15, 1.45)	(-0.25, 1.01)	(-0.32, 0.95)
304	Rhopressa	15	214	17.61	214	16.60	214	16.36	0.02	-0.21	-0.60
	Timolol		209	17.60	209	16.81	209	16.95	(-0.54, 0.58)	(-0.76, 0.35)	(-1.14, -0.06)
	Rhopressa	43	214	17.89	214	16.93	214	16.77	0.30	0.00	0.09
	Timolol		209	17.59	209	16.93	209	16.68	(-0.24, 0.85)	(-0.56, 0.56)	(-0.45, 0.63)
	Rhopressa	90	214	18.00	214	17.00	214	16.96	0.65	0.30	0.21
	Timolol		209	17.35	209	16.70	209	16.75	(0.10, 1.20)	(-0.26, 0.86)	(-0.37, 0.78)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on statistical reviewer's calculation, Table 14.2.1.6.1 of Study 302 report; and Table 14.2.1.1.6 of Study 304 report.

**Table 50: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Overall Population; ITT LOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
n	IOP	n	IOP	n	IOP						
301	Rhopressa	15	202	18.81	202	17.54	202	17.50	0.48	0.03	-0.17
	Timolol		209	18.33	209	17.51	209	17.68	(-0.11, 1.07)	(-0.56, 0.61)	(-0.77, 0.43)
	Rhopressa	43	202	19.46	202	18.22	202	18.07	1.21	0.72	0.28
	Timolol		209	18.26	209	17.50	209	17.79	(0.56, 1.86)	(0.10, 1.34)	(-0.36, 0.91)
	Rhopressa	90	202	19.97	202	19.03	202	18.68	1.48	1.07	0.83
	Timolol		209	18.48	209	17.96	209	17.85	(0.85, 2.12)	(0.43, 1.71)	(0.20, 1.46)
302	Rhopressa	15	251	19.01	251	17.87	251	17.54	0.74	0.32	0.33
	Timolol		251	18.28	251	17.54	251	17.81	(0.22, 1.25)	(-0.21, 0.86)	(-0.14, 0.80)
	Rhopressa	43	251	19.32	251	18.24	251	17.95	1.24	0.93	0.65
	Timolol		251	18.08	251	17.30	251	17.30	(0.67, 1.81)	(0.37, 1.50)	(0.13, 1.17)
	Rhopressa	90	251	19.67	251	18.54	251	18.06	1.49	1.08	0.45
	Timolol		251	18.18	251	17.46	251	17.61	(0.87, 2.10)	(0.49, 1.67)	(-0.13, 1.02)
304	Rhopressa	15	351	19.17	351	17.98	351	17.76	0.56	0.12	-0.12
	Timolol		357	18.61	357	17.86	357	17.88	(0.02, 1.10)	(-0.40, 0.65)	(-0.63, 0.39)
	Rhopressa	43	351	19.51	351	18.36	351	18.12	0.96	0.47	0.23
	Timolol		357	18.55	357	17.89	357	17.88	(0.41, 1.51)	(-0.04, 0.99)	(-0.28, 0.75)
	Rhopressa	90	351	19.65	351	18.59	351	18.37	1.21	0.85	0.62
	Timolol		357	18.44	357	17.73	357	17.75	(0.65, 1.78)	(0.32, 1.39)	(0.10, 1.14)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on Table 14.2.1.6 of Study 301 report, Table 14.2.1.5.2 of Study 302 report; and Table 14.2.1.3.2 of Study 304 report.

## BOCF Results

**Table 51: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg; PP BOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
n	IOP	n	IOP	n	IOP						
301	Rhopressa	15	113	17.56	113	16.44	113	16.44	-0.24	-0.60	-0.73
	Timolol		124	17.80	124	17.04	124	17.17	(-0.91, 0.42)	(-1.25, 0.05)	(-1.38, -0.07)
	Rhopressa	43	113	18.21	113	17.19	113	16.83	0.31	0.14	-0.54
	Timolol		124	17.91	124	17.05	124	17.38	(-0.44, 1.05)	(-0.53, 0.82)	(-1.25, 0.16)
	Rhopressa	90	113	18.73	113	17.83	113	17.42	0.66	0.28	-0.04
	Timolol		124	18.07	124	17.56	124	17.46	(-0.05, 1.37)	(-0.45, 1.00)	(-0.71, 0.63)
302	Rhopressa	15	129	18.11	129	16.80	129	16.72	0.42	-0.15	0.04
	Timolol		142	17.69	142	16.95	142	16.86	(-0.20, 1.04)	(-0.76, 0.46)	(-0.50, 0.59)
	Rhopressa	43	129	18.20	129	17.19	129	17.20	0.72	0.54	0.57
	Timolol		142	17.49	142	16.65	142	16.63	(0.08, 1.35)	(-0.09, 1.17)	(-0.05, 1.18)
	Rhopressa	90	129	18.68	129	17.53	129	17.51	1.15	0.58	0.47
	Timolol		142	17.49	142	16.65	142	16.63			

	Timolol		142	17.52	142	16.96	142	17.04	(0.43, 1.88)	(-0.12, 1.27)	(-0.24, 1.18)
304	Rhopressa	15	186	17.71	186	16.67	186	16.44	0.15	-0.11	-0.53
	Timolol		187	17.56	187	16.78	187	16.97	(-0.45, 0.75)	(-0.68, 0.47)	(-1.09, 0.03)
	Rhopressa	43	186	18.07	186	16.99	186	16.82	0.42	-0.07	0.04
	Timolol		187	17.66	187	17.07	187	16.78	(-0.17, 1.01)	(-0.67, 0.53)	(-0.54, 0.61)
	Rhopressa	90	186	18.34	186	17.40	186	17.25	0.90	0.54	0.32
	Timolol		187	17.44	187	16.86	187	16.93	(0.31, 1.49)	(-0.06, 1.14)	(-0.29, 0.94)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on statistical reviewer's calculation, Table 14.2.1.3.1 of Study 302 report; and Table 14.2.1.1.6 of Study 304 report.

**Table 52: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Overall Population; PP BOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
		n	IOP	n	IOP	n	IOP				
301	Rhopressa	15	182	18.78	182	17.42	182	17.34	0.43	-0.16	-0.36
	Timolol		188	18.35	188	17.58	188	17.71	(-0.18, 1.04)	(0.77, 0.45)	(-0.98, 0.25)
	Rhopressa	43	182	19.63	182	18.40	182	18.09	1.29	0.87	0.29
	Timolol		188	18.34	188	17.53	188	17.80	(0.61, 1.98)	(0.22, 1.52)	(-0.38, 0.96)
	Rhopressa	90	182	20.33	182	19.39	182	18.91	1.71	1.31	1.04
	Timolol		188	18.62	188	18.08	188	17.86	(1.04, 2.38)	(0.64, 1.98)	(0.39, 1.70)
302	Rhopressa	15	206	19.12	206	17.90	206	17.47	0.87	0.38	-0.16
	Timolol		217	18.25	217	17.52	217	17.63	(0.32, 1.42)	(-0.20, 0.95)	(-0.72, 0.40)
	Rhopressa	43	206	19.64	206	18.50	206	18.26	1.52	1.17	0.97
	Timolol		217	18.12	217	17.34	217	17.29	(0.89, 2.15)	(0.56, 1.77)	(0.40, 1.54)
	Rhopressa	90	206	20.08	206	18.96	206	18.52	1.80	1.38	0.76
	Timolol		217	18.27	217	17.57	217	17.76	(1.15, 2.46)	(0.74, 2.03)	(0.13, 1.40)
304	Rhopressa	15	306	19.25	306	18.07	306	17.92	0.61	0.22	0.02
	Timolol		317	18.64	317	17.85	317	17.90	(0.04, 1.19)	(-0.33, 0.78)	(-0.52, 0.55)
	Rhopressa	43	306	19.73	306	18.50	306	18.26	1.12	0.50	0.26
	Timolol		317	18.61	317	18.00	317	18.00	(0.53, 1.70)	(-0.06, 1.05)	(-0.30, 0.82)
	Rhopressa	90	306	20.07	306	19.17	306	18.85	1.44	1.25	0.86
	Timolol		317	18.63	317	17.92	317	17.99	(0.83, 2.05)	(0.65, 1.85)	(0.27, 1.45)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on Table 14.2.1.3 of Study 301 report, Table 14.2.1.3.2 of Study 302 report; and Table 14.2.1.1.9 of Study 304 report.

**Table 53: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Baseline < 25 mmHg; ITT BOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
		n	IOP	n	IOP	n	IOP				
301	Rhopressa	15	125	17.55	125	16.55	125	16.61	-0.17	-0.39	-0.46
	Timolol		138	17.72	138	16.95	138	17.07	(-0.79, 0.45)	(-1.02, 0.23)	(-1.09, 0.18)
	Rhopressa	43	125	18.17	125	17.19	125	16.88	0.36	0.15	-0.45
	Timolol		138	17.81	138	17.03	138	17.33	(-0.34, 1.06)	(-0.48, 0.79)	(-1.11, 0.21)

	Rhopressa	90	125	18.82	125	17.95	125	17.54	0.74	0.47	0.07
	Timolol		138	18.09	138	17.48	138	17.47	(0.06, 1.42)	(-0.22, 1.15)	(-0.57, 0.70)
302	Rhopressa	15	155	17.91	155	16.75	155	16.73	0.30	-0.17	-0.10
	Timolol		163	17.61	163	16.92	163	16.83	(-0.28, 0.88)	(-0.74, 0.41)	(-0.67, 0.47)
	Rhopressa	43	155	18.13	155	17.18	155	17.24	0.73	0.58	0.63
	Timolol		163	17.40	163	16.60	163	16.61	(0.14, 1.32)	(-0.01, 1.18)	(0.04, 1.21)
Rhopressa	90	155	18.75	155	17.61	155	17.57	1.27	0.58	0.51	
		Timolol	163	17.49	163	17.03	163	17.06	(0.59, 1.95)	(-0.07, 1.22)	(-0.14, 1.16)
304	Rhopressa	15	214	17.61	214	16.60	214	16.36	0.02	-0.21	-0.60
	Timolol		209	17.60	209	16.81	209	16.95	(-0.54, 0.58)	(-0.76, 0.35)	(-1.14, -0.06)
	Rhopressa	43	214	18.05	214	17.07	214	16.85	0.46	0.11	0.11
	Timolol		209	17.60	209	16.96	209	16.74	(-0.10, 1.01)	(-0.46, 0.67)	(-0.43, 0.66)
	Rhopressa	90	214	18.47	214	17.49	214	17.37	0.91	0.53	0.41
	Timolol		209	17.56	209	16.96	209	16.96	(0.34, 1.48)	(-0.05, 1.12)	(-0.18, 0.99)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on statistical reviewer's calculation, Table 14.2.1.7.1 of Study 302 report; and Table 14.2.1.1.7 of Study 304 report.

**Table 54: Summary of Mean IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; Rhopressa QD vs. Timolol BID; Overall Population; ITT BOCF)**

Study	Treatment	Day	IOP						Treatment Difference (95% CI) <sup>1</sup>		
			Time						Time		
			8:00		10:00		16:00		8:00	10:00	16:00
		n	IOP	n	IOP	n	IOP				
301	Rhopressa	15	202	18.81	202	17.54	202	17.50	0.48	0.03	-0.17
	Timolol		209	18.33	209	17.51	209	17.68	(-0.11, 1.07)	(-0.56, 0.61)	(-0.77, 0.43)
	Rhopressa	43	202	19.59	202	18.40	202	18.18	1.28	0.84	0.34
	Timolol		209	18.31	209	17.56	209	17.84	(0.62, 1.93)	(0.21, 1.47)	(-0.30, 0.98)
	Rhopressa	90	202	20.39	202	19.47	202	19.03	1.69	1.35	1.06
	Timolol		209	18.70	209	18.13	209	17.97	(1.05, 2.33)	(0.70, 1.99)	(0.44, 1.68)
302	Rhopressa	15	251	19.01	251	17.87	251	17.54	0.74	0.32	-0.08
	Timolol		251	18.28	251	17.54	251	17.62	(0.22, 1.25)	(-0.21, 0.86)	(-0.60, 0.44)
	Rhopressa	43	251	19.63	251	18.54	251	18.27	1.47	1.16	0.91
	Timolol		251	18.16	251	17.38	251	17.36	(0.89, 2.06)	(0.58, 1.73)	(0.37, 1.44)
	Rhopressa	90	251	20.24	251	19.11	251	18.66	1.92	1.44	0.83
	Timolol		251	18.32	251	17.67	251	17.83	(1.31, 2.54)	(0.84, 2.04)	(0.24, 1.42)
304	Rhopressa	15	351	19.17	351	17.98	351	17.76	0.56	0.12	-0.12
	Timolol		357	18.61	357	17.86	357	17.88	(0.02, 1.10)	(-0.40, 0.65)	(-0.63, 0.39)
	Rhopressa	43	351	19.69	351	18.51	351	18.24	1.11	0.56	0.29
	Timolol		357	18.58	357	17.95	357	17.96	(0.56, 1.66)	(0.04, 1.08)	(-0.24, 0.81)
	Rhopressa	90	351	20.20	351	19.24	351	18.98	1.49	1.22	0.95
	Timolol		357	18.70	357	18.02	357	18.03	(0.92, 2.07)	(0.66, 1.78)	(0.39, 1.50)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Statistical reviewer's summary based on Table 14.2.1.7 of Study 301 report, Table 14.2.1.7.2 of Study 302 report; and Tables 14.2.1.3.3 of Study 304 report.

