

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208259Orig1s000**

**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 208259  
**Supplement #:** 0001  
**Drug Name:** Rocklatan™ (Netarsudil and Lantanoprost Ophthalmic Solution)  
0.02%/0.005%  
**Indication(s):** For the reduction of elevated intraocular pressure (IOP) in patients with  
open angle glaucoma or ocular hypertension  
**Applicant:** Aerie Pharmaceuticals  
**Date(s):** Submitted: 05/14/2018  
Review Completion Goal Date: 02/01/2019  
PDUFA Goal date: 03/14/2019  
**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  
**Keywords:** elevated intraocular pressure (IOP), fixed combination product, superiority

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## 1 EXECUTIVE SUMMARY

This NDA seeks approval of Rocklatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% dosed once daily (QD) 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.

Rocklatan (also referred to as PG324 throughout this review) is a fixed dose combination (FDC) ophthalmic solution of netarsudil 0.02% and latanoprost 0.005%. Rhopressa® (netarsudil ophthalmic solution) 0.02% was approved by FDA under NDA 208254 for reducing elevated IOP in patients with OAG or OHT in December 2017. Latanoprost ophthalmic solution 0.005%, is a prostaglandin F2 $\alpha$  analogue indicated for the reduction of elevated IOP in patients with OAG or OHT and was initially approved for marketing as Xalatan® by FDA in 1996 and is available as a generic medicine now.

The efficacy of Rocklatan was evaluated in two pivotal Phase 3 clinical trials: PG324-CS301 (referred to as Study 301), a 3-month efficacy and 12-month safety study; and PG324-CS302 (referred to as Study 302), a 3-month efficacy and safety study. Study 301 was a 12-month study with the first 3-month having the same design as study 302 for efficacy evaluation and followed by an additional 9-month treatment period mainly for safety evaluation purpose. Both studies were double-masked, randomized, multicenter, active-controlled, parallel-group safety and efficacy trial in adult subjects with open angle glaucoma or ocular hypertension, evaluating the ocular hypotensive efficacy of PG324 compared to each of its active components, netarsudil 0.02%, and latanoprost 0.005%.

The primary efficacy endpoint was the mean IOP in the study eye at 8am, 10am, and 4pm at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. The mean IOP change from baseline at each of those post-baseline time points was a secondary efficacy endpoint.

Both studies had significantly higher discontinuation rates prior to Month 3 due to adverse events (AE) in the netarsudil containing groups (PG324 and netarsudil groups) compared to the latanoprost group: 10% vs. 0% in Study 301 and 6.4% vs. 2% in Study 302 (Table 1). In Study 301, the overall discontinuation rates were 16.7% in the netarsudil containing groups and 5.5% in the latanoprost group. In Study 302, the overall discontinuation rates were 10% in the netarsudil containing groups and 5.6% in the latanoprost group. In Study 301, the proportion of patients who discontinued the study due to adverse events prior to 12 months was 20% in the netarsudil containing groups and 2% in the latanoprost group.

Overall, both studies demonstrated statistically significantly higher mean IOP reductions in the PG324 group compared with its two components at the nine post-baseline time points. As shown in Table 2, in Study 301, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.1 to 9.1 mmHg in the PG324 group, 4.9 to 6.1 mmHg in the netarsudil group, and 5.4 to 6.9 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.2 mmHg to -2.0 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.6 mmHg to -1.3 mmHg.

In Study 302, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.0 to 8.7 mmHg in the PG324 group, 4.6 to 5.4 mmHg in the netarsudil group, and 5.5 to 6.8 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.6 mmHg to -2.2 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.4 to -1.5 mmHg.

In conclusion, the two pivotal studies demonstrated that Rocklatan was efficacious in reducing elevated intraocular pressure; the studies also demonstrated superiority of Rocklatan compared to its two active components: netarsudil and latanoprost. Therefore, the statistical reviewer recommends the approval of Rocklatan for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

**Table 1: Summary of Subjects Disposition (Studies 301 and 302)**

	PG324 n (%)	Netarsudil n (%)	PG324 & Netarsudil n (%)	Latanoprost n (%)
<b>Study 301</b>				
<b>ITT</b>	238	244	482	236
<b>Completed Month 3</b>	201 (84.5)	201 (84.4)	434 (83.3)	223 (94.5)
<b>Discontinued Prior to Month 3</b>	37 (15.5)	43 (17.6)	80 (16.6)	13 (5.5)
Discontinued Prior to Month 3 Due to AE	25 (10.5)	23 (9.4)	48 (10.0)	0
<b>Completed Month 12</b>	159 (66.8)	148 (60.7)	307 (63.7)	203 (86.0)
<b>Discontinued Prior to Month 12</b>	79 (33.2)	96 (39.3)	175 (36.3)	33 (14.0)
Discontinued Prior to Month 12 Due to AE	47 (19.7)	53 (21.7)	100 (20.7)	4 (1.7)
<b>Study 302</b>				
<b>ITT</b>	245	255	500	250
<b>Completed Month 3</b>	221 (90.2)	228 (89.4)	449 (89.8)	236 (94.4)
<b>Discontinued Prior to Month 3</b>	24 (9.8)	27 (10.6)	51 (10.2)	14 (5.6)
Discontinued Prior to Month 3 Due to AE	17 (6.9)	15 (5.9)	32 (6.4)	5 (2.0)

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

**Table 2: Studies 301 and 302 Mean IOP and Mean IOP Change from Baseline by Visit and Time (Based on Observed Data)**

	PG324			Netarsudil			Latanoprost			PG324 vs. Netarsudil Differences (95% CI*) <sup>1</sup>	PG324 vs. Latanoprost Differences (95% CI*) <sup>1</sup>
	N	IOP	Ch*	N	IOP	Ch*	N	IOP	Ch*		
<b>Study 301</b>											
<b>Baseline</b>											
<b>8am</b>	238	24.8	n/a	244	24.8	n/a	236	24.6	n/a	0.0 (-0.6, 0.6)	0.3 (-0.3, 0.8)
<b>10am</b>	238	23.7	n/a	244	23.5	n/a	236	23.4	n/a	0.3 (-0.4, 0.9)	0.3 (-0.3, 0.9)
<b>4pm</b>	238	22.6	n/a	244	22.6	n/a	236	22.4	n/a	-0.0 (-0.7, 0.6)	0.2 (-0.5, 0.8)
<b>Day 15</b>											
<b>8am</b>	231	15.6	-9.1	241	18.6	-6.1	234	17.8	-6.9	-3.0 (-3.6, -2.5)	-2.3 (-2.8, -1.7)
<b>10am</b>	232	14.9	-8.7	236	17.9	-5.7	232	17.4	-6.1	-3.0 (-3.6, -2.4)	-2.6 (-3.2, -2.0)
<b>4pm</b>	231	14.8	-7.7	237	17.2	-5.3	231	17.2	-5.4	-2.4 (-3.0, -1.9)	-2.3 (-2.9, -1.8)

<b>Day 43</b>											
<b>8am</b>	221	16.0	-8.9	227	19.1	-5.6	226	17.7	-7.1	-3.2 (-3.8, -2.6)	-1.7 (-2.4, -1.1)
<b>10am</b>	217	15.2	-8.3	223	18.1	-5.5	225	17.1	-6.5	-2.8 (-3.5, -2.3)	-1.9 (-2.5, -1.2)
<b>4pm</b>	216	15.3	-7.2	223	17.6	-4.9	225	17.0	-5.5	-2.3 (-2.8, -1.7)	-1.7 (-2.2, -1.1)
<b>Day 90</b>											
<b>8am</b>	204	16.1	-8.6	205	19.3	-5.5	223	17.6	-7.2	-3.1 (-3.8, -2.5)	-1.5 (-2.1, -0.9)
<b>10am</b>	200	15.2	-8.3	200	18.4	-5.2	223	16.9	-6.7	-3.2 (-3.8, -2.5)	-1.7 (-2.3, -1.1)
<b>4pm</b>	200	15.4	-7.1	198	17.4	-5.1	223	16.7	-5.9	-2.0 (-2.6, -1.4)	-1.3 (-1.9, -0.7)
<b>Study 302</b>	<b>N</b>	<b>IOP</b>	<b>Ch*</b>	<b>N</b>	<b>IOP</b>	<b>Ch*</b>	<b>N</b>	<b>IOP</b>	<b>Ch*</b>		
<b>Baseline</b>											
<b>8am</b>	245	24.7	n/a	255	24.7	n/a	250	24.8	n/a	0.0 (-0.5, 0.6)	-0.1 (-0.6, 0.5)
<b>10am</b>	245	23.3	n/a	255	23.4	n/a	250	23.2	n/a	-0.1 (-0.7, 0.5)	0.1 (-0.5, 0.7)
<b>4pm</b>	245	22.4	n/a	255	22.8	n/a	250	22.6	n/a	-0.4 (-1.0, 0.2)	-0.2 (-0.8, 0.4)
<b>Day 15</b>											
<b>8am</b>	238	16.1	-8.7	252	19.4	-5.3	246	18.1	-6.6	-3.4 (-3.9, -2.8)	-2.0 (-2.6, -1.5)
<b>10am</b>	236	15.3	-8.1	249	18.0	-5.4	247	17.7	-5.7	-2.7 (-3.2, -2.2)	-2.4 (-2.9, -1.9)
<b>4pm</b>	235	15.2	-7.3	248	17.5	-5.1	247	17.1	-5.5	-2.2 (-2.8, -1.7)	-1.9 (-2.4, -1.3)
<b>Day 43</b>											
<b>8am</b>	234	16.4	-8.3	248	19.6	-5.2	242	17.9	-6.8	-3.2 (-3.8, -2.6)	-1.5 (-2.1, -0.9)
<b>10am</b>	233	15.5	-7.8	247	18.4	-5.0	242	17.4	-6.0	-2.9 (-3.4, -2.3)	-1.9 (-2.4, -1.3)
<b>4pm</b>	232	15.5	-7.1	247	17.9	-4.7	241	17.1	-5.5	-2.3 (-2.9, -1.8)	-1.6 (-2.1, -1.0)
<b>Day 90</b>											
<b>8am</b>	223	16.4	-8.3	231	20.0	-4.7	236	17.9	-6.8	-3.6 (-4.2, -3.0)	-1.5 (-2.2, -0.9)
<b>10am</b>	222	15.6	-7.8	228	18.4	-5.0	236	17.5	-5.8	-2.8 (-3.4, -2.3)	-2.0 (-2.5, -1.4)
<b>4pm</b>	221	15.6	-7.0	228	18.0	-4.6	236	17.1	-5.5	-2.4 (-2.9, -1.9)	-1.5 (-2.1, -1.0)

Ch\* = Change in IOP from baseline. CI = Confidence Interval.