## Median IOP in the Study Eye

**Table 55: Summary of Median IOP (mmHg) in Study Eye by Visit and Time (Studies 301, 302, and 304; PP Observed)**

Study 301			
	Baseline < 25 mmHg	Baseline ≥ 25 mmHg	Overall

Day Time	Rhopressa		Timolol		Rhopressa		Timolol		Rhopressa		Timolol	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
<b>Baseline</b>												
<b>08:00</b>	113	22.00	124	22.50	69	25.50	64	25.00	182	23.00	188	23.00
<b>10:00</b>	113	21.50	124	21.00	69	24.50	64	24.00	182	22.00	188	22.00
<b>16:00</b>	113	20.00	124	20.00	69	24.00	64	23.00	182	22.00	188	21.25
<b>Day 15</b>												
<b>08:00</b>	108	17.00	123	18.00	69	20.50	64	19.00	177	18.00	187	18.00
<b>10:00</b>	107	16.00	122	17.00	69	19.00	64	18.50	176	17.00	186	18.00
<b>16:00</b>	107	16.00	122	17.00	69	18.00	64	18.00	176	17.00	186	17.50
<b>Day 43</b>												
<b>08:00</b>	105	17.50	121	18.00	65	21.50	63	19.00	170	18.50	184	18.00
<b>10:00</b>	105	16.50	121	17.00	65	20.00	63	19.00	170	17.50	184	17.00
<b>16:00</b>	105	16.00	120	17.25	65	20.00	63	18.00	170	17.50	183	17.50
<b>Day 90</b>												
<b>08:00</b>	99	18.00	119	18.00	58	22.75	62	19.50	157	19.5	181	18.00
<b>10:00</b>	99	17.00	119	17.00	59	21.00	62	19.00	158	19.00	181	18.00
<b>16:00</b>	99	17.00	119	17.50	59	21.00	62	18.00	158	18.00	181	18.00
<b>Study 302</b>												
	Baseline < 25 mmHg				Baseline ≥ 25 mmHg				Overall			
Day Time	Rhopressa		Timolol		Rhopressa		Timolol		Rhopressa		Timolol	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
<b>Baseline</b>												
<b>08:00</b>	129	22.50	142	22.50	77	25.50	75	25.50	206	23.00	217	23.00
<b>10:00</b>	129	21.00	142	21.50	77	24.00	75	24.00	206	22.00	217	22.00
<b>16:00</b>	129	20.50	142	20.50	77	24.00	75	24.00	206	21.50	217	21.50
<b>Day 15</b>												
<b>08:00</b>	127	18.00	142	18.00	74	20.50	75	19.50	201	19.00	217	18.00
<b>10:00</b>	126	17.00	141	17.00	73	19.50	74	18.75	199	17.50	215	17.50
<b>16:00</b>	126	17.00	141	17.00	74	18.25	74	19.00	200	17.00	215	17.50
<b>Day 43</b>												
<b>08:00</b>	122	18.00	141	17.50	71	21.00	74	19.00	193	19.00	215	18.00
<b>10:00</b>	120	17.00	141	16.50	67	20.00	74	18.00	187	17.50	215	17.00
<b>16:00</b>	120	17.00	141	16.50	67	19.50	74	18.00	187	18.00	215	17.00
<b>Day 90</b>												
<b>08:00</b>	116	18.00	140	17.25	61	22.00	74	19.75	177	19.00	214	18.00
<b>10:00</b>	114	17.00	140	17.00	59	20.00	73	19.00	173	18.00	213	17.50
<b>16:00</b>	114	17.00	139	17.00	56	19.00	73	19.00	170	18.00	212	17.50
<b>Study 304</b>												
	Baseline < 25 mmHg				Baseline ≥ 25 mmHg				Overall			
Day Time	Rhopressa		Timolol		Rhopressa		Timolol		Rhopressa		Timolol	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
<b>Baseline</b>												
<b>08:00</b>	186	22.00	187	22.00	120	26.00	130	26.00	306	23.00	317	23.00
<b>10:00</b>	186	21.00	187	21.00	120	25.00	130	25.00	306	22.00	317	22.50
<b>16:00</b>	186	21.00	187	20.50	120	25.00	130	24.00	306	22.00	317	22.00
<b>Day 15</b>												
<b>08:00</b>	184	17.50	184	17.50	118	22.00	129	20.00	302	19.00	313	18.00
<b>10:00</b>	181	16.50	184	16.50	116	20.00	129	19.00	297	18.00	313	17.50
<b>16:00</b>	181	16.00	184	17.00	116	20.00	129	19.00	297	17.50	313	17.50
<b>Day 43</b>												

<b>08:00</b>	177	18.00	184	18.00	112	21.00	127	20.00	289	19.00	311	18.00
<b>10:00</b>	177	16.50	183	17.00	109	20.00	127	19.00	286	18.00	310	18.00
<b>16:00</b>	176	16.00	182	16.00	109	20.00	127	19.50	285	17.00	309	18.00
<b>Day 90</b>												
<b>08:00</b>	167	17.50	180	17.00	94	21.00	121	19.50	261	18.00	301	18.00
<b>10:00</b>	166	17.00	180	16.50	93	21.00	120	18.50	259	18.00	300	17.00
<b>16:00</b>	165	16.00	180	16.50	93	20.00	120	19.00	258	17.50	300	17.00

Source: Statistical reviewer's Calculation.

## Appendix 4: Subgroup Analysis Results for Gender, Race, and Age

**Table 56: Study 301 Mean IOP Subgroup Analyses by Gender, Age, and Race (PP, Observed, Subjects with Maximum Baseline IOP < 25 mmHg)**

Sub group	Treatment	Day	Mean IOP						Treatment Difference (95% CI) <sup>1</sup>			
			Time						Time			
			8:00		10:00		16:00		8:00	10:00	16:00	
			N	IOP	N	IOP	N	IOP				
Gender	Female	15	Rhopressa	56	17.37	56	16.06	56	16.33	-0.48	-1.13	-1.04
			Timolol	74	17.85	73	17.19	73	17.37	(-1.30, 0.34)	(-1.95, 0.31)	(-1.90, 0.17)
	Male		Rhopressa	52	17.41	51	16.22	51	16.08	-0.14	-0.54	-0.76
			Timolol	49	17.55	49	16.76	49	16.84	(-1.06, 0.77)	(-1.47, 0.39)	(-1.73, 0.22)
	Female	43	Rhopressa	55	17.54	55	16.65	55	16.56	-0.22	-0.44	-0.66
			Timolol	72	17.76	72	17.09	71	17.23	(-1.16, 0.73)	(-1.30, 0.43)	(-1.59, 0.26)
	Male		Rhopressa	50	18.32	50	17.05	50	16.53	0.58	0.19	-0.83
			Timolol	49	17.74	49	16.86	49	17.36	(-0.48, 1.63)	(-0.78, 1.16)	(-1.87, 0.21)
	Female	90	Rhopressa	50	18.22	50	17.33	50	16.96	0.24	-0.37	-0.56
			Timolol	71	17.98	71	17.70	71	17.52	(-0.65, 1.14)	(-1.32, 0.58)	(-1.46, 0.35)
	Male		Rhopressa	49	18.34	49	17.26	49	17.04	0.66	0.13	-0.13
			Timolol	48	17.68	48	17.13	48	17.17	(-0.32, 1.64)	(-0.92, 1.17)	(-1.13, 0.87)
Age	< 65	15	Rhopressa	45	17.61	43	16.33	41	16.17	-0.62	-0.90	-1.60
			Timolol	59	18.23	57	17.23	57	17.77	(-1.52, 0.28)	(-1.82, 0.02)	(-2.56, 0.64)
	≥ 65		Rhopressa	63	17.23	62	15.99	58	16.24	-0.04	-0.83	-0.36
			Timolol	64	17.27	64	16.83	62	16.60	(-0.84, 0.76)	(-1.66, 0.01)	(-1.21, 0.50)
	< 65	43	Rhopressa	45	17.97	43	16.55	41	16.45	-0.32	-0.81	-1.07
			Timolol	58	18.28	57	17.35	57	17.52	(-1.37, 0.74)	(-1.77, 0.17)	(-2.11, 0.03)
	≥ 65		Rhopressa	62	17.87	62	17.04	58	16.62	0.59	0.36	-0.45
			Timolol	64	17.28	64	17.35	62	17.07	(-0.34, 1.52)	(-0.49, 1.22)	(-1.37, 0.47)
	< 65	90	Rhopressa	45	18.49	43	16.87	41	16.51	-0.06	-1.09	-1.49
			Timolol	58	18.56	57	17.96	57	18.00	(-1.03, 0.91)	(-2.13, 0.05)	(-2.47, 0.66)
	≥ 65		Rhopressa	62	18.13	62	17.59	58	17.35	0.91	0.58	0.53
			Timolol	64	17.21	63	17.02	62	16.82	(0.05, 1.77)	(-0.35, 1.50)	(-0.35, 1.41)

Race	White	Rhopressa	15	85	17.10	84	15.79	84	15.98	-0.35	-1.17	-0.94
		Timolol		93	17.45	93	16.96	93	16.92	(-1.02, 0.32)	(-1.86, 0.48)	(-1.66, -0.22)
Other	Rhopressa	23	18.46	23	17.38	23	17.04	-0.16	0.17	-0.87		
	Timolol	30	18.62	29	17.21	29	17.90	(-1.40, 1.08)	(-1.10, 1.44)	(-2.21, 0.48)		
White	Rhopressa	82	17.73	82	16.72	82	16.61	0.10	-0.21	-0.61		
	Timolol	92	17.63	92	16.92	91	17.22	(-0.70, 0.90)	(-0.94, 0.53)	(-1.39, 0.17)		
Other	Rhopressa	23	18.57	23	17.28	23	16.34	0.42	0.05	-1.15		
	Timolol	29	18.16	29	17.23	29	17.49	(-1.05, 1.88)	(-1.30, 1.39)	(-2.59, 0.29)		
White	Rhopressa	76	17.98	76	17.15	76	17.05	0.51	-0.21	-0.24		
	Timolol	90	17.47	90	17.36	90	17.29	(-0.21, 1.24)	(-1.02, 0.59)	(-1.01, 0.52)		
Other	Rhopressa	23	19.24	23	17.77	23	16.84	0.18	-0.04	-0.82		
	Timolol	29	19.06	29	17.80	29	17.65	(-1.12, 1.49)	(-1.46, 1.39)	(-2.19, 0.55)		

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs and p-values are based on the ANCOVA comparing AR-13324 QD vs Timolol 0.5%; the ANCOVA model has treatment as a factor, baseline and corresponding baseline characteristics (gender, or age, or race) as covariates, and includes the interaction of treatment and gender (or age, or race).

Source: Tables 14.2.9.1, 14.2.10.1, and 14.2.11.1 of Study 301 Report

**Table 57: Study 302 Mean IOP Subgroup Analyses by Gender, Age, and Race (PP, Observed, Subjects with Maximum Baseline IOP < 25 mmHg)**

IOP ≤ 25 mmHg													
Day		Time						QD vs. Timolol BID Difference (95% CI)			BID vs. Timolol BID Difference (95% CI)		
		8:00		10:00		16:00		8:00	10:00	16:00	8:00	10:00	16:00
		N	IOP	N	IOP	N	IOP						
<b>Gender</b>													
<b>Day 15</b>													
Female	Rhopressa QD	75	18.09	74	16.80	74	16.86	0.00	-0.63	-0.35	-0.91	-1.04	-1.41
	Rhopressa BID	84	17.18	83	16.39	81	15.79	(-0.82, 0.81)	(-1.42, 0.16)	(-1.11, 0.42)	(-1.71, -0.12)	(-1.81, 0.27)	(-2.16, -0.66)
	Timolol	86	18.09	86	17.43	86	17.20						
Male	Rhopressa QD	52	18.02	52	16.60	52	16.53	0.92	0.42	0.39	0.14	0.42	-0.79
	Rhopressa BID	38	17.25	37	16.22	37	15.35	(-0.08, 1.91)	(-0.55, 1.39)	(-0.54, 1.33)	(-0.94, 1.22)	(-1.02, 1.11)	(-1.81, 0.24)
	Timolol	56	17.11	55	16.18	55	16.14						
<b>Day 43</b>													
Female	Rhopressa QD	71	17.88	69	16.83	69	17.07	-0.07	-0.15	0.05	-0.46	-0.72	-1.04
	Rhopressa BID	76	17.49	72	16.26	72	15.98	(-0.87, 0.73)	(-0.94, 0.64)	(-0.74, 0.83)	(-1.24, 0.32)	(-1.49, 0.06)	(-1.82, 0.27)
	Timolol	86	17.95	86	16.98	86	17.02						
Male	Rhopressa QD	51	18.07	51	17.06	51	17.03	1.38	0.93	1.22	1.25	0.16	-0.53
	Rhopressa BID	35	17.94	34	16.30	34	15.28	(0.41, 2.34)	(-0.02, 1.88)	(0.28, 2.16)	(0.17, 2.33)	(-0.90, 1.23)	(-1.59, 0.52)
	Timolol	55	16.69	55	16.13	55	15.81						
<b>Day 90</b>													
Female	Rhopressa QD	66	18.15	66	17.20	66	17.28	0.19	-0.20	0.12	-0.61	-0.68	-0.80
	Rhopressa BID	59	17.36	56	16.73	56	16.36	(-0.70, 1.07)	(-1.06, 0.65)	(-0.75, 0.98)	(-1.52, 0.31)	(-1.58, 0.22)	(-1.71, 0.10)
	Timolol	86	17.96	86	17.41	86	17.16						
Male	Rhopressa	50	18.38	48	16.83	48	17.11	1.72	0.66	0.64	1.35	17.20	0.30

	<b>QD</b>							(0.66, 2.78)	(-0.38, 1.69)	(-0.41, 1.70)	(0.14, 2.55)	(-0.14, 2.19)	(-0.89, 1.48)
	<b>Rhopressa BID</b>	32	18.00	32	17.20	32	16.76						
	<b>Timolol</b>	54	16.65	54	16.17	53	16.47						
<b>Age</b>													
<b>Day 15</b>													
<b>&gt; 65</b>	<b>Rhopressa QD</b>	48	18.37	48	17.22	48	16.95	0.62 (-0.34, 1.58)	0.25 (-0.69, 1.18)	0.21 (-0.69, 1.11)	-0.79 (-1.71, 0.14)	-0.78 (-1.67, 0.11)	-1.08 (-1.95, 0.21)
	<b>Rhopressa BID</b>	55	16.97	56	16.19	55	15.65						
	<b>Timolol</b>	74	17.75	74	16.97	74	16.73						
<b>≤ 65</b>	<b>Rhopressa QD</b>	79	17.88	78	16.41	78	16.59	0.23 (-0.63, 1.09)	-0.50 (-1.34, 0.34)	-0.26 (-1.08, 0.55)	-0.26 (-1.15, 0.63)	-0.44 (-1.32, 0.44)	-1.19 (-2.05, -0.34)
	<b>Rhopressa BID</b>	67	17.39	64	16.47	63	15.66						
	<b>Timolol</b>	68	17.65	67	16.91	67	16.85						
<b>Day 43</b>													
<b>&lt; 65</b>	<b>Rhopressa QD</b>	48	18.34	47	17.37	47	17.60	0.65 (-0.28, 1.59)	0.64 (-0.27, 1.55)	1.13 (0.22, 2.04)	-0.18 (-1.11, 0.74)	-0.46 (-1.37, 0.46)	-0.54 (-1.46, 0.38)
	<b>Rhopressa BID</b>	49	17.50	46	16.27	46	15.93						
	<b>Timolol</b>	74	17.68	74	17.73	74	16.47						
<b>≥ 65</b>	<b>Rhopressa QD</b>	75	17.72	73	16.65	73	16.70	0.51 (-0.33, 1.36)	0.08 (-0.75, 0.91)	0.07 (-0.76, 0.89)	0.53 (-0.36, 1.41)	-0.29 (-1.15, 0.58)	-1.02 (-1.89, -0.15)
	<b>Rhopressa BID</b>	62	17.74	60	16.28	60	15.62						
	<b>Timolol</b>	67	17.21	67	16.56	67	16.64						
<b>Day 90</b>													
<b>&gt; 65</b>	<b>Rhopressa QD</b>	47	18.64	46	17.71	46	17.47	1.14 (0.12, 2.16)	0.58 (-0.41, 1.57)	0.65 (-0.35, 1.65)	0.40 (-0.69, 1.49)	-0.33 (-1.39, 0.74)	-0.32 (-0.35, 1.65)
	<b>Rhopressa BID</b>	38	17.90	36	16.81	36	16.51						
	<b>Timolol</b>	73	17.50	73	17.13	73	16.82						
<b>≤ 65</b>	<b>Rhopressa QD</b>	69	17.98	68	16.60	68	17.03	0.57 (-0.36, 1.51)	-0.11 (-1.02, 0.79)	0.05 (-0.87, 0.97)	-0.05 (-1.05, 0.95)	0.25 (-0.72, 1.22)	-0.48 (-1.46, 0.51)
	<b>Rhopressa BID</b>	53	17.35	52	16.96	52	16.50						
	<b>Timolol</b>	67	17.40	67	16.71	66	16.98						
<b>Race</b>													
<b>Day 15</b>													
<b>White</b>	<b>Rhopressa QD</b>	92	17.87	91	16.55	91	16.66	0.14 (-0.61, 0.90)	-0.56 (-1.30, 0.19)	-0.33 (-1.04, 0.39)	-0.73 (-1.51, 0.05)	-0.76 (-1.52, 0.01)	-1.50 (-2.24, -0.76)
	<b>Rhopressa BID</b>	82	16.99	80	16.35	78	15.49						
	<b>Timolol</b>	95	17.73	94	17.11	94	16.99						
<b>Other</b>	<b>Rhopressa QD</b>	35	18.54	35	17.15	35	16.89	0.89 (-0.27, 2.04)	0.54 (-0.59, 1.66)	0.50 (-0.60, 1.60)	-0.03 (-1.14, 1.08)	-0.30 (-1.38, 0.78)	-0.41 (-1.46, 0.64)
	<b>Rhopressa BID</b>	40	17.62	40	16.32	40	15.98						
	<b>Timolol</b>	47	17.65	47	16.61	47	16.39						
<b>Day 43</b>													
<b>White</b>	<b>Rhopressa QD</b>	88	17.87	86	16.81	86	16.86	0.49 (-0.26, 1.23)	0.07 (-0.66, 0.80)	0.19 (-0.54, 0.92)	0.40 (-0.38, 1.19)	-0.49 (-1.26, 0.27)	-0.86 (-1.62, -0.09)
	<b>Rhopressa BID</b>	74	17.78	72	16.25	72	15.81						
	<b>Timolol</b>	94	17.38	94	16.75	94	16.67						
<b>Other</b>	<b>Rhopressa QD</b>	34	18.20	34	17.21	34	17.55	0.58 (-0.55, 1.71)	0.76 (-0.35, 1.86)	1.24 (0.13, 2.36)	-0.29 (-1.39, 0.82)	-0.14 (-1.24, 0.96)	-0.68 (-1.79, 0.43)
	<b>Rhopressa BID</b>	37	17.33	34	16.32	34	15.63						
	<b>Timolol</b>	47	17.62	47	16.46	47	16.30						

Day 90													
White	Rhopressa QD	82	18.04	81	17.02	81	16.96	0.55 (-0.27, 1.37)	0.04 (-0.76, 0.84)	-0.12 (-0.93, 0.68)	0.31 (-0.58, 1.20)	-0.01 (-0.89, 0.87)	-0.58 (-1.46, 0.29)
	Rhopressa BID	62	17.80	59	16.97	59	16.50						
	Timolol	94	17.49	94	16.98	93	17.08						
Other	Rhopressa QD	34	18.75	33	17.10	33	17.83	1.36 (0.13, 2.59)	0.27 (-0.94, 1.48)	1.32 (0.10, 2.54)	-0.26 (-1.55, 1.03)	-0.07 (-1.33, 1.18)	0.01 (-1.25, 1.26)
	Rhopressa BID	29	17.12	29	16.76	29	16.52						
	Timolol	46	17.38	46	16.83	46	16.52						

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs and p-values are based on the ANCOVA comparing AR-13324 QD vs Timolol 0.5%; the ANCOVA model has treatment as a factor, baseline and corresponding baseline characteristics (gender, or age, or race) as covariates, and includes the interaction of treatment and gender (or age, or race).

Source: Tables 14.2.9.1, 14.2.10.1, and 14.2.11.1 of Study 302 Report

**Table 58: Study 304 Mean IOP Subgroup Analyses by Gender, Age, and Race (PP, Observed, Subjects with Maximum Baseline IOP < 25 mmHg)**

Sub group	Treatment	Day	Mean IOP						Treatment Difference (95% CI) <sup>1</sup>			
			Time						Time			
			8:00		10:00		16:00		8:00	10:00	16:00	
		N	IOP	N	IOP	N	IOP					
Gender	Female	Rhopressa	15	109	17.96	107	16.99	107	16.32	0.21	0.00	-0.94
		Timolol		125	17.75	125	16.99	125	17.25	(-0.52, 0.93)	(-0.64, 0.65)	(-1.56, -0.31)
	Male	Rhopressa		75	17.30	74	16.09	74	16.32	0.41	0.22	0.13
		Timolol		59	16.89	59	15.87	59	16.19	(-0.55, 1.38)	(-0.64, 1.08)	(-0.70, 0.96)
	Female	Rhopressa	43	105	17.84	105	16.97	104	16.62	0.03	-0.16	-0.28
		Timolol		125	17.81	124	17.13	124	16.90	(-0.67, 0.72)	(-0.84, 0.52)	(-0.92, 0.36)
	Male	Rhopressa		72	17.91	72	16.65	72	16.51	0.89	0.27	0.35
		Timolol		59	17.02	59	16.37	58	16.16	(-0.03, 1.81)	(-0.63, 1.18)	(-0.50, 1.20)
	Female	Rhopressa	90	97	18.10	96	17.11	95	16.73	0.53	0.27	-0.28
		Timolol		122	17.57	122	16.84	122	17.02	(-0.18, 1.24)	(-0.41, 0.95)	(-1.00, 0.43)
	Male	Rhopressa		70	17.59	70	16.81	70	16.79	1.02	0.72	0.57
		Timolol		58	16.56	58	16.09	58	16.22	(0.09, 1.95)	(-0.17, 1.62)	(-0.35, 1.50)
Age	< 65	Rhopressa	15	84	18.30	84	16.90	84	16.66	0.29	0.06	-0.47
		Timolol		81	18.01	81	16.84	81	17.13	(-0.57, 1.15)	(-0.71, 0.84)	(-1.21, 0.27)
	≥ 65	Rhopressa		100	17.18	97	16.38	97	16.02	0.12	-0.08	-0.72
		Timolol		103	17.05	103	16.46	103	16.74	(-0.65, 0.90)	(-0.79, 0.62)	(-1.39, -0.05)
	< 65	Rhopressa	43	82	18.06	82	16.65	81	16.35	0.03	-0.52	-0.41
		Timolol		81	18.02	80	17.17	79	16.76	(-0.79, 0.85)	(-1.32, 0.29)	(-1.17, 0.35)
	≥ 65	Rhopressa		95	17.71	95	17.00	95	16.77	0.52	0.34	0.17
		Timolol		103	17.19	103	16.67	103	16.69	(-0.23, 1.26)	(-0.40, 1.07)	(-0.51, 0.86)
	< 65	Rhopressa	90	76	17.87	76	17.00	75	16.78	0.07	0.00	-0.47
		Timolol		77	17.79	77	17.00	77	17.25	(-0.77, 0.92)	(-0.80, 0.81)	(-1.32, 0.37)
	≥ 65	Rhopressa		91	17.90	90	16.98	90	16.74	1.07	0.67	0.35
		Timolol		103	16.83	103	16.30	103	16.39	(0.31, 1.82)	(-0.05, 1.40)	(-0.40, 1.09)

<b>Race</b>	<b>White</b>	<b>Rhopressa</b>	15	134	17.57	131	16.43	131	16.13	-0.18	-0.23	-0.86
		<b>Timolol</b>		143	17.75	143	16.65	143	16.99	(-0.84, 0.49)	(-0.83, 0.37)	(-1.44, -0.29)
	<b>Other</b>	<b>Rhopressa</b>		50	18.01	50	17.13	50	16.83	1.49	0.59	0.18
		<b>Timolol</b>		41	16.52	41	16.54	41	16.65	(0.32, 2.66)	(-0.45, 1.64)	(-0.83, 1.18)
	<b>White</b>	<b>Rhopressa</b>	43	129	17.70	129	16.58	128	16.60	0.01	-0.34	-0.05
		<b>Timolol</b>		143	17.69	143	16.92	143	16.65	(-0.63, 0.65)	(-0.97, 0.28)	(-0.64, 0.53)
	<b>Other</b>	<b>Rhopressa</b>		48	18.33	48	17.54	48	16.51	1.23	0.76	-0.20
		<b>Timolol</b>		41	17.10	40	16.78	39	16.71	(0.11, 2.34)	(-0.33, 1.86)	(-1.24, 0.83)
	<b>White</b>	<b>Rhopressa</b>	90	119	17.73	118	16.74	117	16.90	0.24	0.04	-0.04
		<b>Timolol</b>		142	17.49	142	16.70	142	16.94	(-0.41, 0.89)	(-0.58, 0.66)	(-0.69, 0.60)
	<b>Other</b>	<b>Rhopressa</b>		48	18.26	48	17.59	48	16.41	1.95	1.35	0.33
		<b>Timolol</b>		38	16.31	38	16.23	38	16.08	(0.81, 3.09)	(0.27, 2.43)	(-0.79, 1.46)

<sup>1</sup> Difference from Timolol 0.5% and two-sided CIs and p-values are based on the ANCOVA comparing Rhopressa QD vs Timolol 0.5%; the ANCOVA model has treatment as a factor, baseline and corresponding baseline characteristics (gender, or age, or race) as covariates, and includes the interaction of treatment and gender (or age, or race).

Source: Tables 14.2.9.1, 14.2.10.1, and 14.2.11.1 of Study 304 Report

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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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YUNFAN DENG  
12/11/2017

YAN WANG  
12/11/2017  
I concur.

TSAE YUN D LIN  
12/11/2017

## STATISTICAL REVIEW AND EVALUATION FILING REVIEW OF AN NDA/BLA

**NDA/BLA #:** NDA 208-254  
**Supplement #:** Original  
**Related IND #:** 113064  
**Product Name:** Rhopressa™ (Netarsudil Ophthalmic) 0.02%  
**Indication(s):** For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension  
**Applicant:** Aerie Pharmaceuticals  
**Dates:** Submission Date: February 28, 2017  
Receipt Date: February 28, 2017  
Complete Primary Reviews: October 27, 2017  
PDUFA goal date: February 28, 2018  
**Review Priority:** Standard  
**Biometrics Division:** DBIV  
**Statistical Reviewer:** Yunfan Deng, Ph.D.  
**Concurring Reviewers:** Yan Wang, Ph.D.  
**Medical Division:** Division of Transplant and Ophthalmology Products  
**Clinical Team:** Sonal Wadhwa, MD  
William Boyd, MD, Team Leader  
**Project Manager:** Eithu Lwin

### 1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

This NDA seeks approval of Rhopressa™ (netarsudil ophthalmic solution) 0.02% dosed once daily in the affected eye(s) in the evening for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). This is a standard review NDA. This is a re-submission of the NDA. The applicant submitted the original NDA on August 30, 2016, and later withdrew it on October 27, 2016 due to manufacturing issues .

The original NDA included the efficacy and safety data from two completed pivotal studies. In this re-submission, the applicant submitted the 3-month interim efficacy and safety report of an additional ongoing pivotal study but did not submit any datasets for this ongoing study. The statistical reviewer considers the efficacy results of this ongoing study important to support the proposed indication; and requests the applicant submit its efficacy and safety datasets to facilitate the review of this NDA.