<sup>1</sup> The treatment differences and two-sided CIs for comparing PG324 vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.2 of Study 301 Report and Table 14.2.1.1.2 of Study 302 Report for IOP; Statistical Reviewer's analyses for the mean IOP change from baseline.

## 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.

The investigational product PG324 is a fixed dose combination of netarsudil 0.02% and latanoprost 0.005% ophthalmic solutions and is being developed to treat elevated IOP in adult patients with OAG or OHT. The applicant previously developed netarsudil, a Rho kinase inhibitor, which showed in non-inferiority studies to reduce IOP. Rhopressa® (netarsudil ophthalmic solution) 0.02% was approved by FDA under NDA 208254 for reducing elevated IOP in patients with OAG or OHT in December 2017. Latanoprost ophthalmic solution 0.005%, is a prostaglandin F2 $\alpha$  analogue indicated for the reduction of elevated IOP in patients with OAG or OHT and was initially approved for marketing as Xalatan® by FDA in 1996 (NDA 020597) and now available as generic medicine.

### 2.1.2 History of Drug Development

The applicant conducted all clinical studies for PG324 under IND 113064. The applicant submitted the end-of-phase 2 meeting briefing package on February 20, 2015 (located at [\cdsesub4\NONECTD\IND113064\5753436](#)) that included an outline for Studies 301 and 302. In the outline, the applicant proposed the following statistical analysis methods, indicating that the mean changes from baseline IOP at the 9 post-baseline time points were considered as the primary efficacy endpoint:

**Statistical Methods:**  
 The primary analysis of the primary outcome will employ a linear model with change from baseline 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 intent to treat population with multiple imputation techniques used to impute missing data. The least squares mean differences (test – control) between PG324 Ophthalmic Solution and each of latanoprost Ophthalmic Solution, 0.005% and AR-13324 Ophthalmic Solution, 0.02% will be presented as well as 2-sided p-values and 95% confidence intervals. Inference will be made on the p-value < 0.05 and the point estimate < 0 for all time points at the Week 2, Week 6, and Month 3 Visits. Additionally, the point estimate must be <-1 mm Hg for a majority of the time points and visits.

Although the statistical review team had no objection to the applicant’s proposal, the clinical review team recommended that the mean IOP at the post-baseline time points be used as the primary efficacy endpoint.

### 2.1.3 Studies Reviewed

The efficacy of PG324 was evaluated in two pivotal Phase 3 clinical trials: Studies 301 and 302. Both studies had 3 treatment arms (netarsudil/latanoprost 0.02%/0.005% QD [PG324], netarsudil 0.02% QD, and latanoprost 0.005% QD).

**Table 3: Summary of Efficacy Studies to be assessed in the Statistical Review**

Study No	Design	Objective	Treatment Groups Randomized/Completed	Study Population
PG324-CS301	Multi-center, randomized,	to evaluate the ocular hypotensive efficacy of netarsudil/latanoprost QD	Netarsudil/latanoprost ophthalmic solution QD / 238	Adult subjects with OAG or

	double-masked, parallel group, active-control 3-arm	relative to each of its active components, netarsudil 0.02% QD, and latanoprost 0.005% QD in patients with elevated intraocular pressure over a 3-month period, and to evaluate the ocular and systemic safety of netarsudil/latanoprost over a 12-month period.	Netarsudil ophthalmic solution 0.02% QD / 244 Latanoprost ophthalmic solution 0.005% QD / 236	OHT in both eyes
PG324-CS302	Multi-center, randomized, double-masked, parallel group, active-control 3-arm	to evaluate the ocular hypotensive efficacy of netarsudil/latanoprost QD relative to each of its active components, netarsudil 0.02% QD, and latanoprost 0.005% QD in patients with elevated intraocular pressure over 3-month period	Netarsudil/latanoprost ophthalmic solution QD / 245 Netarsudil ophthalmic solution 0.02% QD / 255 Latanoprost ophthalmic solution 0.005% QD / 250	Adult subjects with 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, and 302. The study reports are available at the following locations:

<\\CDSESUB1\evsprod\NDA208259\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\pg324-cs301>

<\\CDSESUB1\evsprod\NDA208259\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\multiple-ophthalmic-use\5351-stud-rep-contr\pg324-cs302>

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

<\\CDSESUB1\evsprod\NDA208259\0001\m5\datasets\pg324-cs301>

<\\CDSESUB1\evsprod\NDA208259\0001\m5\datasets\pg324-cs302>

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

<\\CDSESUB1\evsprod\NDA208259\0001\m5\datasets\pg324-cs301\analysis\adam\programs>

<\\CDSESUB1\evsprod\NDA208259\0001\m5\datasets\pg324-cs302\analysis\adam\programs>

The IOP assessments were included in the "adefl1.xpt" dataset with variable names "AVAL" for IOP readings and "CHG" for IOP change from baseline. The treatment variable, given both as numeric (TRTPN) and character (TRTP), was also included in the "adefl1.xpt" dataset. 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 two pivotal studies were submitted.

#### 3.2 Evaluation of Efficacy

##### 3.2.1 Study Design and Endpoints

The two pivotal efficacy studies 301 and 302 were the same in design except for study duration: 12 months in Study 301 and 3 months in Study 302. Both studies were double-masked, randomized, multi-center, active controlled, parallel-group studies to evaluate the ocular hypotensive efficacy of PG324 once daily (QD) relative to each of its active components, netarsudil 0.02% QD, and latanoprost 0.005% QD over a 3-month period. For Study 301, it was also designed to evaluate the ocular and systemic safety of netarsudil/latanoprost over a 12-month period. Study 301 was conducted in the United States (56 sites) and Study 302 was conducted in the United States (54 sites enrolled 732 subjects) and Canada (6 sites enrolled 18 subjects).

Both studies enrolled adult 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 depending on different medication class as presented in the following table.

**Table 4: Ocular Hypertensive Medication Washout Period**

Medication Class	Minimum Washout Period
Prostaglandins	4 weeks
$\beta$ -adrenoceptor antagonists	4 weeks
Adrenergic agonists (including $\alpha$ -agonists such as brimonidine and apraclonidine)	2 weeks
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. Both eyes must qualify at all qualification visit time points. Please also see Appendix 1 for key inclusion and exclusion criteria.

**Table 5: IOP Entry Criteria (Studies 301, and 302)**

Study	Qual. 1	Qual. 2	Eye
301	>20 and < 36 mmHg at 8am both eyes	>20 and < 36 mmHg at 8am >17 and < 36 mmHg at 10am >17 and < 36 mmHg at 4pm	Both eyes
302	>20 and < 36 mmHg at 8am both eyes	>20 and < 36 mmHg at 8am >17 and < 36 mmHg at 10am >17 and < 36 mmHg at 4pm	Both eyes

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 PG324-CS301; and Protocol for PG324-CS302.

At Day 1, qualified subjects were randomized in a 1:1:1 ratio to one of the three treatment group (stratified by investigative site and by maximum baseline IOP [ $< 25$  mmHg vs  $\geq 25$  mmHg]). Subjects were instructed to self-administer their masked study medication to both eyes at home between 20:00-22:00 hours (8pm – 10pm) once daily during the treatment period (12 months in Study 301 and 3 months in Study 302).

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 301, subjects also had office visits at Day 180 (Month 6), Day 270 (Month 9), Day 365 (Month 12), and optional post-treatment visits at Day 395 (Month 13) and Day 425 (Month 14). For both studies, a visit variance of  $\pm 3$  days was allowed for the Week 2, Week 6, and Month 3 study visits while subsequent study visits had an allowed visit variance of  $\pm 7$  days. The study visits, efficacy assessment time points, and overall study duration of the two trials are presented in the following table. Please also refer to Appendix 1 for the schedule of assessments for both studies.

**Table 6: Study Duration and Visits (Studies 301, and 302)**

Study	Screening	Efficacy Assessment up to Month 3	Efficacy Assessment After Month 3
301	Qual. 1 (8am) Qual. 2 (8am, 10am, 4pm)	Day 15 (8am, 10am, 4pm) Day 43 (8am, 10am, 4pm) Day 90 (8am, 10am, 4pm)	Month 6 (8am, 10am, 4pm) Month 9 (8am, 10am, 4pm) Month 12 (8am, 10am, 4pm) Month 13 (optional) Month 14 (optional)
302	Qual. 1 (8am) Qual. 2 (8am, 10am, 4pm)	Day 15 (8am, 10am, 4pm) Day 43 (8am, 10am, 4pm) Day 90 (8am, 10am, 4pm)	Not Applicable

Qual. 1 = Qualification Visit 1; Qual. 2 = Qualification Visit 2;  
Source: Protocol for PG324-CS301; and Protocol for PG324-CS302.

For both studies, the primary efficacy endpoint was the mean IOP in the study eye at 8am, 10am, and 4pm at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits. The study eye was the eye with the higher IOP at 8am on Visit 3. If both eyes have the same IOP at 8am on Visit 3, then the right eye was the study eye.

The following secondary endpoints were listed in the applicant’s statistical analysis plan (SAP):

- Mean IOP within a treatment group at each post-treatment time point
- Mean diurnal IOP within a treatment group at each post-treatment visit
- Mean change from diurnally adjusted baseline IOP at each post-treatment time point

- Mean change from baseline in diurnal IOP at each post-treatment visit
- Mean percent change from diurnally adjusted baseline IOP at each post-treatment time point
- Mean percent change from baseline in diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified mean, mean change, and percent mean change diurnal IOP levels at each post-treatment time point:
  - Diurnal mean IOP of  $\leq 22, \leq 21, \leq 20, \leq 19, \leq 18, \leq 17, \leq 16, \leq 15, \leq 14$
  - IOP reduction from baseline of  $\geq 2, \geq 4, \geq 6, \geq 8, \geq 10, \geq 12$  (IOP reduction at a visit from baseline was calculated as  $\text{IOP} [\text{baseline}] - \text{IOP} [\text{visit}]$ , using mean [integral or non-integral] IOP values)
  - IOP percent reduction from baseline of  $\geq 5, \geq 10, \geq 15, \geq 20, \geq 25, \geq 30, \geq 35, \geq 40$  (IOP percent reduction at a visit from baseline was calculated as  $[\text{IOP reduction from baseline} / \text{IOP (baseline)}] * 100\%$ )

The sample size estimations of both studies were based on the following assumptions:

- 0.05 two-sided level of significance at each of the 9 time points
- Independent among time points
- Standard deviation of 3.5 mmHg
- Treatment difference between PG324 and latanoprost is 1.5 mmHg
- Treatment difference between PG324 and Netarsudil is 2.0 mmHg
- 90% power to conclude statistical superiority of PG324 to latanoprost
- 99% power to conclude statistical superiority of PG324 to Netarsudil

Based on the above assumption, the estimated sample size was approximately 196 subjects per arm.