The efficacy of netarsudil ophthalmic solution 0.02% was evaluated in two completed active-controlled Phase 3 clinical trials: AR-13324-CS301 (referred to as Study 301 throughout this review), ,

and AR-13324-CS302 (referred to as Study 302 throughout this review). Study 301 was a 3-month efficacy and safety study with 2 treatment arms (netarsudil once-daily [QD] and timolol 0.5% twice-daily [BID]). Study 302 was a 3-month efficacy and 12-month safety study with 3 treatment arms (netarsudil QD and BID; and timolol 0.5% BID). Efficacy was also evaluated in an additional ongoing active-controlled Phase 3 clinical trial AR-13324-CS304 (referred to as Study 304 throughout this review). Study 304 is a 6-month study with a 3-month interim analysis. Study 304 has 2 treatment arms (netarsudil QD and timolol 0.5% BID). Please also see the attachment for a brief summary of the three studies.

**Table 1: Summary of Trials to be Assessed in the Statistical Review**

<b>Trial ID</b>	<b>Design*</b>	<b>Treatment/ Sample Size</b>	<b>Endpoint/Analysis</b>	<b>Preliminary Findings</b>
AR-13324-CS301	MC, R, DB, PG, AC trial (3 months)	Netarsudil QD / 202 Timolol BID / 209	Primary: mean IOP at 08:00, 10:00 and 16:00 at Day 15, Day 43, and Day 90	The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points. It did not meet the pre-specified criteria for noninferiority.
AR-13324-CS302	MC, R, DB, PG, AC (3 months for efficacy and 12 months for safety)	Netarsudil QD / 251 Netarsudil BID/ 254 Timolol BID / 251	Primary: mean IOP at 08:00, 10:00 and 16:00 at Day 15, Day 43, and Day 90 in subjects with baseline IOP < 25 mm Hg	The applicant concludes that non-inferiority of Netarsudil QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between Netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points.
AR-13324-CS304	MC, R, DB, PG, AC trial (3-month interim results of a 6-month ongoing study)	Netarsudil QD / 351 Timolol BID / 357	Primary: mean IOP at 08:00, 10:00 and 16:00 at Day 15, Day 43, and Day 90 in subjects with baseline IOP < 25 mm Hg	The applicant concludes that non-inferiority of Netarsudil QD to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between Netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 8 of the 9 time points.

\* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled.

## 2. Assessment of Protocols and Study Reports

**Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)**

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	Yes.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes.
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	Yes.
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes.

## 3. Electronic Data Assessment

**Table 3: Information Regarding the Data**

Content Parameter	Response/Comments
Dataset location	<a href="#">\\cdsesub1\evsprod\NDA208254\0001\m5\datasets</a>
Were analysis datasets provided?	Datasets and SAS program codes for Studies 301 and 302 were submitted; however datasets and SAS program codes for Study 304 were not submitted.
Dataset structure (e.g., SDTM or ADaM)	Yes
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	
Are the <i>analysis datasets</i> sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	NA
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

\* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

## 4. Filing Issues

**Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):**

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	<input checked="" type="checkbox"/>			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<input checked="" type="checkbox"/>			<ul style="list-style-type: none"> <li>ISS datasets were included in the submission.</li> <li>Complete study reports were available for Studies 301 and 302; interim study report was available for Study 304.</li> </ul>
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	<input checked="" type="checkbox"/>			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	<input checked="" type="checkbox"/>			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	<input checked="" type="checkbox"/>			

**IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?**

Yes.

## 5. Comments to be Conveyed to the Applicant

### *5.1. Refuse-to-File Issues*

NA

### *5.2. Information Requests/Review Issues*

This NDA resubmission included a 3-month interim clinical study report for an on-going Phase 3 study (AR-13324-CS304). However, we cannot locate the raw and derived analysis datasets and SAS programs used to generate the efficacy and safety results presented in the interim study report. Please submit these datasets and program codes along with their define

documents to us if they are not included in the resubmission or clarify where they are located in the resubmission.

## ***Appendix: Brief Summary of NDA208254***

According to the applicant (Aerie Pharmaceuticals), Netarsudil is a novel, potent, Rho kinase inhibitor shown in non-clinical studies to produce large reductions in IOP with a long duration of action. Therefore, the applicant developed Rhopressa™ (Netarsudil Ophthalmic) 0.02% (also known as AR-13324 Ophthalmic Solution) for the reduction of IOP in patients with OAG or OHT.

The efficacy of netarsudil ophthalmic solution 0.02% was evaluated in 2 completed active-controlled Phase 3 clinical trials (Studies 301 and 302) and an ongoing trial (Study 304). Study 301 was a 3-month efficacy and safety study with 2 treatment arms – netarsudil QD and timolol BID. Study 302 was a 3-month efficacy and 12-month safety study with 3 treatment arms – netarsudil QD, netarsudil BID, and timolol BID. Study 304 is an ongoing 6-month study with a 3-month interim analysis. Study 304 has 2 treatment arms – netarsudil QD and timolol 0.5% BID.

### **Summary of Studies 301, 302, and 304**

The three studies were similar in design except for the following key differences:

- The duration of the studies: Study 301 had a 3-month duration while Study 302 had a 12-month duration with the first 3 months having the same design as Study 301. The additional 9-month treatment period was mainly for safety evaluation. Study 304 has a 6-month duration with the first 3 months having the same design as Study 301. The additional 3-month treatment period in Study 304 is mainly for safety evaluation.
- Dosing of the study: Both Studies 301 and 304 evaluated AR-13324 0.02% dosed once-daily (QD) in the evening (PM) compared to timolol 0.5% dosed twice daily (BID) in the morning (AM) and PM. Study 302 evaluated AR-13324 QD in the PM and AR-13324 BID in AM and PM compared to timolol in AM and PM.
- Primary efficacy analysis for the study: Before the database lock of Study 302, it was found in Study 301 that AR-13324 did not achieve non-inferiority to timolol for all subjects in the per-protocol (PP) population, but AR-13324 did achieve non-inferiority for a pre-specified efficacy endpoint (a comparison for PP population subjects with maximum baseline IOP  $\leq 23$  mmHg) as well as in a post hoc analysis in the PP population subjects with maximum baseline IOP  $< 25$  mmHg. Therefore, the applicant had a teleconference with the FDA. During that teleconference, the Agency accepted the applicant's proposal to change the primary efficacy analysis population for Study 302 to subjects with maximum baseline IOP  $< 25$  mmHg. From the study design stage, the primary efficacy objective of Study 304 was to demonstrate the non-inferiority of

AR-13324 QD (PM) to timolol BID (AM and PM) in the study eye for enrolled subjects with maximum baseline IOP < 25 mmHg and was not changed.

Pediatric subjects <18 years of age were eligible to enroll into both 301 and 302; however, no subjects <18 years of age were enrolled in Study 301 and only 2 subjects <18 years of age were enrolled in Study 302. The subjects were 11 and 14, respectively. Study 304 enrolled only adult subjects. Therefore, the applicant is requesting a full waiver from the requirements for pediatric information.

All three studies enrolled subjects with diagnosis of OAG or OHT. Prior to randomization, subjects who qualified for enrollment at screening but were using ocular hypertension medications were required to go through a washout period. Subjects were also required to meet minimum IOP criteria while off ocular hypotensive medication, if applicable, at multiple time points at one or two qualification visits prior to enrollment. The following table presents the IOP entry criteria.

**IOP Entry Criteria (Studies 301, 302, and 304)**

Study	Visit 1	Visit 2	Eye
301	>20 and < 27 mmHg at 8:00 h	>20 and < 27 mmHg at 8:00 h >17 and < 27 mmHg at 10:00 h >17 and < 27 mmHg at 16:00 h	Same eye at all qualification time points
302	>20 and < 27 mmHg at 8:00 h	>20 and < 27 mmHg at 8:00 h >17 and < 27 mmHg at 10:00 h >17 and < 27 mmHg at 16:00 h	Same eye at all qualification time points
304	>20 and < 30 mmHg at 8:00 h	>20 and < 30 mmHg at 8:00 h >17 and < 30 mmHg at 10:00 h >17 and < 30 mmHg at 16:00 h	Same eye at all qualification time points

Source: Protocol for AR-13324-CS301; Protocol for AR-13324-CS302; and Protocol for AR-13324-CS304.

The study visits, efficacy assessment time points, and overall study duration of the three trials is presented in the following table.

**Study Duration and Visits (Studies 301, 302, and 304)**

Study	Screening	Efficacy Assessment up to Month 3	Efficacy Assessment After Month 3
301	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Not Applicable
302	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Month 6 (08:00 h) Month 9 (08:00 h) Month 12 (08:00 h)
304	Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Month 4 (08:00, 10:00, 16:00 h) Month 5 (08:00, 10:00, 16:00 h) Month 6 (08:00, 10:00, 16:00 h)

Qual. 1 = Qualification Visit 1; Qual. 2 = Qualification Visit 2;

Source: Protocol for AR-13324-CS301; Protocol for AR-13324-CS302; and Protocol for AR-13324-CS304.

For all three studies, the primary efficacy outcome was the mean IOP in the study eye at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. According to the applicant, two consecutive IOP measurements of each eye were to

be obtained. If the 2 measurements differed by more than 2 mmHg, a third measurement was to be obtained. IOP was to be analyzed as the mean of 2 measurements or as the median of 3 measurements (called mean IOP by the applicant).

The primary efficacy analysis population is the per protocol (PP) population, which was a subset of the Intent-to-Treat (ITT) population that included subjects who did not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. The ITT population included all randomized subjects who received at least one dose of study medication.

For all three studies, the primary efficacy analyses were conducted using two-sample t-tests separately at each time point (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3) for the PP population. The corresponding 95% confidence intervals (CIs) at each time point were constructed based on the two-sample t-test. According to the applicant (based on FDA clinical team recommendations), if the upper limits of the 95% CIs for the difference (AR-13324 - timolol) were within 1.5 mmHg at all time points and within 1.0 mmHg at a majority of time points (at least 5 of 9), then the null hypothesis was to be rejected in favor of the alternative hypothesis and AR-13324 was to be considered clinically non-inferior to timolol. For Study 304, the primary efficacy analysis of the study was for the 3-month IOP measurements and therefore no alpha adjustment for this interim analysis were implemented.

### **Study 301**

Study 301 was a double-masked, randomized, multicenter, active-controlled, parallel-group, 3-month study to assess the safety and ocular hypotensive efficacy of AR-13324 dosed QD (PM) compared to timolol BID (AM and PM) in adult subjects with elevated intraocular pressure (IOP) associated with open angle glaucoma and/or ocular hypertension.

Four hundred and eleven (411) subjects who met the eligibility criteria were randomized in a 1:1 ratio stratified by site to receive AR-13324 or timolol. Subjects were instructed to self-administer their masked treatment in both eyes (OU) BID, in the morning and evening, for 90 days. After the start of study medication, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3).

Forty-four subjects discontinued the study early (31 AR-13324, 13 timolol). The most frequent reason for discontinuation was an adverse event (AE). Twenty-four subjects were discontinued for AEs (20 AR-13324, 4 timolol), 8 for protocol violations, 5 for withdrawal of consent, 3 for lack of efficacy (all in the AR-13324 group), 2 for investigator decision, and one each for non-compliance and lost to follow-up.

**Study 301 Summary of Subject Disposition (Randomized Population)**

	<b>AR-13324 0.02% n (%)</b>	<b>Timolol 0.5% n (%)</b>	<b>All Subjects n (%)</b>
Number of Randomized Subjects	202	209	411
Study Completion			
Completed	171 (84.7)	196 (93.8)	367 (89.3)
Discontinued	31 (15.3)	13 (6.2)	44 (10.7)
Reason for Subject Discontinuation <sup>1</sup>			
Adverse Event	20 (64.5)	4 (30.8)	24 (54.5)
Withdrawal of Consent	3 (9.7)	2 (15.4)	5 (11.4)
Non-Compliant	0	1 (7.7)	1 (2.3)
Lost to Follow-Up	0	1 (7.7)	1 (2.3)
Lack of Efficacy	3 (9.7)	0	3 (6.8)
Investigator Decision	2 (6.5)	0	2 (4.5)
Protocol Violation	3 (9.7)	5 (38.5)	8 (18.2)

Source: Table 5 of Study 301 Report.

As presented in the following table, the safety and ITT populations both included 411 subjects and the PP population included 370 subjects.

**Study 301 Analysis Population**

<b>Population</b>	<b>AR-13324 0.02% N = 202 n (%)</b>	<b>Timolol 0.5% N = 209 n (%)</b>	<b>All Subjects N = 411 n (%)</b>
Safety	203 (100.5) <sup>1</sup>	208 (99.5)	411 (100.0)
Intent-to-Treat (ITT)	202 (100.0)	209 (100.0)	411 (100.0)
Per Protocol (PP)	182 (90.1)	188 (90.0)	370 (90.0)

Source: Table 6 of Study 301 Report.

Differences in mean IOP between AR-13324 and timolol for the 9 time points over the 3-month efficacy assessment ranged from -0.45 to +1.33 mmHg. Based on a preliminary review, noninferiority of AR-13324 dosed QD to timolol dosed BID was not demonstrated in the overall PP population (baseline IOP < 27 mmHg). The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points.

**Study 301 Study Eye Intraocular Pressure (mmHg) by Visit (Per-Protocol Population)**

Day and Time	Mean IOP		AR-13324 – Timolol (95% CI)	
	AR-13324 (N = 182)	Timolol (N = 188)	Mean Difference <sup>1</sup>	95% CI
<b>Baseline (Visit 3)</b>				
08:00 hours	23.42 (N = 182)	23.37 (N = 188)	0.06	(-0.29, 0.41)
10:00 hours	22.28 (N = 182)	21.92 (N = 188)	0.36	(-0.07, 0.79)
16:00 hours	21.78 (N = 182)	21.45 (N = 188)	0.33	(-0.15, 0.82)
<b>Day 15</b>				
08:00 hours	18.68 (N = 177)	18.33 (N = 187)	0.35	(-0.27, 0.96)
10:00 hours	17.29 (N = 176)	17.55 (N = 186)	-0.26	(-0.87, 0.36)
16:00 hours	17.24 (N = 176)	17.70 (N = 186)	-0.45	(-1.08, 0.17)
<b>Day 43</b>				
08:00 hours	19.35 (N = 170)	18.24 (N = 184)	1.11	(0.42, 1.80)
10:00 hours	18.14 (N = 170)	17.44 (N = 184)	0.70	(0.04, 1.36)
16:00 hours	17.86 (N = 170)	17.71 (N = 183)	0.15	(-0.52, 0.83)
<b>Day 90</b>				
08:00 hours	19.81 (N = 157)	18.47 (N = 181)	1.33	(0.64, 2.03)
10:00 hours	18.92 (N = 158)	17.96 (N = 181)	0.96	(0.26, 1.66)
16:00 hours	18.48 (N = 158)	17.74 (N = 181)	0.74	(0.07, 1.42)

<sup>1</sup> Difference from timolol and two-sided CIs and p-values are based on 2-sample t-tests comparing AR-13324 vs timolol.

Source: Table 8 of Study 301 Report.

According to the applicant, post hoc analyses were conducted on the PP subgroup of 237 subjects who had maximum baseline IOP < 25 mmHg (113 AR-13324-treated subjects and 124 timolol-treated subjects). The mean baseline IOP was in the range 20.62 to 22.39 mmHg for this AR-13324 subgroup and 20.52 to 22.50 mmHg for this timolol subgroup. The change from baseline in mean IOP from these baseline values was similar for both treatment groups, and was in the range -3.65 to -5.11 mmHg for the AR-13324 subgroup and -3.19 to -4.74 mmHg for the timolol subgroup at the 9 time points during the 3-month treatment period. Based on a preliminary assessment, these IOP changes were statistically significant (p < 0.0001) and clinically relevant at all 9 time points for both treatment groups. The statistical criteria for noninferiority were demonstrated for AR-13324 subjects in this subgroup, with the

upper limit of the 95% CIs for the differences (AR-13324 – timolol) in mean IOP within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 8 time points.

**Study 301 Study Eye Mean Intraocular Pressure (mmHg) by Visit for Subjects with Baseline IOP < 25 mmHg at All Time points (Per Protocol Population)**

Day and Time	Mean IOP		AR-13324 – Timolol (95% CI)	
	AR-13324 (N = 113)	Timolol (N = 124)	Mean Difference <sup>1</sup>	95% CI
<b>Baseline (Visit 3)</b>				
08:00 hours	22.39 (N = 113)	22.50 (N = 124)	-0.11	(-0.39, 0.18)
10:00 hours	21.28 (N = 113)	21.07 (N = 124)	0.21	(-0.21, 0.64)
16:00 hours	20.62 (N = 113)	20.52 (N = 124)	0.10	(-0.36, 0.56)
<b>Day 15</b>				
08:00 hours	17.34 (N = 108)	17.78 (N = 123)	-0.44	(-1.10, 0.22)
10:00 hours	16.18 (N = 107)	16.98 (N = 122)	-0.81	(-1.44, -0.17)
16:00 hours	16.22 (N = 107)	17.14 (N = 122)	-0.92	(-1.58, -0.26)
<b>Day 43</b>				
08:00 hours	17.85 (N = 105)	17.81 (N = 121)	0.05	(-0.68, 0.77)
10:00 hours	16.88 (N = 105)	16.96 (N = 121)	-0.08	(-0.74, 0.58)
16:00 hours	16.57 (N = 105)	17.26 (N = 120)	-0.69	(-1.40, 0.02)
<b>Day 90</b>				
08:00 hours	18.22 (N = 99)	17.91 (N = 119)	0.31	(-0.40, 1.02)
10:00 hours	17.34 (N = 99)	17.43 (N = 119)	-0.09	(-0.82, 0.63)
16:00 hours	17.02 (N = 99)	17.37 (N = 119)	-0.35	(-1.03, 0.34)

<sup>1</sup> Difference from timolol and two-sided CIs and p-values are based on 2-sample t-tests comparing AR-13324 vs timolol.  
Source: Table 9 of Study 301 Report.

**Study 302**

Study 302 was a 12-month, double-masked, randomized, multi-center, active-controlled, parallel-group safety and efficacy trial in pediatric subjects 0-17 years of age or adult subjects at least 18 years of age for reduction of intraocular pressure (IOP) with AR-13324 dosed QD (PM), or with AR-13324 dosed BID (AM and PM), each compared to Timolol dosed BID

(AM and PM). For entry into this study, the diagnosis of OAG or OHT was required in BOTH eyes. A diagnosis of OAG in one eye and OHT in the fellow eye was acceptable. Subjects were instructed to self-administer their masked medication OU BID in the AM and PM, for 365 days, with IP bottles labeled “AM” to be used for AM dosing and IP bottles labeled “PM” for PM dosing. For pediatric or adult subjects unable to self-administer the doses, a parent/guardian or caregiver was instructed to administer the study medication.

After the start of study medication, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), Day 90 (Month 3), Day 180 (Month 6), Day 270 (Month 9), and Day 365 (Month 12). A visit variance of  $\pm 3$  days was allowed for the Week 2 and Week 6 study visits while subsequent study visits had an allowed visit variance of  $\pm 5$  days.

Seven hundred and fifty-six (756) subjects who met the eligibility criteria were randomized in a 1:1:1 ratio stratified by site to receive AR-13324 QD, (b)(4) BID, or timolol BID. Among these 756 subjects, four hundred and seventy-seven (477) had maximum baseline IOP < 25 mm Hg. The following two tables present the subject disposition for all randomized subjects, and the subgroup of subjects who had maximum baseline IOP < 25 mm Hg respectively.

**Study 302 Summary of Subject Disposition (Population: All Subjects)**

	<b>AR-13324 0.02% QD (N=251) n (%)</b>	<b>AR-13324 0.02% BID (N=254) n (%)</b>	<b>Timolol 0.5% BID (N=251) n (%)</b>	<b>Total (N=756) n (%)</b>
Number of Randomized Subjects	251	254	251	756
Analysis Populations				
Safety	251 (100.0)	253 (99.6)	251 (100.0)	755 (99.9)
Intent-to-Treat	251 (100.0)	253 (99.6)	251 (100.0)	755 (99.9)
Per Protocol	206 (82.1)	209 (82.3)	217 (86.5)	632 (83.6)
Study Completion				
Completed Month 3	205 (81.7)	153 (60.2)	237 (94.4)	595 (78.7)
Discontinued Prior to Month 3	46 (18.3)	101 (39.8)	14 (5.6)	161 (21.3)
Completed Month 12	146 (58.2)	86 (33.9)	204 (81.3)	436 (57.7)
Discontinued Prior to Month 12	105 (41.8)	168 (66.1)	47 (18.7)	320 (42.3)
Reason for Subject Discontinuation <sup>1</sup>				
Adverse Event	71 ( 67.6)	132 ( 78.6)	15 ( 31.9)	218 ( 68.1)
Withdrawal of Consent	9 ( 8.6)	13 ( 7.7)	9 ( 19.1)	31 ( 9.7)
Non-Compliant	3 ( 2.9)	1 ( 0.6)	3 ( 6.4)	7 ( 2.2)
Lost to Follow-Up	1 ( 1.0)	3 ( 1.8)	0	4 ( 1.3)
Lack of Efficacy	10 ( 9.5)	4 ( 2.4)	2 ( 4.3)	16 ( 5.0)
Disallowed Concurrent Medication	2 ( 1.9)	2 ( 1.2)	5 ( 10.6)	9 ( 2.8)
Investigator Decision	1 ( 1.0)	2 ( 1.2)	2 ( 4.3)	5 ( 1.6)
Protocol Violation	4 ( 3.8)	6 ( 3.6)	10 ( 21.3)	20 ( 6.3)
Death	2 ( 1.9)	0	0	2 ( 0.6)
Other	2 ( 1.9)	5 ( 3.0)	1 ( 2.1)	8 ( 2.5)

<sup>1</sup> Percentages are based on the total number of discontinuations.

Source: Table 7 of Study 302 Report.

**Study 302 Summary of Subject Disposition (Population: Randomized Population with Maximum Baseline IOP < 25 mmHg)**

	<b>AR-13324 0.02% QD (N=155) n (%)</b>	<b>AR-13324 0.02% BID (N=159) n (%)</b>	<b>Timolol 0.5% BID (N=163) n (%)</b>	<b>Total (N=477) n (%)</b>
Number of Randomized Subjects	155	159	163	477
Analysis Populations				
Safety	155 (100.0)	159 (100.0)	163 (100.0)	477 (100.0)
Intent-to-Treat	155 (100.0)	159 (100.0)	163 (100.0)	477 (100.0)
Per Protocol	129 (83.2)	132 (83.0)	142 (87.1)	403 (84.5)
Study Completion				
Completed Month 3	133 (85.8)	100 (62.9)	154 (94.5)	387 (81.1)
Discontinued Prior to Month 3	22 (14.2)	59 (37.1)	9 (5.5)	90 (18.9)
Completed Month 12	98 (63.2)	62 (39.0)	133 (81.6)	293 (61.4)
Discontinued Prior to Month 12	57 (36.8)	97 (61.0)	30 (18.4)	184 (38.6)
Reason for Subject Discontinuation <sup>1</sup>				
Adverse Event	43 (75.4)	77 (79.4)	12 (40.0)	132 (71.7)
Withdrawal of Consent	6 (10.5)	7 (7.2)	4 (13.3)	17 (9.2)
Non-Compliant	2 (3.5)	1 (1.0)	3 (10.0)	6 (3.3)
Lost to Follow-Up	0	2 (2.1)	0	2 (1.1)
Lack of Efficacy	2 (3.5)	0	1 (3.3)	3 (1.6)
Disallowed Concurrent Medication	0	1 (1.0)	2 (6.7)	3 (1.6)
Investigator Decision	1 (1.8)	2 (2.1)	0	3 (1.6)
Protocol Violation	2 (3.5)	5 (5.2)	8 (26.7)	15 (8.2)
Death	0	0	0	0
Other	1 (1.8)	2 (2.1)	0	3 (1.6)

<sup>1</sup> Percentages are based on the total number of discontinuations.

Source: Table 7 of Study 302 Report.

As presented above, for the primary efficacy analysis in subjects with maximum baseline IOP < 25 mmHg, the ITT population included 477 subjects and the PP population included 403 subjects.

Since this study tested two difference doses of AR-13324 vs. timolol, the primary analysis was conducted using a hierarchical strategy to preserve the overall Type I error rate: first test AR-13324 QD to timolol; if QD demonstrates clinical non-inferiority, test AR-13324 BID to timolol.

Mean IOP at baseline (Visit 3) in the PP population with maximum baseline IOP < 25 mmHg (N = 403) was similar among the treatment groups at each observation time of 08:00, 10:00, and 16:00 hours, ranging from 20.4 to 22.5 mmHg and 20.6 to 22.6 mmHg in the AR-13324 QD and BID groups, respectively, and from 20.7 to 22.5 mmHg in the timolol group. Based on a preliminary assessment, non-inferiority of AR-13324 QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between AR-13324 QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority. The upper 95% confidence limit for the differences in mean IOP between AR-13324 BID and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at all of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority.

**Study 302 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population with Baseline IOP < 25 mmHg)**

Day and Time	Mean IOP			QD vs. Timolol	BID vs. Timolol
	AR-13324 QD	AR-13324 BID	Timolol	Difference (95% CI)	Difference (95% CI)
<b>Baseline 08:00</b>	22.54	22.55	22.54		
<b>10:00</b>	21.29	21.27	21.27		
<b>16:00</b>	20.43	20.56	20.71		
<b>Day 15 08:00</b>	18.07	17.21	17.69	0.37 (-0.25, 0.99)	-0.48 (-1.19, 0.22)
<b>10:00</b>	16.72	16.35	16.93	-0.21 (-0.82, 0.41)	-0.57 (-1.24, 0.09)
<b>16:00</b>	16.68	15.65	16.83	-0.15 (-0.75, 0.46)	-1.18 (-1.82, -0.54)
<b>Day 43 08:00</b>	17.95	17.64	17.46	0.49 (-0.13, 1.12)	0.17 (-0.51, 0.86)
<b>10:00</b>	16.95	16.28	16.63	0.32 (-0.31, 0.95)	-0.34 (-1.02, 0.33)
<b>16:00</b>	17.00	15.75	16.60	0.40 (-0.22, 1.02)	-0.85 (-1.53, -0.17)
<b>Day 90 08:00</b>	18.24	17.58	17.47	0.77 (0.03, 1.50)	0.11 (-0.64, 0.86)
<b>10:00</b>	17.03	16.94	16.92	0.10 (-0.59, 0.80)	0.02 (-0.72, 0.77)
<b>16:00</b>	17.13	16.51	16.95	0.18 (-0.55, 0.91)	0.44 (-1.16, 0.27)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 QD and BID vs Timolol.

Source: Tables 13 and 14 of Study 302 Report.

For the overall population, the mean baseline IOP was in the range 21.6 to 23.5 mmHg and 21.5 to 23.5 mmHg for AR-13324 QD and BID, respectively, and 21.6 to 23.5 mmHg for timolol. AR-13324 dosed QD was not non-inferior to timolol dosed BID in the analysis of the overall population of PP subjects. The upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at 7 of 9 time points and within 1.0 mmHg at 3 of the 9 time points. Differences in mean IOP between AR-13324 QD and timolol for the 9 time points over the 3-month efficacy assessment ranged from -0.2 to 1.3 mmHg in the PP analyses. Based on a preliminary review, AR-13324 dosed BID was non-inferior to timolol dosed BID in analysis of all PP subjects. The upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 7 of the 9 time points. Differences in mean IOP between AR-13324 BID and timolol for the 9 time points over the 3-month efficacy assessment ranged from -1.3 to 0.5 mmHg in the PP analyses.