### 3.2.2 Statistical Methodologies

The applicant-defined primary hypotheses for both studies were:

- H01: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with latanoprost Ophthalmic Solution 0.005% (PG324 - latanoprost), in mean IOP at the following time points: 8am, 10am, and 4pm at the Week 2, Week 6, and Month 3 Visits, is  $\geq 0$  mmHg for at least one time point over all visits  
VS.  
H11: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with latanoprost Ophthalmic Solution 0.005% (PG324 - latanoprost), in mean IOP at the following- time points: 8am, 10am, and 4pm at the Week 2, Week 6, and Month 3 Visits, is  $< 0$  mmHg for all time points over all visits.
- H02: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with Netarsudil Ophthalmic Solution 0.02% (PG324 - Netarsudil), in mean IOP at the following time points: 8am, 10am, and 4pm at the Week 2, Week 6, and Month 3 Visits, is  $\geq 0$  mmHg for at least one time point over all visits  
VS.  
H12: The difference between study eyes treated with PG324 Ophthalmic Solution and study eyes treated with Netarsudil Ophthalmic Solution 0.02% (PG324 - Netarsudil), in mean

IOP at the following time points: 8am, 10am, and 4pm at the Week 2, Week 6, and Month 3 Visits, is  $< 0$  mmHg for all time points over all visits.

A study would be considered a success if both  $H_{01}$  and  $H_{02}$  are rejected.

For both studies, four analysis populations (also known as analysis sets) were defined:

- **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 the primary efficacy analyses of both studies were based on the ITT population.
- **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 PP population was the secondary population for efficacy analyses.
- **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 applicant-proposed primary analysis was based on the analysis of covariance (ANCOVA) model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (8am, 10am, and 4pm) as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the ITT population with multiple imputation (MI) techniques (Monte Carlo Markov Chain [MCMC]) to impute missing data. Please refer to Appendix 2 for the SAS program codes that the applicant used to implement the MCMC MI. Each time point within each visit was modeled separately. The least squares (LS) mean differences (test – control) between PG324 Ophthalmic Solution and each of Latanoprost Ophthalmic Solution, 0.005% and Netarsudil Ophthalmic Solution, 0.02% were presented as well as 2-sided p-values and 95% confidence intervals. For a given comparator (latanoprost and netarsudil), if the p-value is  $P < 0.05$  and the point estimate  $< 0$  for all time points at the Week 2, Week 6, and Month 3 Visits, then the corresponding null hypothesis were rejected in favor of the alternative hypothesis and PG324 were considered superior to the comparator.

To evaluate the robustness of the primary analysis results, the applicant conducted various supportive analyses of the primary efficacy variables, including different imputation methods for missing data:

- Last observation carried forward (LOCF) for missing observations
- Baseline observation carried forward (BOCF) for missing observations
- Observed data only

and using different analysis models:

- Individual two-sample t-test and corresponding 95% confidence intervals for each comparison (PG324 vs latanoprost and vs Netarsudil) at each time point (8am, 10am, and 4pm at the Week 2, Week 6, and Month 3 Visits) using the ITT 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 mean IOP change from baseline by the applicant. In the SAP, the applicant stated that they didn't conduct the ANCOVA analysis for the mean change from baseline IOP because inference will be identical when the primary endpoint and the endpoint of mean change from baseline IOP are analyzed using this ANCOVA model. The statistical reviewer performed this ANCOVA analysis to obtain the estimated mean change from baseline IOP at each post-baseline time point for each treatment group. The following table summarized the different analyses approaches conducted.

**Table 7: Summary of Analysis Methods Conducted**

	Two-Sample t-test <sup>1</sup>	ANCOVA <sup>2</sup>	MMRM <sup>3</sup>	Missing Data Imputation
<b>Primary Analysis for the Primary Endpoint</b>		X		MCMC
<b>Supportive Analyses for the Primary Endpoint</b>				
Mean IOP at each time point at Week 2, Week 6, and Month 3		X		LOCF, BOCF, Observed
			X	Observed
	X			MCMC, Observed, LOCF, BOCF
<b>Secondary Endpoint</b>				
Mean change from diurnally adjusted baseline IOP at each post-treatment time point	X	X*	X	MCMC, Observed, LOCF, BOCF

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

<sup>1</sup> Two-sample t-test comparing actual mean IOP value at each time point between netarsudil/latanoprost and each of its active comparator (latanoprost and netarsudil)

<sup>2</sup> ANCOVA model including treatment as the main effect and baseline as covariate. Individual models were fit for each visit and time point.

<sup>3</sup> Mixed Model Repeated Measures analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment\*visit, treatment\*time point, visit\*time point, and treatment\*visit\*time point as model terms. Repeated measures were used to account for the correlation among measures within a subject. The model included all post-dose visits and time points.

\* Analyses conducted by the statistical reviewer.

**Review Team's Comment:**

In the primary analysis, the applicant considered all patients who discontinued the study prior to 3 months as having missing data after discontinuation. The applicant imputed the missing data at a given time point by using the observed data from the patients who were still on their study treatment. We find this imputation approach problematic for the patients who discontinued study due to netarsudil-induced adverse events. These patients undoubtedly could no longer benefit from their discontinued study drug at 3 months. However, as presented in Table 8, their imputed values at 3 months showed an IOP reduction ranging from 5 to 9 mm Hg, indicating that these patients would still benefit significantly from their discontinued study drug. Therefore, we found these imputed values to be unreasonable. (b) (4)

As a supportive analysis, the applicant conducted the analysis of observed data only. The applicant’s analysis of the observed data is an example of “while on treatment strategy” discussed in the ICH E9(R1) Addendum “Estimands and Sensitivity Analysis in Clinical Trials” ([https://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E9/E9-R1EWG\\_Step2\\_Guideline\\_2017\\_0616.pdf](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf)). We find this analysis acceptable as the majority of the dropouts were due to toxicity and no dropout was due to lack of efficacy in the PG324 group for both studies (see Table 9 and Table 12). Thus, we recommend presenting the results of this analysis along with information pertaining to the percentages of dropouts due to toxicity in the labeling, (b) (4). Therefore, in the following sections, we focused on the results of the analysis based on the observed data. Of note, the conclusions from both the primary and supportive analyses are the same.

**Table 8: Imputed IOP Change from Baseline (mm Hg) for Subjects Discontinued Due to AE in PG324 Group Based on MCMC MI (5 Imputations)**

		IOP Change from Baseline (mmHg) for PG324 Group				
		Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5
<b>Study 301</b>						
<b>Day 90</b>	<b>8am</b>	-8.6	-6.6	-7.6	-8.1	-8.8
	<b>10am</b>	-7.1	-8.1	-7.1	-7.9	-8.0
	<b>4pm</b>	-6.5	-7.1	-5.8	-6.3	-7.1
<b>Study 302</b>						
<b>Day 90</b>	<b>8am</b>	-7.0	-7.2	-8.7	-6.4	-8.0
	<b>10am</b>	-6.9	-5.5	-6.4	-6.4	-6.8
	<b>4pm</b>	-6.7	-6.7	-6.7	-6.4	-5.2

Source: Statistical Reviewer’s Analysis.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

#### 3.2.3.1 Study 301

Seven hundred and eighteen (718) subjects were randomized into the study, including 238 in the PG324 group, 244 in the Netarsudil group, and 236 in the Latanoprost group. A total of ninety-three (93, 13.0%) subjects discontinued the study prior to Month 3; and 208 (29.0%) subjects discontinued the study prior to Month 12. More subjects in both PG324 and netarsudil arms discontinued the 12-month study early (79 [33.2%] for PG324, and 96 [39.2%] for Netarsudil) than subjects in latanoprost group (33 [14.0%]). The most frequent reason for discontinuation was adverse event (AE); and much more subjects in both netarsudil-containing arms (PG324 and netarsudil along) discontinued the study treatment due to AEs than subjects in the latanoprost arm. By Month 12, there were 47 subjects (19.7%) discontinued the study due to AEs in the PG324 arm; 53 (21.7%) in the netarsudil arm discontinued the study due to AEs; and 4 (1.7%) in latanoprost group.

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

	PG324 n (%)	Netarsudil n (%)	Latanoprost n (%)	Overall n (%)
<b>Number of Subjects Randomized</b>	238	244	236	718

<b>Study Completion</b>				
Completed Month 3	201 (84.5)	201 (84.4)	223 (94.5)	625 (87.0)
Discontinued Prior to Month 3	37 (15.5)	43 (17.6)	13 (5.5)	93 (13.0)
Completed Month 12	159 (66.8)	148 (60.7)	203 (86.0)	510 (71.0)
Discontinued Prior to Month 12	79 (33.2)	96 (39.3)	33 (14.0)	208 (29.0)
<b>Discontinued Prior to Month 3</b>	37 (15.5)	43 (17.6)	13 (5.5)	93 (13.0)
<b>Reasons for Early Discontinuation</b>				
Adverse Event	25 (10.5)	23 (9.4)	0	48 (6.7)
Withdrawal of Consents	4 (1.7)	4 (1.6)	4 (1.7)	12 (1.7)
Non-Compliant	0	1 (0.4)	1 (0.4)	2 (0.3)
Lost to Follow-up	1 (0.4)	3 (1.2)	1 (0.4)	5 (0.7)
Lack of efficacy	0	5 (2.0)	1 (0.4)	6 (0.8)
Disallowed Concurrent Medication	1 (0.4)	4 (1.6)	2 (0.8)	7 (1.0)
Investigator Decision	2 (0.8)	0	0	2 (0.3)
Protocol Violation	4 (1.7)	1 (0.4)	4 (1.7)	9 (1.3)
Death	0	0	0	0
Other	0	2 (0.8)	0	2 (0.3)
<b>Discontinued Prior to Month 12</b>	79 (33.2)	96 (39.3)	33 (14.0)	208 (29.0)
<b>Reasons for Early Discontinuation</b>				
Adverse Event	47 (19.7)	53 (21.7)	4 (1.7)	104 (14.5)
Withdrawal of Consents	13 (5.5)	9 (3.7)	8 (3.4)	30 (4.2)
Non-Compliant	0	1 (0.4)	3 (1.3)	4 (0.6)
Lost to Follow-up	5 (2.1)	5 (2.0)	4 (1.7)	14 (1.9)
Lack of efficacy	0	13 (5.3)	1 (0.4)	14 (1.9)
Disallowed Concurrent Medication	6 (2.5)	7 (2.9)	5 (2.1)	18 (2.5)
Investigator Decision	2 (0.8)	2 (0.8)	0	4 (0.6)
Protocol Violation	6 (2.5)	3 (1.2)	8 (3.4)	17 (2.4)
Death	0	1 (0.4)	0	1 (0.1)
Other	0	2 (0.8)	0	2 (0.3)

Source: Table 5 of Study 301 Report.

All 718 randomized subjects were included in both the safety and the ITT population. Subject (b) (6) was randomized to PG324 group but received netarsudil; Subject (b) (6) was randomized to netarsudil group but received PG324; and Subject (b) (6) was randomized to netarsudil but received latanoprost. Therefore, one less subject is in the netarsudil group and one additional subject is in the latanoprost group in the Safety population. The PP population had 593 subjects (82.6%).

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

	<b>PG324 n (%)</b>	<b>Netarsudil n (%)</b>	<b>Latanoprost n (%)</b>	<b>Overall n (%)</b>
<b>Safety</b>	238 (100)	243 (99.6)	237 (100.4)	718 (100.0)
<b>ITT</b>	238 (100)	244 (100)	236 (100)	718 (100.0)
<b>PP</b>	195 (81.9)	203 (83.2)	195 (82.6)	593 (82.6)

Source: Table 5 of Study 301 Report.

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

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

Characteristics	PG324	Netarsudil	Latanoprost	Overall
	N=238	N=244	N=236	N=718
	n (%)	n (%)	n (%)	n (%)
<b>Study Eye Diagnosis</b>				
Ocular Hypertension (OHT)	65 (27.3)	57 (23.4)	55 (23.3)	177 (24.7)
Open Angle Glaucoma (OAG)	173 (72.7)	187 (76.6)	181 (76.7)	541 (75.3)
<b>Gender</b>				
Male	104 (43.7)	108 (44.3)	100 (42.4)	312 (43.5)
Female	134 (56.3)	136 (55.7)	136 (57.6)	406 (56.5)
<b>Age</b>				
Mean (Std)	64.6 (11.3)	64.6 (11.0)	65.4 (11.0)	64.8 (11.1)
Min, Max	18, 88	27, 91	22, 89	18, 91
Median	65.0	66.0	67.0	66.0
< 65	109 (45.8)	107 (43.9)	95 (40.3)	311 (43.4)
≥ 65	129 (54.2)	137 (56.1)	141 (59.7)	407 (56.7)
<b>Race</b>				
Asian	7 (2.9)	6 (2.5)	10 (4.2)	23 (3.2)
Black/African American	69 (29.0)	70 (28.7)	67 (28.4)	206 (28.7)
White	162 (68.1)	167 (68.4)	157 (66.5)	486 (67.7)
Other	0	1 (0.4)	2 (0.8)	3 (0.4)
<b>Ethnicity</b>				
Hispanic or Latino	30 (12.6)	32 (13.1)	30 (12.7)	92 (12.8)
Non-Hispanic or Latino	20.8 (87.4)	212 (86.9)	206 (87.3)	626 (87.2)
<b>Iris Color of Study Eye</b>				
Blue/Grey/Green	68 (28.6)	73 (29.9)	62 (26.3)	203 (28.3)
Brown/Black	141 (59.2)	137 (56.1)	154 (65.3)	432 (60.2)
Hazel	29 (12.2)	34 (13.9)	20 (8.5)	83 (11.6)
Other	0	0	0	0
<b>Time Since Current Diagnosis (weeks)</b>				
Mean (Std)	403.6 (451.3)	335.4 (349.3)	336.2 (356.8)	358.3 (389.2)
Min, Max	1, 2912	1, 2128	1, 1628	1, 2912
Median	238.0	211.0	200.0	211.0
<b>Prior Hypotensive Therapy</b>				
Combination Therapy	31 (13.0)	30 (12.3)	23 (9.7)	84 (11.7)
Prostaglandins (Monotherapy)	134 (56.3)	144 (59.0)	125 (53.0)	403 (56.1)
Other (Monotherapy)	19 (8.0)	12 (4.9)	19 (8.1)	50 (7.0)
No Prior Therapy	54 (22.7)	58 (23.8)	69 (29.2)	181 (25.2)
<b>Prior Hypotensive Therapy</b>				
Prior Prostaglandin Therapy	162 (68.1)	171 (70.1)	144 (61.0)	477 (66.4)
No Prior Prostaglandin Therapy	76 (31.9)	73 (29.9)	92 (39.0)	241 (33.6)

Source: Tables 6 of Study 301 report.

### 3.2.3.2 Study 302

Seven hundred and fifty (750) subjects were randomized into the study, including 245 in the PG324 group, 255 in the Netarsudil group, and 250 in the Latanoprost group. Sixty-five (65, 8.7%) subjects discontinued the study prior to Month 3. More subjects in both netarsudil-containing arms (PG324 and netarsudil) discontinued the 3-month study early (24 [9.8%] for PG324, and 27 [10.6%] for Netarsudil) than subjects in latanoprost group (14 [5.6%]). The most frequent reason for discontinuation was AE; and much more subjects in both netarsudil-containing arms (PG324 and netarsudil along) discontinued the study treatment due to AE than subjects in the latanoprost arm. By Month 3, there were 17 (6.9%) subjects in the PG324 group discontinued the study due to AEs; 15 (5.9%) in the netarsudil group discontinued the study due to AEs; and 5 (2.0%) in the latanoprost group.

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

	<b>PG324 n (%)</b>	<b>Netarsudil n (%)</b>	<b>Latanoprost n (%)</b>	<b>Overall n (%)</b>
<b>Number of Subjects Randomized</b>	245	255	250	750
<b>Study Completion</b>				
Completed Month 3	221 (90.2)	228 (89.4)	236 (94.4)	685 (91.3)
Discontinued Prior to Month 3	24 (9.8)	27 (10.6)	14 (5.6)	65 (8.7)
<b>Discontinued Prior to Month 3</b>	24 (9.8)	27 (10.6)	14 (5.6)	65 (8.7)
<b>Reasons for Early Discontinuation</b>				
Adverse Event	17 (6.9)	15 (5.9)	5 (2.0)	37 (4.9)
Withdrawal of Consents	1 (0.4)	5 (2.0)	4 (1.6)	10 (1.3)
Non-Compliant	1 (0.4)	0	1 (0.4)	2 (0.3)
Lost to Follow-up	1 (0.4)	0	2 (0.8)	3 (0.4)
Lack of efficacy	0	3 (1.2)	0	3 (0.4)
Disallowed Concurrent Medication	2 (0.8)	2 (0.8)	0	4 (0.5)
Investigator Decision	0	0	0	0
Protocol Violation	1 (0.4)	1 (0.4)	2 (0.8)	4 (0.5)
Death	0	1 (0.4)	0	1 (0.1)
Other	1 (0.4)	0	0	1 (0.1)

Source: Table 7 of Study 302 Report.

All 750 randomized subjects were included in both the safety and the ITT population. The PP population had 671 subjects (89.5%).

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

	<b>PG324 n (%)</b>	<b>Netarsudil n (%)</b>	<b>Latanoprost n (%)</b>	<b>Overall n (%)</b>
<b>Safety</b>	244 (99.6)	255 (100.0)	251 (100.4)	750 (100.0)
<b>ITT</b>	245 (100.0)	255 (100.0)	250 (100.0)	750 (100.0)
<b>PP</b>	217 (88.6)	228 (89.4)	226 (90.4)	671 (89.5)

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	PG324	Netarsudil	Latanoprost	Overall
	N=245	N=255	N=250	N=750
	n (%)	n (%)	n (%)	n (%)
<b>Study Eye Diagnosis</b>				
Ocular Hypertension (OHT)	72 (29.4)	68 (26.7)	79 (31.6)	219 (29.2)
Open Angle Glaucoma (OAG)	172 (70.2)	187 (73.3)	171 (68.4)	530 (70.7)
<b>Gender</b>				
Male	93 (38.0)	102 (40.0)	106 (42.4)	301 (40.1)
Female	152 (62.0)	153 (60.0)	144 (57.6)	449 (59.9)
<b>Age</b>				
Mean (Std)	64.2 (11.8)	64.5 (10.6)	64.3 (11.4)	64.3 (11.3)
Min, Max	18, 88	22, 93	24, 99	24, 99
Median	65.0	66.0	66.0	66.0
< 65	118 (48.2)	109 (42.7)	112 (44.8)	339 (45.2)
≥ 65	127 (51.8)	146 (57.3)	138 (55.2)	411 (54.8)
<b>Race</b>				
Asian	7 (2.9)	11 (4.3)	6 (2.4)	24 (3.2)
Black/African American	74 (30.2)	76 (29.8)	79 (31.6)	229 (30.5)
White	161 (65.7)	165 (64.7)	163 (65.2)	489 (65.2)
Other	1 (0.4)	0	2 (0.8)	3 (0.4)
<b>Ethnicity</b>				
Hispanic or Latino	45 (18.4)	48 (18.8)	55 (22.0)	148 (19.7)
Non-Hispanic or Latino	200 (81.6)	207 (81.2)	195 (78.0)	602 (80.3)
<b>Iris Color of Study Eye</b>				
Blue/Grey/Green	49 (20.0)	48 (18.8)	52 (20.8)	149 (19.9)
Brown/Black	172 (70.2)	185 (72.5)	174 (69.6)	531 (70.8)
Hazel	24 (9.8)	22 (8.6)	24 (9.6)	70 (9.3)
<b>Time Since Current Diagnosis (weeks)</b>				
Mean (Std)	317.5 (325.8)	339.7 (360.5)	360.0 (380.5)	339.3 (356.5)
Min, Max	1, 1552	1, 2444	1, 2077	1, 2444
Median	230.0	233.0	237.5	235.0
<b>Prior Hypotensive Therapy</b>				
Combination Therapy	24 (9.8)	35 (13.7)	30 (12.0)	89 (11.9)
Prostaglandins (Monotherapy)	119 (48.6)	112 (43.9)	112 (44.8)	343 (45.7)
Other (Monotherapy)	16 (6.5)	14 (5.5)	25 (10.0)	55 (7.3)
No Prior Therapy	86 (35.1)	94 (36.9)	83 (33.2)	263 (35.1)
<b>Prior Hypotensive Therapy</b>				
Prior Prostaglandin Therapy	134 (54.7)	140 (54.9)	132 (52.8)	406 (54.1)
No Prior Prostaglandin Therapy	111 (45.3)	115 (45.1)	118 (47.2)	344 (45.9)