**Study 302 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population Based on All Enrolled Subjects)**

Day and Time	Mean IOP			QD vs. Timolol	BID vs. Timolol
	AR-13324 QD	AR-13324 BID	Timolol	Difference (95% CI)	Difference (95% CI)
<b>Baseline 08:00</b>	23.51	23.50	23.45		
<b>10:00</b>	22.31	22.26	22.18		
<b>16:00</b>	21.56	21.49	21.61		
<b>Day 15 08:00</b>	19.02	18.20	18.25	0.77 (0.22, 1.32)	-0.05 (-0.67, 0.56)
<b>10:00</b>	17.74	16.91	17.49	0.25 (-0.33, 0.82)	-0.58 (-1.17, 0.00)
<b>16:00</b>	17.37	16.28	17.59	-0.22 (-0.78, 0.34)	-1.31 (-1.89, -0.73)
<b>Day 43 08:00</b>	19.37	18.57	18.08	1.29 (0.66, 1.93)	0.49 (-0.11, 1.08)
<b>10:00</b>	18.11	17.09	17.31	0.80 (0.19, 1.41)	-0.22 (-0.82, 0.38)
<b>16:00</b>	17.88	16.58	17.25	0.63 (0.07, 1.19)	-0.67 (-1.28, -0.06)
<b>Day 90 08:00</b>	19.43	18.66	18.21	1.21 (0.54, 1.89)	0.45 (-0.24, 1.14)
<b>10:00</b>	18.18	17.81	17.52	0.66 (0.01, 1.31)	0.28 (-0.40, 0.97)
<b>16:00</b>	17.73	17.08	17.67	0.06 (-0.58, 0.70)	-0.59 (-1.25, 0.08)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 QD and BID vs Timolol.

Source: Tables 13 and 14 of Study 302 Report.

### **Study 304**

Study 304 was a double-masked, randomized, multi-center, active-controlled, parallel-group 6-month study with a 3-month interim analysis assessing the ocular hypotensive efficacy and safety of AR-13324 Ophthalmic Solution, 0.02% QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in adult patients with elevated intraocular pressure. For entry into this study, the diagnosis of OAG or OHT was required in BOTH eyes. . A diagnosis of OAG in one eye and OHT in the fellow eye was acceptable. Subjects were instructed to self-administer their masked medication OU BID in the AM and PM, for 365 days, with IP bottles labeled “AM” to be used for AM dosing and IP bottles labeled “PM” for PM dosing.

After the start of study medication, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), Day 90 (Month 3), Day 120 (Month 4), Day 150 (Month 5), and Day 180 (Month 6). A visit variance of  $\pm 3$  days was allowed for the Week 2, Week 6, Month 3, Month 4, and Month 5 study visits while Month 6 had an allowed visit variance of  $\pm 7$  days.

Seven hundred and eight (708) subjects who met the eligibility criteria were randomized in a 1:1 ratio stratified by site to receive AR-13324 QD, or timolol BID. Among these 756 subjects, four hundred and twenty-three (423) had maximum baseline IOP < 25 mm Hg. The following two tables present the subject disposition at the 3-month interim analysis for all randomized subjects, and for the subgroup of subjects who had maximum baseline IOP < 25 mm Hg respectively.

**Study 304 Summary of Subject Disposition – 3-Month Interim Analysis (Population: All Subjects)**

	Netarsudil (AR-13324) 0.02%		Timolol 0.5% BID	All Subjects N=708 n (%)
	QD N=351 n (%)			
Number of Randomized Subjects	351		357	708
Analysis Populations <sup>1</sup>				
Safety	351 (100.0)		357 (100.0)	708 (100.0)
Intent-to-Treat (ITT)	351 (100.0)		357 (100.0)	708 (100.0)
Per Protocol (PP)	306 ( 87.2)		317 ( 88.8)	623 ( 88.0)
Study Completion				
Completed Month 3	290 ( 82.6)		335 ( 93.8)	625 ( 88.3)
Discontinued Prior to Month 3	61 ( 17.4)		22 ( 6.2)	83 ( 11.7)
Missing	0		0	0
Reason for Subject Discontinuation				
Adverse Event	39 ( 11.1)		6 ( 1.7)	45 ( 6.4)
Withdrawal of Consent	7 ( 2.0)		7 ( 2.0)	14 ( 2.0)
Non-Compliant	1 ( 0.3)		1 ( 0.3)	2 ( 0.3)
Lost to Follow-Up	0		0	0
Lack of Efficacy	5 ( 1.4)		0	5 ( 0.7)
Disallowed Concurrent Medication	1 ( 0.3)		2 ( 0.6)	3 ( 0.4)
Investigator Decision	0		2 ( 0.6)	2 ( 0.3)
Protocol Violation	4 ( 1.1)		3 ( 0.8)	7 ( 1.0)
Death	1 ( 0.3)		0	1 ( 0.1)
Other	3 ( 0.9)		1 ( 0.3)	4 ( 0.6)

Percentages are based on the total number of discontinuations.

<sup>1</sup> For the treatment assignments, ITT uses as Randomized; Safety and PP use as Treated.

Source: Table 5 of Study 304 Report.

**Study 304 Summary of Subject Disposition – 3-Month Interim Analysis (Subjects with Maximum Baseline IOP < 25 mmHg)**

	Netarsudil (AR-13324) 0.02%		Timolol 0.5%	All Subjects N=423 n (%)
	QD N=214 n (%)	BID N=209 n (%)		
Number of Randomized Subjects	214	209		423
Analysis Populations <sup>1</sup>				
Safety	214 (100.0)	209 (100.0)		423 (100.0)
Intent-to-Treat (ITT)	214 (100.0)	209 (100.0)		423 (100.0)
Per Protocol (PP)	186 (86.9)	187 (89.5)		373 (88.2)
Study Completion				
Completed Month 3	189 (88.3)	199 (95.2)		388 (91.7)
Discontinued Prior to Month 3	25 (11.7)	10 (4.8)		35 (8.3)
Missing	0	0		0
Reason for Subject Discontinuation				
Adverse Event	16 (7.5)	4 (1.9)		20 (4.7)
Withdrawal of Consent	3 (1.4)	2 (1.0)		5 (1.2)
Non-Compliant	1 (0.5)	1 (0.5)		2 (0.5)
Lost to Follow-Up	0	0		0
Lack of Efficacy	1 (0.5)	0		1 (0.2)
Disallowed Concurrent Medication	1 (0.5)	1 (0.5)		2 (0.5)
Investigator Decision	0	1 (0.5)		1 (0.2)
Protocol Violation	2 (0.9)	1 (0.5)		3 (0.7)
Death	1 (0.5)	0		1 (0.2)
Other	0	0		0

<sup>1</sup> Percentages are based on the total number of discontinuations.

Source: Table 6 of Study 304 Report.

As presented above, for the primary efficacy analysis in subjects with maximum baseline IOP < 25 mmHg, the ITT population included 423 subjects and the PP population included 373 subjects.

Mean IOP at baseline (Visit 3) in the PP population with maximum baseline IOP < 25 mmHg (N = 373) was similar among the treatment groups at each observation time of 08:00, 10:00, and 16:00 hours, ranging from 20.7 to 22.4 mmHg in the AR-13324 group, and from 20.7 to 22.4 mmHg in the timolol group. Based on a preliminary assessment, non-inferiority of AR-13324 to timolol was demonstrated in the primary efficacy analysis (PP population with maximum baseline IOP < 25 mmHg). The upper 95% confidence limit for the differences in mean IOP between AR-13324 and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 8 of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority.

**Study 304 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population with Baseline IOP < 25 mmHg)**

Day and Time	Mean IOP				AR-13324 vs. Timolol Difference (95% CI)
	AR-13324		Timolol		
	N	IOP	N	IOP	
<b>Baseline 08:00</b>	186	22.40	187	22.44	
<b>10:00</b>	186	21.06	187	21.28	
<b>16:00</b>	186	20.69	187	20.68	
<b>Day 15 08:00</b>	184	17.68	184	17.49	0.19 (-0.41, 0.79)
<b>10:00</b>	181	16.55	184	16.70	-0.15 (-0.72, 0.42)
<b>16:00</b>	181	16.32	184	16.91	-0.59 (-1.15, -0.04)
<b>Day 43 08:00</b>	177	17.84	184	17.58	0.26 (-0.32, 0.85)
<b>10:00</b>	177	16.75	183	16.97	-0.22 (-0.81, 0.37)
<b>16:00</b>	176	16.57	182	16.67	-0.10 (-0.66, 0.46)
<b>Day 90 08:00</b>	167	17.86	180	17.27	0.59 (0.00, 1.17)
<b>10:00</b>	166	16.90	180	16.68	0.22 (-0.36, 0.80)
<b>16:00</b>	165	16.73	180	16.78	-0.05 (-0.66, 0.56)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 vs Timolol.

Source: Tables 10 and 11 of Study 304 Report.

For the overall population, the mean baseline IOP ranged from 22.2 to 23.9 mmHg for AR-13324 and 22.0 to 23.9 mmHg for timolol. The changes in mean IOP from these baseline values ranged from -4.0 to -4.7 mmHg for AR-13324 and -4.1 to -5.5 mmHg for timolol across the 9 time points during the 3 month treatment period. Differences in mean IOP between AR-13324 and timolol for the 9 time points over the 3-month efficacy assessment ranged from -0.08 to 0.91 mmHg in the PP analyses.

**Study 304 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population Based on All Enrolled Subjects)**

Day and Time	Mean IOP				AR-13324 vs. Timolol Difference (95% CI)
	AR-13324		Timolol		
	N	IOP	N	IOP	
<b>Baseline 08:00</b>	306	23.93	317	23.89	
<b>10:00</b>	306	22.67	317	22.77	
<b>16:00</b>	306	22.17	317	22.04	
<b>Day 15 08:00</b>	302	19.20	313	18.58	0.61 (0.04, 1.19)
<b>10:00</b>	297	17.93	313	17.79	0.14 (-0.41, 0.70)
<b>16:00</b>	297	17.76	313	17.85	-0.08 (-0.61, 0.44)
<b>Day 43 08:00</b>	289	19.45	311	18.50	0.95 (0.36, 1.53)
<b>10:00</b>	286	18.12	310	17.88	0.24 (-0.31, 0.78)
<b>16:00</b>	285	17.89	309	17.88	0.01 (-0.54, 0.56)
<b>Day 90 08:00</b>	261	19.24	301	18.33	0.91 (0.31, 1.51)
<b>10:00</b>	259	18.30	300	17.59	0.71 (0.14, 1.28)
<b>16:00</b>	258	18.02	300	17.65	0.38 (-0.19, 0.94)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 vs Timolol.

Source: Tables 14.2.1.2.1 of Study 304 Report.

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/s/  
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YUNFAN DENG  
04/11/2017

YAN WANG  
04/11/2017

## STATISTICAL REVIEW AND EVALUATION FILING REVIEW OF AN NDA/BLA

**NDA/BLA #:** NDA 208-254  
**Supplement #:** Original  
**Related IND #:** 113064  
**Product Name:** Rhopressa™ (Netarsudil Ophthalmic) 0.02%  
**Indication(s):** For the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension  
**Applicant:** Aerie Pharmaceuticals  
**Dates:** Submission Date: August 30, 2016  
Receipt Date: August 30, 2016  
Complete Primary Reviews: May 1<sup>st</sup>, 2017  
PDUFA goal date: August 30, 2017  
**Review Priority:** Standard  
**Biometrics Division:** DBIV  
**Statistical Reviewer:** Yunfan Deng, Ph.D.  
**Concurring Reviewers:** Yan Wang, Ph.D.  
**Medical Division:** Division of Transplant and Ophthalmology Products  
**Clinical Team:** Sonal Wadhwa, MD  
William Boyd, MD, Team Leader  
**Project Manager:** Eithu Lwin

### 1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

This NDA seeks approval of Rhopressa™ (netarsudil ophthalmic solution) 0.02% dosed once daily in the affected eye(s) in the evening for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). This is a standard review NDA.

The efficacy of netarsudil ophthalmic solution 0.02% was evaluated in 2 active-controlled Phase 3 clinical trials: AR-13324-CS301, a 3-month efficacy and safety study with 2 treatment arms (netarsudil once-daily [QD]; timolol 0.5% twice-daily [BID]), and AR-13324-CS302, a 3-month efficacy and 12-month safety study with 3 treatment arms (netarsudil QD and BID; timolol 0.5% BID). Please also see the attachment for a brief summary of both studies.

**Table 1: Summary of Trials to be Assessed in the Statistical Review**

<b>Trial ID</b>	<b>Design*</b>	<b>Treatment/ Sample Size</b>	<b>Endpoint/Analysis</b>	<b>Preliminary Findings</b>
AR-13324-CS301	MC, R, DB, PG, AC trial (3 months)	Netarsudil / 202 Timolol / 209	Primary: mean intraocular pressure (IOP) at 08:00, 10:00 and 16:00 at Day 15, Day 43, and Day 90	The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points; therefore it did not meet the pre-specified criteria for noninferiority.
AR-13324-CS302	MC, R, DB, PG, AC (3 months for efficacy and 12 months for safety)	Netarsudil QD / 251 Netarsudil BID/ 254 Timolol / 251	Primary: mean IOP at 08:00, 10:00 and 16:00 at Day 15, Day 43, and Day 90 in subjects with baseline IOP < 25 mm Hg	Non-inferiority of Netarsudil QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between Netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points, therefore meeting the prespecified criteria for non-inferiority.

\* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

## 2. Assessment of Protocols and Study Reports

**Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)**

<b>Content Parameter</b>	<b>Response/Comments</b>
Designs utilized are appropriate for the indications requested.	Yes.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	Yes.
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	N/A
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	N/A
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	Yes.