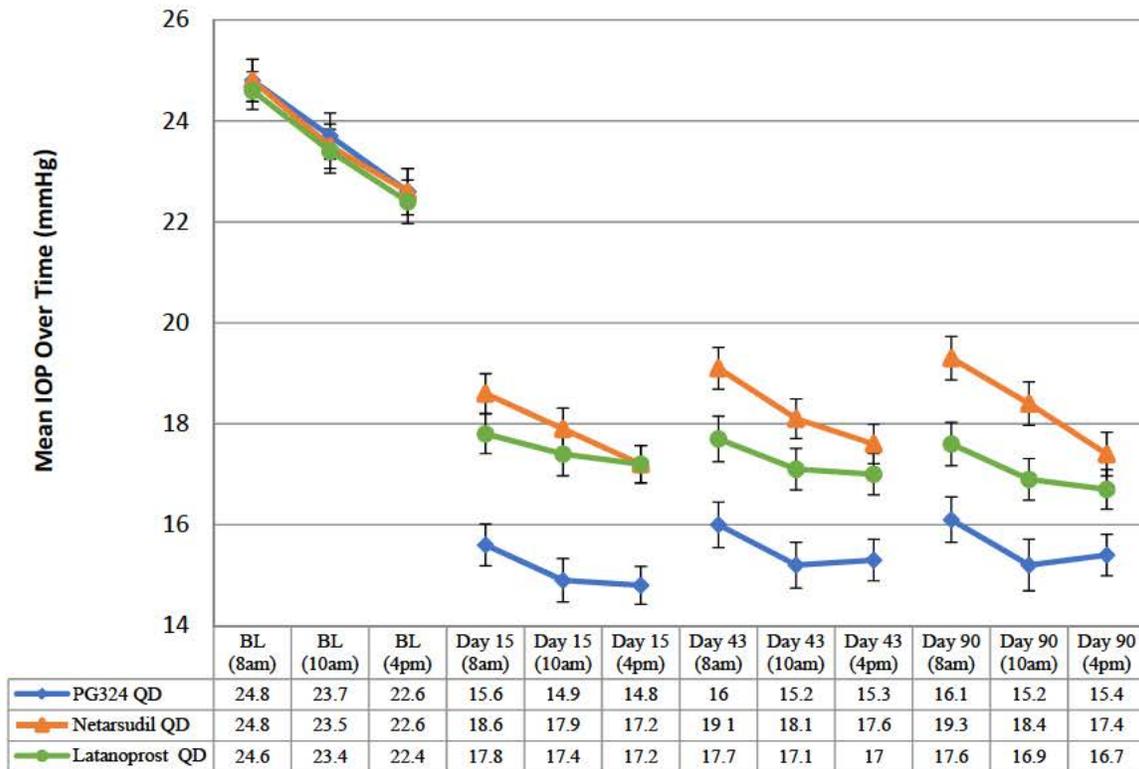
Source: Tables 6 of Study 302 report.

### 3.2.4 Results and Conclusions

#### 3.2.4.1 Study 301

The three treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 22.6 to 24.8 mmHg for the PG324 QD group, 22.6 to 24.8 for the netarsudil QD group, and 22.4 to 24.6 mmHg for the latanoprost QD group. From Day 15 to Month 3 of the treatment period, mean IOP over time ranged from 14.8 to 16.1 mmHg for study eyes treated with PG324, 17.2 to 19.1 mmHg for netarsudil, and 16.7 to 17.8 mmHg for latanoprost across all 9 time points.

Figure 1: Study 301 Mean IOP over Time



\* BL: Baseline. The figure was based on observed data for all randomized subjects

\* Mean IOP estimates are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point

Source: Table 14.2.1.1.2 of Study 301 Report.

IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.1 to 9.1 mmHg in the PG324 group, 4.9 to 6.1 mmHg in the netarsudil group, and 5.4 to 6.9 mmHg in the latanoprost group. PG324 had a statistically significantly higher IOP reduction compared to its two active components at all post-baseline time points. The treatment differences between PG324 and netarsudil groups ranged from -3.2 mmHg to -2.0 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.6 mmHg to -1.3 mmHg.

**Table 15: Study 301 Mean IOP and Mean IOP Change from Baseline by Visit and Time (Based on Observed Data)**

	PG324			Netarsudil			Latanoprost			PG324 vs. Netarsudil Differences (95% CI*) <sup>1</sup>	PG324 vs. Latanoprost Differences (95% CI*) <sup>1</sup>
	N	IOP	Ch*	N	IOP	Ch*	N	IOP	Ch*		
<b>Baseline</b>											
<b>8am</b>	238	24.8	n/a	244	24.8	n/a	236	24.6	n/a	0.0 (-0.6, 0.6)	0.3 (-0.3, 0.8)
<b>10am</b>	238	23.7	n/a	244	23.5	n/a	236	23.4	n/a	0.3 (-0.4, 0.9)	0.3 (-0.3, 0.9)
<b>4pm</b>	238	22.6	n/a	244	22.6	n/a	236	22.4	n/a	-0.0 (-0.7, 0.6)	0.2 (-0.5, 0.8)
<b>Day 15</b>											
<b>8am</b>	231	15.6	-9.1	241	18.6	-6.1	234	17.8	-6.9	-3.0 (-3.6, -2.5)	-2.3 (-2.8, -1.7)
<b>10am</b>	232	14.9	-8.7	236	17.9	-5.7	232	17.4	-6.1	-3.0 (-3.6, -2.4)	-2.6 (-3.2, -2.0)
<b>4pm</b>	231	14.8	-7.7	237	17.2	-5.3	231	17.2	-5.4	-2.4 (-3.0, -1.9)	-2.3 (-2.9, -1.8)
<b>Day 43</b>											
<b>8am</b>	221	16.0	-8.9	227	19.1	-5.6	226	17.7	-7.1	-3.2 (-3.8, -2.6)	-1.7 (-2.4, -1.1)
<b>10am</b>	217	15.2	-8.3	223	18.1	-5.5	225	17.1	-6.5	-2.8 (-3.5, -2.3)	-1.9 (-2.5, -1.2)
<b>4pm</b>	216	15.3	-7.2	223	17.6	-4.9	225	17.0	-5.5	-2.3 (-2.8, -1.7)	-1.7 (-2.2, -1.1)
<b>Day 90</b>											
<b>8am</b>	204	16.1	-8.6	205	19.3	-5.5	223	17.6	-7.2	-3.1 (-3.8, -2.5)	-1.5 (-2.1, -0.9)
<b>10am</b>	200	15.2	-8.3	200	18.4	-5.2	223	16.9	-6.7	-3.2 (-3.8, -2.5)	-1.7 (-2.3, -1.1)
<b>4pm</b>	200	15.4	-7.1	198	17.4	-5.1	223	16.7	-5.9	-2.0 (-2.6, -1.4)	-1.3 (-1.9, -0.7)

Ch\* = Change in IOP from baseline. CI = Confidence Interval.

<sup>1</sup> The treatment differences and two-sided CIs for comparing PG324 vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.2 of Study 301 Report for mean IOP; Statistical Reviewer’s analyses for the mean IOP change from baseline.

The following analyses for mean IOP and the mean IOP change from baseline (Table 16) were conducted by the applicant (or by the statistical reviewer). Other than the supplementary analyses based on BOCF method comparing PG324 vs. latanoprost (see Section 3.2.4.3 for a detailed discussion of BOCF analysis results) at Day 90 visit, the other analyses yielded the same conclusion as the above analysis based on observed data. Although the BOCF analysis results failed to demonstrate superiority of PG324 to latanoprost at the three time points on Day 90, it showed a trend favoring PG324 over latanoprost in mean IOP reduction from baseline at these endpoints (Table 17). Other selected supportive analyses results are provided in Appendix 3.

**Table 16: Study 301 Summary of Superiority of Netarsudil/Latanoprost to Netarsudil 0.02% and Latanoprost 0.005% (ITT)**

Endpoint	Analysis Method	Missing Data Imputation	Superiority of PG324 to Its Each Individual Component	
			Netarsudil 0.02%	Latanoprost 0.005%
Mean IOP	Baseline-Adjusted ANCOVA	MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	No
	Two-Sample t-test	MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	No
	MMRM	Observed	Yes	Yes

Mean IOP Change from Baseline	Baseline-Adjusted ANCOVA	MCMC*	Yes	Yes
		Observed*	Yes	Yes
		LOCF*	Yes	Yes
		BOCF*	Yes	No
	Two-Sample t-test	MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	No
	MMRM	Observed	Yes	Yes

ANCOVA = Analysis of Covariant; MMRM = Mixed Model Repeated Measures; Yes: Superiority was demonstrated. No: Superiority was not demonstrated.

<sup>1</sup> Two-sample t-test comparing actual mean IOP value at each time point between netarsudil/latanoprost and each of its individual comparator (latanoprost and netarsudil)

<sup>2</sup> ANCOVA model including treatment as the main effect and baseline as covariate. Individual models were fit for each visit and time point.

<sup>3</sup> Mixed Model Repeated Measures analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment\*visit, treatment\*time point, visit\*time point, and treatment\*visit\*time point as model terms. Repeated measures were used to account for the correlation among measures within a subject. The model included all post-dose visits and time points.

\* Statistical Reviewer's Analysis.

**Table 17: BOCF Analyses Results of Mean IOP Change from Baseline (mmHg) in Study Eye by Visit and Time (Studies 301; PG324 QD vs. Latanoprost QD)**

Study	Treatment	Day	Mean IOP Change from Baseline			Treatment Difference (95% CI) <sup>1</sup>		
			Time			Time		
			8am	10am	4pm	8am	10am	4pm
301	PG324	BL	24.8	23.7	22.6	0.3	0.3	0.2
	Latanoprost		24.6	23.4	22.4	(-0.3, 0.8)	(-0.3, 0.9)	(-0.5, 0.8)
	PG324	15	-8.9	-8.6	-7.5	-2.1	-2.6	-2.3
	Latanoprost		-6.8	-6.0	-5.2	(-2.8, -1.5)	(-3.3, -1.9)	(-2.9, -1.6)
	PG324	43	-8.2	-7.7	-6.5	-1.5	-1.5	-1.3
	Latanoprost		-6.8	-6.1	-5.2	(-2.1, -0.8)	(-2.3, -0.8)	(-2.0, -0.6)
PG324	90	-7.4	-7.0	-6.0	-0.7	-0.7	-0.5	
Latanoprost		-6.7	-6.3	-5.5	(-1.4, 0.1)	(-1.5, 0.0)	(-1.2, 0.2)	

BL = Baseline

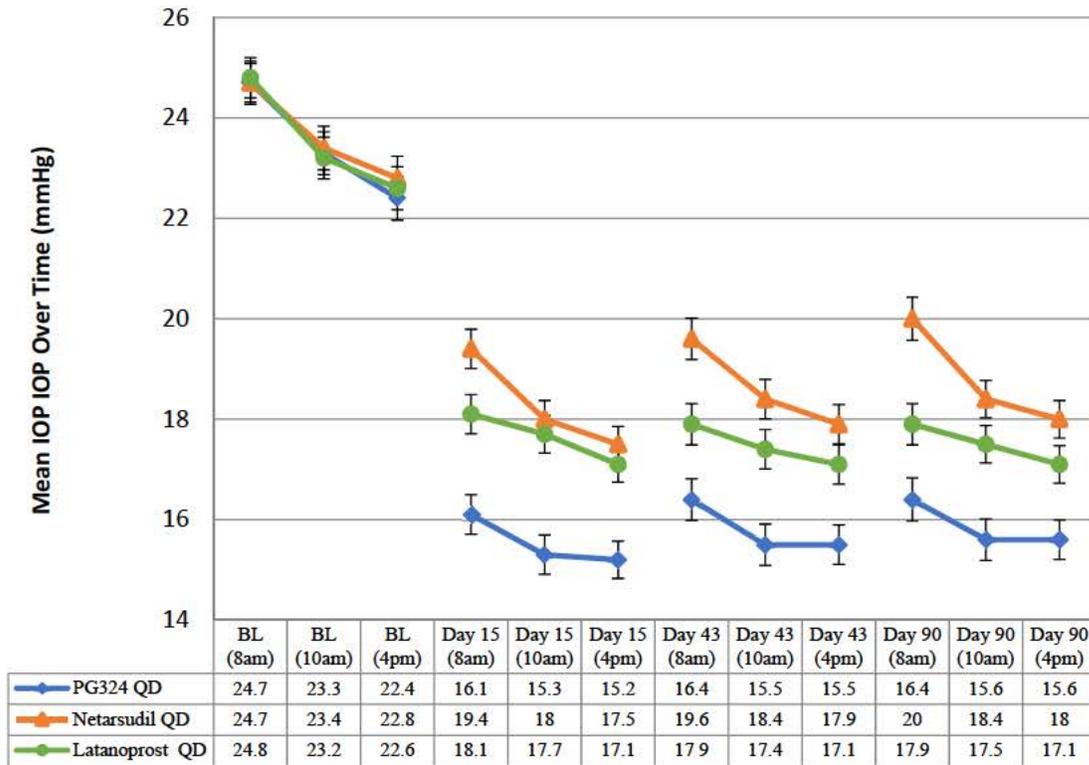
<sup>1</sup> The treatment differences and two-sided CIs for comparing Rocklatan vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Statistical Reviewer's analysis.

### 3.2.4.2 Study 302

For the ITT population, the three treatment groups had comparable mean baseline IOP. The mean baseline IOP was in the range of 22.4 to 24.7 mmHg for the PG324 QD group, 22.8 to 24.7 for the netarsudil QD group, and 22.6 to 24.8 mmHg for the latanoprost QD group. IOP reductions were observed in all three groups while subjects were on treatment. From Day 15 to Month 3, mean IOP over time ranged from 15.2 to 16.4 mmHg for study eyes treated with PG324, 17.5 to 20.0 mmHg for netarsudil, and 17.1 to 18.1 mmHg for latanoprost across all 9 time points.

**Figure 2: Study 302 Mean IOP over Time**



The figure was based on observed data for all randomized subjects.

\* BL: Baseline.

\* Mean IOP estimates are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point

Source: Table 14.2.1.1.2 of Study 303 Report.

IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.0 to 8.7 mmHg in the PG324 group, 4.6 to 5.4 mmHg in the netarsudil group, and 5.5 to 6.8 mmHg in the latanoprost group. PG324 had a statistically significantly higher IOP reduction compared to its two active components at all post-baseline time points. The treatment differences between PG324 and netarsudil groups ranged from -3.6 mmHg to -2.2 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.4 to -1.5 mmHg.

**Table 18: Study 302 Mean IOP and Mean IOP Change from Baseline by Visit and Time (Based on Observed Data)**

	PG324			Netarsudil			Latanoprost			PG324 vs. Netarsudil Differences (95% CI*) <sup>1</sup>	PG324 vs. Latanoprost Differences (95% CI*) <sup>1</sup>
	N	IOP	Ch*	N	IOP	Ch*	N	IOP	Ch*		
<b>Baseline</b>											
<b>8am</b>	245	24.7	n/a	255	24.7	n/a	250	24.8	n/a	0.0 (-0.5, 0.6)	-0.1 (-0.6, 0.5)
<b>10am</b>	245	23.3	n/a	255	23.4	n/a	250	23.2	n/a	-0.1 (-0.7, 0.5)	0.1 (-0.5, 0.7)
<b>4pm</b>	245	22.4	n/a	255	22.8	n/a	250	22.6	n/a	-0.4 (-1.0, 0.2)	-0.2 (-0.8, 0.4)

Day 15											
8am	238	16.1	-8.7	252	19.4	-5.3	246	18.1	-6.6	-3.4 (-3.9, -2.8)	-2.0 (-2.6, -1.5)
10am	236	15.3	-8.1	249	18.0	-5.4	247	17.7	-5.7	-2.7 (-3.2, -2.2)	-2.4 (-2.9, -1.9)
4pm	235	15.2	-7.3	248	17.5	-5.1	247	17.1	-5.5	-2.2 (-2.8, -1.7)	-1.9 (-2.4, -1.3)
Day 43											
8am	234	16.4	-8.3	248	19.6	-5.2	242	17.9	-6.8	-3.2 (-3.8, -2.6)	-1.5 (-2.1, -0.9)
10am	233	15.5	-7.8	247	18.4	-5.0	242	17.4	-6.0	-2.9 (-3.4, -2.3)	-1.9 (-2.4, -1.3)
4pm	232	15.5	-7.1	247	17.9	-4.7	241	17.1	-5.5	-2.3 (-2.9, -1.8)	-1.6 (-2.1, -1.0)
Day 90											
8am	223	16.4	-8.3	231	20.0	-4.7	236	17.9	-6.8	-3.6 (-4.2, -3.0)	-1.5 (-2.2, -0.9)
10am	222	15.6	-7.8	228	18.4	-5.0	236	17.5	-5.8	-2.8 (-3.4, -2.3)	-2.0 (-2.5, -1.4)
4pm	221	15.6	-7.0	228	18.0	-4.6	236	17.1	-5.5	-2.4 (-2.9, -1.9)	-1.5 (-2.1, -1.0)

Ch\* = Change in IOP from baseline. CI = Confidence Interval.

<sup>1</sup> The treatment differences and two-sided CIs for comparing PG324 vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.2 of Study 302 Report for mean IOP; Statistical Reviewer's analyses for the mean IOP change from baseline.

The following analyses for mean IOP over time and for the mean IOP change from baseline were conducted by the applicant (or by the statistical reviewer); all these analyses yielded the same conclusion as the above analysis based on the observed data. Detailed results of selected supportive analyses are provided in Appendix 3.

**Table 19: Study 302 Summary of Superiority of Netarsudil/Latanoprost to Netarsudil 0.02% and Latanoprost 0.005% (ITT)**

Endpoint	Analysis Method	Missing Data Imputation	Superiority of PG324 to Its Each Individual Component	
			Netarsudil 0.02%	Latanoprost 0.005%
Mean IOP	Baseline-Adjusted ANCOVA	MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	Yes
	Two-Sample t-test	MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	Yes
	MMRM	Observed	Yes	Yes
	Mean IOP Change from Baseline	Baseline-Adjusted ANCOVA	MCMC*	Yes
Observed*			Yes	Yes
LOCF*			Yes	Yes
BOCF*			Yes	Yes
Two-Sample t-test		MCMC	Yes	Yes
		Observed	Yes	Yes
		LOCF	Yes	Yes
		BOCF	Yes	Yes
MMRM		Observed	Yes	Yes

ANCOVA = Analysis of Covariant; MMRM = Mixed Model Repeated Measures; Yes: Superiority was demonstrated. No: Superiority was not demonstrated.

<sup>1</sup> Two-sample t-test comparing actual mean IOP value at each time point between netarsudil/latanoprost and each of its individual comparator (latanoprost and netarsudil)

<sup>2</sup> ANCOVA model including treatment as the main effect and baseline as covariate. Individual models were fit for each visit and time point.