### 3. Electronic Data Assessment

**Table 3: Information Regarding the Data**

Content Parameter	Response/Comments
Dataset location	<a href="#">\\cdsesub1\evsprod\NDA208254\0001\m5\datasets</a>
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	Yes
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	The IOP values were included in the “adefl1.xpt” dataset with variable name “AVAL”.
Are the <i>analysis datasets</i> sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	NA
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

\* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

### 4. Filing Issues

**Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):**

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	<input checked="" type="checkbox"/>			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	<input checked="" type="checkbox"/>			<ul style="list-style-type: none"> <li>ISS datasets were included in the submission.</li> <li>Complete study reports were available for individual studies.</li> </ul>
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.	<input checked="" type="checkbox"/>			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	<input checked="" type="checkbox"/>			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete,	<input checked="" type="checkbox"/>			

Content Parameter	Yes	No	NA	Comments
or inconsistent with regulatory requirements				

**IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?**  
Yes.

## 5. Comments to be Conveyed to the Applicant

### *5.1. Refuse-to-File Issues*

NA

### *5.2. Information Requests/Review Issues*

No information request at the time of this filing review.

## Appendix: Brief Summary of NDA208254

This NDA seeks approval of Rhopressa™ (Netarsudil Ophthalmic) 0.02% for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension. This is a standard 12-month review NDA.

According to the applicant (Aerie Pharmaceuticals), Netarsudil is a novel, potent, Rho kinase inhibitor that showed experimentally in non-clinical studies producing large reductions in IOP with a long duration of action. Therefore, the applicant developed Rhopressa™ (Netarsudil Ophthalmic) 0.02% (also known as AR-13324 Ophthalmic Solution) for the reduction of IOP in patients with OAG or OHT.

The efficacy of AR-13324 Ophthalmic Solution (hereafter referred to as AR-13324) was evaluated in two pivotal studies: studies AR-13324-CS301 (referred to as Study 301 throughout this summary) and AR-13324-CS302 (referred to as Study 302 throughout this summary). Both studies are double-masked, randomized, multicenter, active-controlled, parallel-group studies to assess the ocular hypotensive efficacy and the safety of AR-13324 in both eyes (OU) compared to timolol maleate ophthalmic solution (hereafter referred to as timolol), 0.5%, OU in adult subjects with elevated IOP. Please refer to Table 1 in Section 1 of this filing review for the summary table of both studies.

### **Summary of Studies 301 and 302**

Both studies were similar in design except the following key differences:

- The duration of the studies: study 301 was a 3-month study; while study 302 was a 12-month study with the first 3-month having the same design as study 301 and followed by an additional 9-month treatment period mainly for safety evaluation purpose.
- Dosing of the study: Study 301 evaluated one dose of AR-13324 versus timolol – AR-13324 0.02% dosed once-daily (QD) in the evening (PM) versus timolol 0.5% dosed twice daily (BID) in the morning (AM) and PM; study 302 evaluated two doses of AR-13324 – QD in the PM and BID in AM and PM versus timolol BID in AM and PM.
- Primary efficacy analysis for the study: before the database lock of study 302, it was found in the study 301 that AR-13324 did not achieve non-inferiority to timolol for all subjects in the per-protocol (PP) population; but AR-13324 did achieve non-inferiority for a pre-specified subgroup analysis (a comparison for PP population subjects with maximum baseline IOP  $\leq$  23 mmHg) as well as in a post hoc analysis with PP population subjects with maximum baseline IOP  $<$  25 mmHg. Therefore, the applicant had a teleconference with the FDA; and the Agency accepted the applicant’s proposal to change the primary efficacy endpoint for study 302 to demonstration of non-inferiority of AR-13324 QD (PM) and BID (AM and PM), OU to timolol BID (AM and PM), OU for enrolled subjects with maximum baseline IOP  $<$  25 mmHg in that teleconference.

Pediatric subjects  $<$ 18 years of age were eligible to enroll into both studies. However, no subjects  $<$ 18 years of age were enrolled in Study 301. Only 2 subjects  $<$ 18 years of age were enrolled in Study 302 – one aged 11 years and the other aged 14 years; and no subjects 0 to 2 years of age were enrolled into this trial. Therefore, the applicant is requesting a full waiver from the requirements for pediatric information.

Both studies enrolled subjects with diagnosis of OAG or OHT. Prior to randomization, subjects who were qualified for enrollment at screening but were using ocular hypertension medications were required to go through a washout period. Subjects were also required to meet minimum IOP criteria while off ocular hypotensive medication, if applicable, at multiple time points at one or two qualification visits prior to enrollment. The following table presents the IOP entry criteria.

**IOP Entry Criteria (Studies 301 and 302)**

Study	Qualification Visit 1	Qualification Visit 2 (2 to 7 days after Visit 1)	Eye(s)
AR-13324-CS301	$>$ 20 and $<$ 27 mmHg at 08:00 h	$>$ 20 and $<$ 27 mmHg at 08:00 h $>$ 17 and $<$ 27 mmHg at 10:00 h $>$ 17 and $<$ 27 mmHg at 16:00 h	Same eye at all qualification time points
AR-13324-CS302	$>$ 20 and $<$ 27 mmHg at 08:00 h	$>$ 20 and $<$ 27 mmHg at 08:00 h $>$ 17 and $<$ 27 mmHg at 10:00 h $>$ 17 and $<$ 27 mmHg at 16:00 h	Same eye at all qualification time points

Source: Protocol for AR-13324-CS301; and Protocol for AR-13324-CS302.

The study visits, efficacy assessment time points, and overall study duration of the two trials are presented in the following table.

**Study Duration and Visits (Studies 301 and 302)**

AR-13324-CS301	Screening Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Not applicable
AR-13324-CS302	Screening Qual. 1 (08:00 h) Qual. 2 (08:00, 10:00, 16:00 h)	Day 15 (08:00, 10:00, 16:00 h) Day 43 (08:00, 10:00, 16:00 h) Day 90 (08:00, 10:00, 16:00 h)	Month 6 (08:00 h) Month 9 (08:00 h) Month 12 (08:00 h)

Qual. 1 = Qualification Visit 1; Qual. 2 = Qualification Visit 2;

Source: Protocol for AR-13324-CS301; and Protocol for AR-13324-CS302.

For both studies, the primary efficacy outcome for the adult subjects was the mean IOP in the study eye at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. According to the case report form (CRF), two consecutive IOP measurements of each eye were obtained. If the 2 measurements differed by more than 2 mmHg, a third measurement was obtained. IOP was analyzed as the mean of 2 measurements or as the median of 3 measurements (called as mean IOP by the applicant).

The primary efficacy analysis population is the per protocol (PP) population, which was a subset of the Intent-to-Treat (ITT) population that included subjects (and their visits) who did not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. The ITT population included all randomized subjects who received at least one dose of study medication.

For both studies, the primary efficacy analyses were conducted using two-sample t-test separately at each time point (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3) for the PP population. The corresponding 95% confidence intervals (CIs) at each time point were constructed based on the two-sample t-test. According to the SAP, if the upper limits of the 95% CIs for the difference (AR-13324 - timolol) were within 1.5 mmHg at all time points and within 1.0 mmHg at a majority of time points (at least 5 of 9), then the null hypothesis was rejected in favor of the alternative hypothesis and AR-13324 was considered clinically non-inferior to timolol. Primary analyses were performed in PP population on observed data only (without imputation) with supportive analysis performed in ITT population.

Additional sensitivity analyses were performed in both PP and ITT populations using the following approaches for missing observations: last observation carried forward (LOCF) where LOCF were performed using time-relevant measures (i.e. from the same time point of the most recent visit with a nonmissing value); baseline observation carried forward (BOCF) using time-relevant measures; and Markov Chain Monte Carlo (MCMC) multiple imputation methods to determine the robustness of results. In addition, the applicant analysed the primary efficacy endpoint in both PP and ITT populations using analysis of covariance (ANCOVA) model including treatment as the main effect and baseline as the covariance; and using mixed model repeated measures (MMRM) analysis including treatment as the main effect, and

baseline IOP, visit, timepoint, treatment by visit, treatment by timepoint, visit by timepoint, and treatment by visit by timepoint as model terms.

### **Study 301**

Study 301 was a double-masked, randomized, multicenter, active-controlled, parallel-group, 3-month study to assess the safety and ocular hypotensive efficacy of AR-13324 dosed QD (PM) compared to timolol BID (AM and PM) in adult subjects with elevated intraocular pressure (IOP) associated with open angle glaucoma and/or ocular hypertension.

Four hundred and eleven (411) subjects who met the eligibility criteria were randomized in a 1:1 ratio stratified by site to receive AR-13324 or timolol. Subjects were instructed to self-administer their masked treatment in both eyes (OU) BID, in the morning and evening, for 90 days. After the start of study medication, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3).

Forty-four subjects discontinued the study early (31 AR-13324, 13 timolol). The most frequent reason for discontinuation was an adverse event (AE). Twenty-four subjects were discontinued for AEs (20 AR-13324, 4 timolol), 8 for protocol violations, 5 for withdrawal of consent, 3 for lack of efficacy (all in the AR-13324 group), 2 for investigator decision, and one each for non-compliance and lost to follow-up.

#### **Study 301 Summary of Subject Disposition (Randomized Population)**

	<b>AR-13324 0.02% n (%)</b>	<b>Timolol 0.5% n (%)</b>	<b>All Subjects n (%)</b>
Number of Randomized Subjects	202	209	411
Study Completion			
Completed	171 (84.7)	196 (93.8)	367 (89.3)
Discontinued	31 (15.3)	13 (6.2)	44 (10.7)
Reason for Subject Discontinuation <sup>1</sup>			
Adverse Event	20 (64.5)	4 (30.8)	24 (54.5)
Withdrawal of Consent	3 (9.7)	2 (15.4)	5 (11.4)
Non-Compliant	0	1 (7.7)	1 (2.3)
Lost to Follow-Up	0	1 (7.7)	1 (2.3)
Lack of Efficacy	3 (9.7)	0	3 (6.8)
Investigator Decision	2 (6.5)	0	2 (4.5)
Protocol Violation	3 (9.7)	5 (38.5)	8 (18.2)

Source: Table 5 of Study 301 Report.

As presented in the following table, the safety and ITT populations both included 411 subjects and the PP population included 370 subjects.

**Study 301 Analysis Population**

Population	AR-13324 0.02% N = 202 n (%)	Timolol 0.5% N = 209 n (%)	All Subjects N = 411 n (%)
Safety	203 (100.5)	208 (99.5)	411 (100.0)
Intent-to-Treat (ITT)	202 (100.0)	209 (100.0)	411 (100.0)
Per Protocol (PP)	182 (90.1)	188 (90.0)	370 (90.0)

Source: Table 6 of Study 301 Report.

Differences in mean IOP between AR-13324 and timolol for the 9 time points over the 3-month efficacy assessment ranged from -0.45 to +1.33 mmHg. Noninferiority of AR-13324 dosed QD to timolol dosed BID was not demonstrated in the overall PP population (baseline IOP < 27 mmHg). The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points; therefore it did not meet the pre-specified criteria for noninferiority.

**Study 301 Study Eye Intraocular Pressure (mmHg) by Visit (Per-Protocol Population)**

Day and Time	Mean IOP		AR-13324 – Timolol (95% CI)	
	AR-13324 (N = 182)	Timolol (N = 188)	Mean Difference <sup>1</sup>	95% CI
<b>Baseline (Visit 3)</b>				
08:00 hours	23.42 (N = 182)	23.37 (N = 188)	0.06	(-0.29, 0.41)
10:00 hours	22.28 (N = 182)	21.92 (N = 188)	0.36	(-0.07, 0.79)
16:00 hours	21.78 (N = 182)	21.45 (N = 188)	0.33	(-0.15, 0.82)
<b>Day 15</b>				
08:00 hours	18.68 (N = 177)	18.33 (N = 187)	0.35	(-0.27, 0.96)
10:00 hours	17.29 (N = 176)	17.55 (N = 186)	-0.26	(-0.87, 0.36)
16:00 hours	17.24 (N = 176)	17.70 (N = 186)	-0.45	(-1.08, 0.17)
<b>Day 43</b>				
08:00 hours	19.35 (N = 170)	18.24 (N = 184)	1.11	(0.42, 1.80)
10:00 hours	18.14 (N = 170)	17.44 (N = 184)	0.70	(0.04, 1.36)
16:00 hours	17.86 (N = 170)	17.71 (N = 183)	0.15	(-0.52, 0.83)
<b>Day 90</b>				
08:00 hours	19.81 (N = 157)	18.47 (N = 181)	1.33	(0.64, 2.03)
10:00 hours	18.92 (N = 158)	17.96 (N = 181)	0.96	(0.26, 1.66)
16:00 hours	18.48 (N = 158)	17.74 (N = 181)	0.74	(0.07, 1.42)

<sup>1</sup> Difference from timolol and two-sided CIs and p-values are based on 2-sample t-tests comparing AR-13324 vs timolol.  
Source: Table 8 of Study 301 Report.

According to the applicant, post hoc analyses were conducted on the PP subgroup of 237 subjects who had maximum baseline IOP < 25 mmHg (113 AR-13324-treated subjects and 124 timolol-treated subjects). The mean baseline IOP was in the range 20.62 to 22.39 mmHg for this AR-13324 subgroup and 20.52 to 22.50 mmHg for this timolol subgroup. The change from baseline in mean IOP from these baseline values was similar for both treatment groups, and was in the range -3.65 to -5.11 mmHg for the AR-13324 subgroup and -3.19 to -4.74 mmHg for the timolol subgroup at the 9 time points during the 3-month treatment period. These IOP changes were statistically significant ( $p < 0.0001$ ) and clinically relevant at all 9 time points for both treatment groups. The statistical criteria for noninferiority were demonstrated for AR-13324 subjects in this subgroup, with the upper limit of the 95% CIs for the differences (AR-13324 – timolol) in mean IOP within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 8 time points.