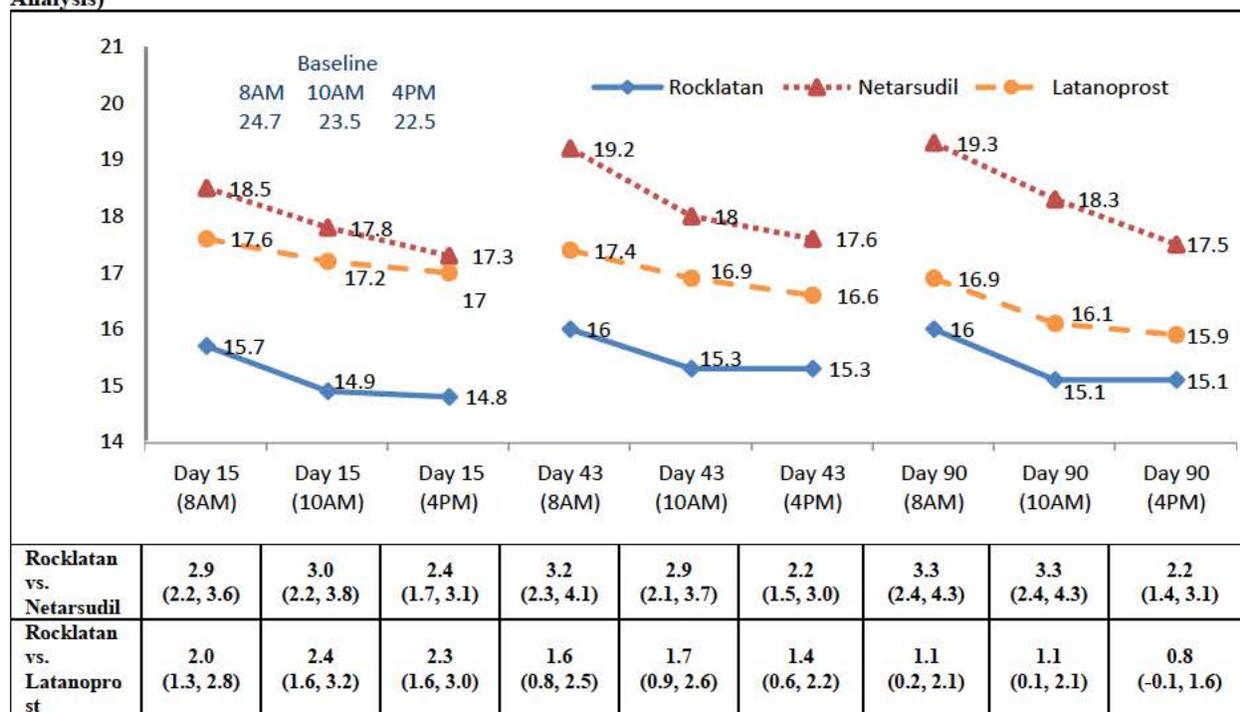
<sup>3</sup> Mixed Model Repeated Measures analysis including treatment as the main effect, and baseline IOP, visit, time point, treatment\*visit, treatment\*time point, visit\*time point, and treatment\*visit\*time point as model terms. Repeated measures were used to account for the correlation among measures within a subject. The model included all post-dose visits and time points.

### 3.2.4.3 Additional Supportive Analyses

To further examine the robustness of the observed data analysis, the statistical reviewer performed an adaptive trimmed mean analysis (Permutt and Li:

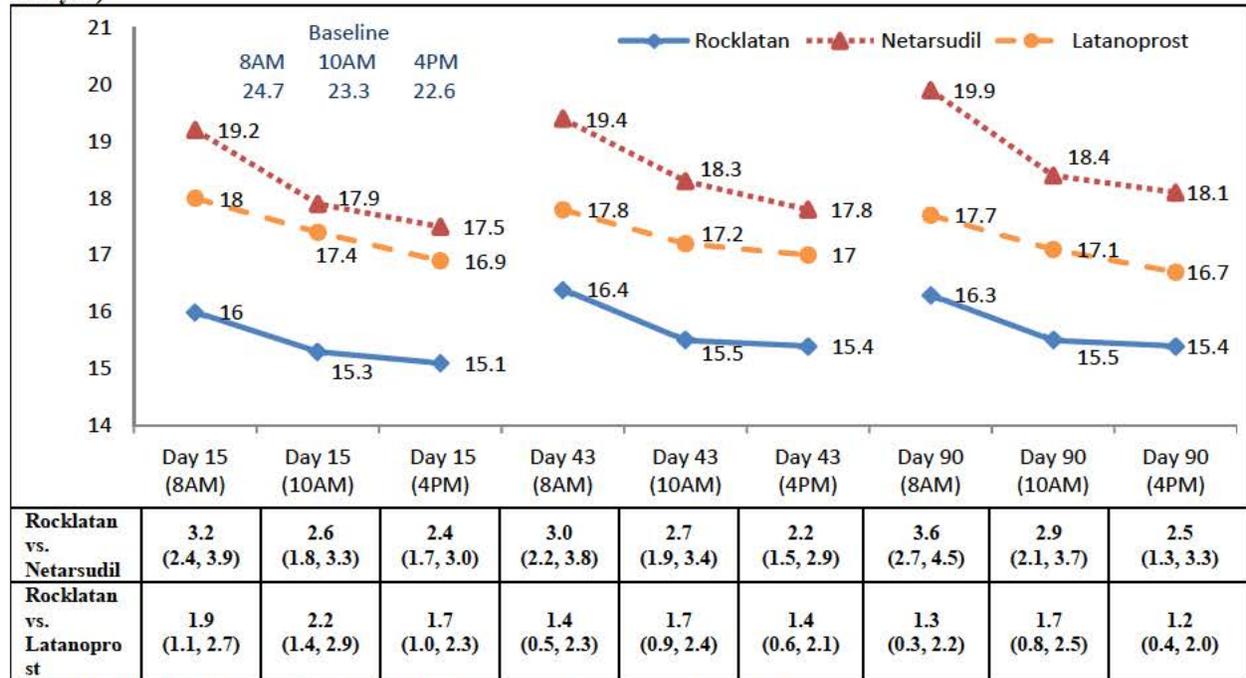
<https://www.ncbi.nlm.nih.gov/pubmed/27523396>). This analysis is an example of “composite strategy” discussed in the ICH E9(R1) Addendum. In this analysis, patients who discontinue study drug due to toxicity or lack of efficacy are not considered as having “missing data”. Instead they are considered as having unfavorable efficacy outcomes (not measured by a numerical number) and are accounted for in the analysis. This analysis is equivalent to the completer analysis in the case when the treatment groups have the same number of non-adherers. The results of the adaptive trimmed analysis for Studies 301 and 302 are presented in Figure 3 and Figure 4, demonstrating superiority of PG324 over its two components in reducing IOP. The mean IOP lowering effect of PG324 was 0.8 to 2.4 mmHg greater than monotherapy with latanoprost and 2.2 to 3.6 mmHg greater than monotherapy with netarsudil.

**Figure 3: Study 301 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP (Trimmed Mean Analysis)**



Source: Statistical Reviewer's analysis based on 1000 permuted datasets at each time point.

**Figure 4: Study 302 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP (Trimmed Mean Analysis)**



Source: Statistical Reviewer's analysis based on 1000 permuted datasets at each time point.

### 3.2.4.4 Long-Term Efficacy Results

The long-term efficacy results post 90 days were presented in the following table for Studies 301. IOP reductions were observed and maintained up to Month 12 in all three groups; mean IOP ranged from 15.3 to 16.5 mmHg in the PG324 group, from 17.6 to 19.2 mmHg in the netarsudil group, and from 16.8 to 17.8 mmHg in the latanoprost group.

PG324 had a statistically significantly higher IOP reduction compared to its two active components at all post-baseline time points. The treatment differences between PG324 and netarsudil groups ranged from -3.0 mmHg to -2.1 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -1.7 to -1.5 mmHg.

**Table 20: Study 301 Baseline Adjusted ANCOVAs for Mean IOP by Visit and Time (Month 6 to Month 12)**

		PG324		Netarsudil		Latanoprost		PG324 vs. Netarsudil Differences	PG324 vs. Latanoprost Differences
		N	IOP	N	IOP	N	IOP	(95% CI) <sup>1</sup>	(95% CI) <sup>1</sup>
Baseline	8am	238	24.8	244	24.8	236	24.6	0.0 (-0.6, 0.6)	0.3 (-0.3, 0.8)
	10am	238	23.7	244	23.5	236	23.4	0.3 (-0.4, 0.9)	0.3 (-0.3, 0.9)

	<b>4pm</b>	238	22.6	244	22.6	236	22.4	-0.0 (-0.7, 0.6)	0.2 (-0.5, 0.8)
<b>Month 6</b>	<b>8am</b>	178	16.3	170	19.2	219	17.7	-2.9 (-3.6, -2.2)	-1.3 (-2.0, -0.7)
	<b>10am</b>	176	15.6	168	18.3	219	16.9	-2.7 (-3.3, -2.0)	-1.3 (-2.0, -0.7)
	<b>4pm</b>	176	15.6	168	17.7	219	16.7	-2.1 (-2.7, -1.4)	-1.1 (-1.7, -0.5)
<b>Month 9</b>	<b>8am</b>	162	16.2	158	18.9	207	17.4	-2.8 (-3.4, -2.1)	-1.3 (-1.9, -0.6)
	<b>10am</b>	162	15.4	157	18.4	206	16.8	-3.0 (-3.7, -2.3)	-1.4 (-2.1, -0.8)
	<b>4pm</b>	162	15.3	156	17.6	206	16.9	-2.3 (-3.0, -1.6)	-1.6 (-2.2, -0.9)
<b>Month 12</b>	<b>8am</b>	159	16.5	148	18.8	203	17.8	-2.3 (-3.0, -1.6)	-1.2 (-1.9, -0.6)
	<b>10am</b>	158	15.6	148	18.4	203	17.3	-2.8 (-3.5, -2.0)	-1.7 (-2.4, -1.0)
	<b>4pm</b>	158	15.6	148	17.7	203	17.3	-2.1 (-2.8, -1.3)	-1.7 (-2.3, -1.0)

\* Based on observed data for all randomized subjects.

<sup>1</sup> The treatment differences and two-sided CIs for comparing Rocklatan vs. each of its active component are based on Analysis of Covariance (ANCOVA) adjusted for baseline IOP, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.2 of Study 301 Report.

### 3.2.4.5 Percentage of Subjects with IOP $\leq$ 18 mmHg, IOP $\leq$ 16 mmHg, and IOP $\leq$ 14 mmHg

Percentages of subjects achieving IOP  $\leq$  18 mmHg, IOP  $\leq$  16 mmHg, and IOP  $\leq$  14 mmHg were three of the protocol-defined secondary endpoints. (b) (4)

(b) (4)



If considering all subjects who discontinued study early as treatment failures, the following table listed the analysis results. The comparison between PG324 group and the latanoprost group was no longer statistically significant for the proportion of subjects who reached mean diurnal IOPs  $\leq 18$  mmHg for both studies. The comparison between PG324 and its active component is still statistically significant in the proportion of subjects who reached mean diurnal IOPs  $\leq 16$  mmHg and  $\leq 14$  mmHg but the treatment differences were much less comparing with the applicant's results.