**Study 301 Study Eye Mean Intraocular Pressure (mmHg) by Visit for Subjects with Baseline IOP < 25 mmHg at All Time points (Per Protocol Population)**

Day and Time	Mean IOP		AR-13324 – Timolol (95% CI)	
	AR-13324 (N = 113)	Timolol (N = 124)	Mean Difference <sup>1</sup>	95% CI
<b>Baseline (Visit 3)</b>				
08:00 hours	22.39 (N = 113)	22.50 (N = 124)	-0.11	(-0.39, 0.18)
10:00 hours	21.28 (N = 113)	21.07 (N = 124)	0.21	(-0.21, 0.64)
16:00 hours	20.62 (N = 113)	20.52 (N = 124)	0.10	(-0.36, 0.56)
<b>Day 15</b>				
08:00 hours	17.34 (N = 108)	17.78 (N = 123)	-0.44	(-1.10, 0.22)
10:00 hours	16.18 (N = 107)	16.98 (N = 122)	-0.81	(-1.44, -0.17)
16:00 hours	16.22 (N = 107)	17.14 (N = 122)	-0.92	(-1.58, -0.26)
<b>Day 43</b>				
08:00 hours	17.85 (N = 105)	17.81 (N = 121)	0.05	(-0.68, 0.77)
10:00 hours	16.88 (N = 105)	16.96 (N = 121)	-0.08	(-0.74, 0.58)
16:00 hours	16.57 (N = 105)	17.26 (N = 120)	-0.69	(-1.40, 0.02)
<b>Day 90</b>				
08:00 hours	18.22 (N = 99)	17.91 (N = 119)	0.31	(-0.40, 1.02)
10:00 hours	17.34 (N = 99)	17.43 (N = 119)	-0.09	(-0.82, 0.63)
16:00 hours	17.02 (N = 99)	17.37 (N = 119)	-0.35	(-1.03, 0.34)

<sup>1</sup> Difference from timolol and two-sided CIs and p-values are based on 2-sample t-tests comparing AR-13324 vs timolol. Source: Table 9 of Study 301 Report.

As stated above, after seeing the efficacy results of study 301, since results of study 301 were available prior to database lock for study 302, the applicant had a teleconference with the FDA; and the Agency accepted the applicant's proposal to change the primary efficacy analysis for study 302 to demonstration of non-inferiority of AR-13324 QD (PM) and BID (AM and PM), to timolol BID (AM and PM) for enrolled subjects with maximum baseline IOP < 25 mmHg in that teleconference.

### **Study 302**

Study 302 was a 12-month, double-masked, randomized, multi-center, active-controlled, parallel-group safety and efficacy trial in pediatric subjects 0-17 years of age or adult subjects at least 18 years of age for reduction of intraocular pressure (IOP) with AR-13324 dosed QD (PM), or with AR-13324 dosed BID (AM and PM), each compared to Timolol dosed BID (AM and PM). For entry into this study, the diagnosis of OAG or OHT must be in BOTH eyes. It can be OAG in one eye and OHT in the fellow eye. Subjects were instructed to self-administer their masked medication OU BID in the AM and PM, for 365 days, with IP bottles labeled "AM" to be used for AM dosing and IP bottles labeled "PM" for PM dosing. For pediatric or adult subjects unable to self-administer the doses, a parent/guardian or caregiver was instructed to administer the study medication.

After the start of study medication, all subjects had office visits at Day 15 (Week 2), Day 43 (Week 6), Day 90 (Month 3), Day 180 (Month 6), Day 270 (Month 9), and Day 365 (Month 12). A visit variance of  $\pm 3$  days was allowed for the Week 2 and Week 6 study visits while subsequent study visits had an allowed visit variance of  $\pm 5$  days.

Seven hundred and fifty-six (756) subjects who met the eligibility criteria were randomized in a 1:1:1 ratio stratified by site to receive AR-13324 QD, (b)(4) BID, or timolol BID. Among these 756 subjects, four hundred and seventy-seven (477) had maximum baseline IOP < 25 mm Hg. The following two tables present the subject disposition for all randomized subjects, and the subgroup of subjects who had maximum baseline IOP < 25 mm Hg respectively.

**Study 302 Summary of Subject Disposition (Population: All Subjects)**

	<b>AR-13324 0.02% QD (N=251) n (%)</b>	<b>AR-13324 0.02% BID (N=254) n (%)</b>	<b>Timolol 0.5% BID (N=251) n (%)</b>	<b>Total (N=756) n (%)</b>
Number of Randomized Subjects	251	254	251	756
Analysis Populations				
Safety	251 (100.0)	253 (99.6)	251 (100.0)	755 (99.9)
Intent-to-Treat	251 (100.0)	253 (99.6)	251 (100.0)	755 (99.9)
Per Protocol	206 (82.1)	209 (82.3)	217 (86.5)	632 (83.6)
Study Completion				
Completed Month 3	205 (81.7)	153 (60.2)	237 (94.4)	595 (78.7)
Discontinued Prior to Month 3	46 (18.3)	101 (39.8)	14 (5.6)	161 (21.3)
Completed Month 12	146 (58.2)	86 (33.9)	204 (81.3)	436 (57.7)
Discontinued Prior to Month 12	105 (41.8)	168 (66.1)	47 (18.7)	320 (42.3)
Reason for Subject Discontinuation <sup>1</sup>				
Adverse Event	71 ( 67.6)	132 ( 78.6)	15 ( 31.9)	218 ( 68.1)
Withdrawal of Consent	9 ( 8.6)	13 ( 7.7)	9 ( 19.1)	31 ( 9.7)
Non-Compliant	3 ( 2.9)	1 ( 0.6)	3 ( 6.4)	7 ( 2.2)
Lost to Follow-Up	1 ( 1.0)	3 ( 1.8)	0	4 ( 1.3)
Lack of Efficacy	10 ( 9.5)	4 ( 2.4)	2 ( 4.3)	16 ( 5.0)
Disallowed Concurrent Medication	2 ( 1.9)	2 ( 1.2)	5 ( 10.6)	9 ( 2.8)
Investigator Decision	1 ( 1.0)	2 ( 1.2)	2 ( 4.3)	5 ( 1.6)
Protocol Violation	4 ( 3.8)	6 ( 3.6)	10 (21.3)	20 ( 6.3)
Death	2 ( 1.9)	0	0	2 ( 0.6)
Other	2 ( 1.9)	5 ( 3.0)	1 ( 2.1)	8 ( 2.5)

<sup>1</sup> Percentages are based on the total number of discontinuations.

Source: Table 7 of Study 302 Report.

**Study 302 Summary of Subject Disposition (Population: Randomized Population with Maximum Baseline IOP < 25 mmHg)**

	<b>AR-13324 0.02% QD (N=155) n (%)</b>	<b>AR-13324 0.02% BID (N=159) n (%)</b>	<b>Timolol 0.5% BID (N=163) n (%)</b>	<b>Total (N=477) n (%)</b>
Number of Randomized Subjects	155	159	163	477
Analysis Populations				
Safety	155 (100.0)	159 (100.0)	163 (100.0)	477 (100.0)
Intent-to-Treat	155 (100.0)	159 (100.0)	163 (100.0)	477 (100.0)
Per Protocol	129 (83.2)	132 (83.0)	142 (87.1)	403 (84.5)
Study Completion				
Completed Month 3	133 (85.8)	100 (62.9)	154 (94.5)	387 (81.1)
Discontinued Prior to Month 3	22 (14.2)	59 (37.1)	9 (5.5)	90 (18.9)
Completed Month 12	98 (63.2)	62 (39.0)	133 (81.6)	293 (61.4)
Discontinued Prior to Month 12	57 (36.8)	97 (61.0)	30 (18.4)	184 (38.6)
Reason for Subject Discontinuation <sup>1</sup>				
Adverse Event	43 ( 75.4)	77 ( 79.4)	12 ( 40.0)	132 ( 71.7)
Withdrawal of Consent	6 ( 10.5)	7 ( 7.2)	4 ( 13.3)	17 ( 9.2)
Non-Compliant	2 ( 3.5)	1 ( 1.0)	3 ( 10.0)	6 ( 3.3)
Lost to Follow-Up	0	2 ( 2.1)	0	2 ( 1.1)
Lack of Efficacy	2 ( 3.5)	0	1 ( 3.3)	3 ( 1.6)
Disallowed Concurrent Medication	0	1 ( 1.0)	2 ( 6.7)	3 ( 1.6)
Investigator Decision	1 ( 1.8)	2 ( 2.1)	0	3 ( 1.6)
Protocol Violation	2 ( 3.5)	5 ( 5.2)	8 (26.7)	15 ( 8.2)
Death	0	0	0	0
Other	1 ( 1.8)	2 ( 2.1)	0	3 ( 1.6)

<sup>1</sup> Percentages are based on the total number of discontinuations.

Source: Table 7 of Study 302 Report.

As presented above, for the primary efficacy analysis in subjects with maximum baseline IOP < 25 mmHg, the ITT population included 477 subjects and the PP population included 403 subjects.

Since this study tested two difference doses of AR-13324 vs. timolol, the primary analysis was conducted in a hierarchical fashion to preserve overall Type I error rate: first testing AR-13324 QD to timolol; if QD demonstrates clinical non-inferiority, secondarily testing AR-13324 BID to timolol.

Mean IOP at baseline (Visit 3) in the PP population with maximum baseline IOP < 25 mmHg (N = 403) was similar among the treatment groups at each observation time of 08:00, 10:00, and 16:00 hours, ranging from 20.4 to 22.5 mmHg and 20.6 to 22.6 mmHg in the AR-13324 QD and BID groups, respectively, and from 20.7 to 22.5 mmHg in the timolol group. Non-inferiority of AR-13324 QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between AR-13324 QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority. The upper 95% confidence limit for the differences in mean IOP between AR-13324 BID and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at all of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority.

**Study 302 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population with Baseline IOP < 25 mmHg)**

Day and Time	Mean IOP			QD vs. Timolol	BID vs. Timolol
	AR-13324 QD	AR-13324 BID	Timolol	Difference (95% CI)	Difference (95% CI)
<b>Baseline 08:00</b>	22.54	22.55	22.54		
<b>10:00</b>	21.29	21.27	21.27		
<b>16:00</b>	20.43	20.56	20.71		
<b>Day 15 08:00</b>	18.07	17.21	17.69	0.37 (-0.25, 0.99)	-0.48 (-1.19, 0.22)
<b>10:00</b>	16.72	16.35	16.93	-0.21 (-0.82, 0.41)	-0.57 (-1.24, 0.09)
<b>16:00</b>	16.68	15.65	16.83	-0.15 (-0.75, 0.46)	-1.18 (-1.82, -0.54)
<b>Day 43 08:00</b>	17.95	17.64	17.46	0.49 (-0.13, 1.12)	0.17 (-0.51, 0.86)
<b>10:00</b>	16.95	16.28	16.63	0.32 (-0.31, 0.95)	-0.34 (-1.02, 0.33)
<b>16:00</b>	17.00	15.75	16.60	0.40 (-0.22, 1.02)	-0.85 (-1.53, -0.17)
<b>Day 90 08:00</b>	18.24	17.58	17.47	0.77 (0.03, 1.50)	0.11 (-0.64, 0.86)
<b>10:00</b>	17.03	16.94	16.92	0.10 (-0.59, 0.80)	0.02 (-0.72, 0.77)
<b>16:00</b>	17.13	16.51	16.95	0.18 (-0.55, 0.91)	0.44 (-1.16, 0.27)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 QD and BID vs Timolol.

Source: Tables 13 and 14 of Study 302 Report.

For the overall population, the mean baseline IOP was in the range 21.6 to 23.5 mmHg and 21.5 to 23.5 mmHg for AR-13324 QD and BID, respectively, and 21.6 to 23.5 mmHg for timolol. AR-13324 dosed QD was not non-inferior to timolol dosed BID in the analysis of the overall population of PP subjects. The upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at 7 of 9 time points and within 1.0 mmHg at 3 of the 9 time points. Differences in mean IOP between AR-13324 QD and timolol for the 9 time points over the 3-month efficacy assessment ranged from -0.2 to 1.3 mmHg in the PP analyses. AR-13324 dosed BID was non-inferior to timolol dosed BID in analysis of all PP subjects. The

upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 7 of the 9 time points. Differences in mean IOP between AR-13324 BID and timolol for the 9 time points over the 3-month efficacy assessment ranged from -1.3 to 0.5 mmHg in the PP analyses.

**Study 302 Study Eye Intraocular Pressure (mmHg) by Visit (PP Population Based on All Enrolled Subjects)**

Day and Time	Mean IOP			QD vs. Timolol	BID vs. Timolol
	AR-13324 QD	AR-13324 BID	Timolol	Difference (95% CI)	Difference (95% CI)
<b>Baseline 08:00</b>	23.51	23.50	23.45		
<b>10:00</b>	22.31	22.26	22.18		
<b>16:00</b>	21.56	21.49	21.61		
<b>Day 15 08:00</b>	19.02	18.20	18.25	0.77 (0.22, 1.32)	-0.05 (-0.67, 0.56)
<b>10:00</b>	17.74	16.91	17.49	0.25 (-0.33, 0.82)	-0.58 (-1.17, 0.00)
<b>16:00</b>	17.37	16.28	17.59	-0.22 (-0.78, 0.34)	-1.31 (-1.89, -0.73)
<b>Day 43 08:00</b>	19.37	18.57	18.08	1.29 (0.66, 1.93)	0.49 (-0.11, 1.08)
<b>10:00</b>	18.11	17.09	17.31	0.80 (0.19, 1.41)	-0.22 (-0.82, 0.38)
<b>16:00</b>	17.88	16.58	17.25	0.63 (0.07, 1.19)	-0.67 (-1.28, -0.06)
<b>Day 90 08:00</b>	19.43	18.66	18.21	1.21 (0.54, 1.89)	0.45 (-0.24, 1.14)
<b>10:00</b>	18.18	17.81	17.52	0.66 (0.01, 1.31)	0.28 (-0.40, 0.97)
<b>16:00</b>	17.73	17.08	17.67	0.06 (-0.58, 0.70)	-0.59 (-1.25, 0.08)

Difference = AR-13324 - Timolol

Difference from Timolol and two-sided CIs are based on 2-sample t-tests comparing AR-13324 QD and BID vs Timolol.

Source: Tables 13 and 14 of Study 302 Report.

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YUNFAN DENG  
10/18/2016

YAN WANG  
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