**Table 21: Proportion of Patients Achieving Mean Diurnal IOP of  $\leq 18$  mmHg,  $\leq 16$  mmHg, and  $\leq 14$  mmHg Where Subjects Who Discontinued Study Considered as Failures (Studies 301 and 302)**

	Study 301			Study 302		
	PG324 N=238	Netarsudil N=244	Latanoprost N=236	PG324 N=245	Netarsudil N=255	Latanoprost N=250
<b>IOP <math>\leq 18</math> mmHg</b>	164 (68.9%)	106 (43.4%)	154 (65.3%)	169 (69.0%)	105 (41.2%)	155 (62.0%)
<b>PG324 vs. Its Components (95% CI)*</b>		25.5% (16.9%, 34.0%)	4.3% (-12.1%, 5.0%)		27.8% (19.4%, 36.2%)	7.0% (-1.0%, 15.3%)

<b>IOP≤16 mmHg</b>	122 (51.3%)	63 (25.8%)	86 (36.4%)	124 (50.6%)	56 (22.0%)	85 (34.0%)
<b>PG324 vs. Its Components (95% CI)*</b>		25.4% (17.1%, 33.8%)	14.8 (6.0%, 23.7%)		28.7% (20.6%, 36.7%)	16.6% (8.0%, 25.2%)
<b>IOP≤14 mmHg</b>	65 (27.3%)	27 (11.1%)	33 (14.0%)	71 (29.0%)	19 (7.5%)	21 (8.4%)
<b>PG324 vs. Its Components (95% CI)*</b>		16.3% (9%, 23.1%)	13.3% (6.0%, 20.5%)		21.5% (15.0%, 28.1%)	20.6% (13.9%, 27.2%)

\* All randomized and treated subjects were included. Missing values were treated as failures.

Source: Statistical Reviewer's analysis.

As observed in Figures 1 and 2, IOP fluctuates over the course of one day; within a visit day, the highest IOP is usually at 8am; and IOPs at 10am and 4pm are similar. As the average of the three time points, mean diurnal IOP may not capture the fluctuation of the IOP readings over the course of one day. Further dichotomizing of the mean diurnal IOP leads more information lost. For example, IOP readings of 20.0 mmHg at 8am, 14.0 mmHg at 10am, and 13.5 mmHg at 4pm for a subject on a visit day result in a mean diurnal IOP of 15.8 mmHg for that visit, which would categorize the subject into proportion of subjects who reached mean diurnal IOPs ≤16 mmHg; but the 20 mmHg IOP at 8am was completely ignored by this simplified dichotomous endpoint.

Comparing with the primary efficacy measures: individual IOP readings at 8am, 10am, 4pm time points on Days 15, 43, and 90 (Month 3), the clinical significance of the proportion of subjects who reached mean diurnal IOPs ≤16 mmHg (or ≤14 mmHg) at one study visit (Month 3) is beyond the scope of this statistical review. (b) (4)

[Redacted]

[Redacted] (b) (4)

### 3.2.4.6 Conclusion

In conclusion, the two pivotal studies 301 and 302 demonstrated that PG324 was efficacious in reducing elevated intraocular pressure; the studies also demonstrated superiority of Rocklatan compared to its two active components: netarsudil and latanoprost.

### 3.3 Evaluation of Safety

For each of the two studies (301 and 302), more subjects in the netarsudil-containing groups (both PG324 and netarsudil groups) discontinued the study early due to AEs than subjects in the latanoprost group. For the first three months of treatment, the most frequent adverse event that lead to discontinuations in both studies 301 and 302 was: conjunctival hyperemia. For Study 301, the most frequent adverse event that lead to discontinuations during the 12-month treatment period in both netarsudil-containing groups were: conjunctival hyperemia, conjunctivitis allergic, eye pruritus, lacrimation increased, cornea verticillata, and vision blurred.

**Table 22: Study 301 Safety Analysis: Adverse Events Associated with Discontinuations  $\geq$  1.0% of Subjects in Either Treatment Group by Month 12 (Safety Population)**

<b>System Organ Class</b> <b>Preferred Term</b>	<b>PG324</b> <b>N=238</b> <b>n (%)</b>	<b>Netarsudil</b> <b>N=243</b> <b>n (%)</b>	<b>Latanoprost</b> <b>N=237</b> <b>n (%)</b>
<b>Any TEAEs Resulting in Test Agent Discontinuation</b>	49 (20.6)	56 (23.0)	4 (1.7)
<b>Eye Disorders</b>	44 (18.5)	46 (18.9)	1 (0.4)
Conjunctival Hyperemia	18 (7.6)	20 (8.2)	0
Conjunctivitis Allergic	3 (1.3)	7 (2.9)	0
Eye Pruritus	6 (2.5)	4 (1.6)	0
Lacrimation Increased	4 (1.7)	4 (1.6)	0
Cornea Verticillata	4 (1.7)	3 (1.2)	0
Vision Blurred	4 (1.7)	3 (1.2)	0
Erythema of Eyelid	2 (0.8)	4 (1.6)	0
Conjunctival Oedema	4 (1.7)	1 (0.4)	0
Eye Irritation	4 (1.7)	1 (0.4)	0

Source: Table 14.3.3.4 of Study 301 Report.

**Table 23: Study 302 Safety Analysis: Adverse Events Associated with Discontinuations ≥ 1.0% of Subjects in Either Treatment Group by Month 3 (Safety Population)**

System Organ Class Preferred Term	PG324 N=244 n (%)	Netarsudil N=255 n (%)	Latanoprost N=251 n (%)
<b>Any TEAEs Resulting in Test Agent Discontinuation</b>	17 (7.0)	16 (6.3)	4 (1.6)
<b>Eye Disorders</b>	16 (6.6)	9 (3.5)	4 (1.6)
Conjunctival Hyperemia	6 (2.5)	5 (2.0)	1 (0.4)

Source: Table 14.3.3.4 of Study 302 Report.

A total of two deaths were reported in the netarsudil group: one due to atherosclerotic and hypertensive cardiovascular disease after 252 days on treatment (in Study 301); and one due to cardiac arrest after 47 days of treatment (Study 302). These deaths were assessed not related to study treatment by study investigators. There was no death in both PG324 and latanoprost groups.

The following tables presented the treatment-emergent adverse events for the two studies. The most frequent AEs reported for netarsudil-treated subjects were conjunctival hyperemia, cornea verticillata, and conjunctival hemorrhage. These netarsudil-related AEs reported in the two studies were consistent with the AEs reported in the Rhopressa labeling.

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

**Table 24: Study 301 Treatment-Emergent Adverse Events Reported for 2.0% or More of Subjects in Any of the Three Treatment Groups (Safety Population; at 12 months)**

	PG324 (N=238) n (%)	Netarsudil (N=243) n (%)	Latanoprost (N=237) n (%)
<b>Ocular Treatment-Emergent Adverse Events</b>			
<b>Eye Disorders</b>			
Conjunctival hyperemia	133 (55.9)	115 (47.3)	44 (18.6)
Cornea Verticillata	39 (16.4)	32 (13.2)	0
Eye pruritus	20 (8.4)	20 (8.2)	2 (0.8)
Lacrimation increased	15 (6.3)	17 (7.0)	1 (0.4)
Conjunctival hemorrhage	10 (4.2)	14 (5.8)	2 (0.8)
Punctate keratitis	9 (3.8)	13 (5.3)	4 (1.7)
Vision blurred	9 (3.8)	14 (5.8)	3 (1.3)
Eye irritation	10 (4.2)	7 (2.9)	1 (0.4)
Erythema of eyelid	8 (3.4)	8 (3.3)	1 (0.4)
Conjunctivitis allergic	5 (2.1)	9 (3.7)	0
Visual Acuity Reduced	7 (2.9)	6 (2.5)	1 (0.4)
Eyelid edema	5 (2.1)	7 (2.9)	1 (0.4)
Conjunctival oedema	8 (3.4)	4 (1.6)	0
Dry eye	4 (1.7)	3 (1.2)	5 (2.1)
Blepharitis	6 (2.5)	5 (2.1)	0
<b>General Disorders and Administration Site Conditions</b>			
Instillation site pain	52 (21.8)	55 (22.6)	18 (7.6)
Instillation site discomfort	10 (4.2)	7 (2.9)	3 (1.3)
Instillation site erythema	10 (4.2)	5 (2.1)	1 (0.4)
Instillation site foreign body sensation	0	6 (2.5)	2 (0.8)

**Investigations**

Vital dye staining cornea present	6 (2.5)	4 (1.6)	2 (0.8)
<b>Skin and subcutaneous tissue disorders</b>			
Dermatitis contact	5 (2.1)	3 (1.2)	0

Source: Tables 18 of Study 301 Report.

**Table 25: Study 302 Treatment-Emergent Adverse Events Reported for 2.0% or More of Subjects in Any of the Treatment Groups (Safety Population, at 3 months)**

	<b>PG324 (N=244) n (%)</b>	<b>Netarsudil (N=255) n (%)</b>	<b>Latanoprost (N=251) n (%)</b>
<b>Ocular Treatment-Emergent Adverse Events</b>			
<b>Eye Disorders</b>			
Conjunctival hyperemia	133 (54.5)	109 (40.7)	56 (22.3)
Cornea Verticillata	32 (13.1)	25 (9.8)	0
Conjunctival hemorrhage	21 (8.6)	28 (11.0)	2 (0.8)
Corneal disorder	14 (5.7)	12 (4.7)	0
Vision blurred	12 (4.9)	8 (3.1)	4 (1.6)
Punctate keratitis	5 (2.0)	9 (3.5)	4 (1.6)
Eyelid edema	8 (3.3)	6 (2.4)	3 (1.2)
Erythema of eyelid	8 (3.3)	5 (2.0)	3 (1.2)
Lacrimation increased	8 (3.3)	8 (3.1)	0
Eye pruritus	10 (4.1)	1 (0.4)	0
Eye Pain	3 (1.2)	5 (2.0)	4 (1.6)
Blepharitis	4 (1.6)	6 (2.4)	1 (0.4)
Eye irritation	4 (1.6)	6 (2.4)	1 (0.4)
Foreign body sensation in eyes	7 (2.9)	1 (0.4)	2 (0.8)
<b>General Disorders and Administration Site Conditions</b>			
Instillation site pain	42 (17.2)	23 (9.0)	15 (6.0)
Instillation site discomfort	15 (6.1)	16 (6.3)	2 (0.8)
Instillation site erythema	10 (4.1)	6 (2.4)	4 (1.6)
<b>Investigations</b>			
Vital dye staining cornea present	10 (4.1)	14 (5.5)	7 (2.8)

Source: Tables 16 of Study 302 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 3). In both studies, all the subgroup analyses results were similar to those seen for the overall population for each demographic subgroup. Analyses by geographic region were not conducted since all clinical sites were in the United States/Canada.

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

Regarding the statistical issues, the statistical review team has the following comments:

In the primary analysis, the applicant considered all patients who discontinued the study prior to 3 months as having missing data after discontinuation. The applicant imputed the missing data at a given time point by using the observed data from the patients who were still on their study treatment. We find this imputation approach problematic for the patients who discontinued study due to netarsudil-induced adverse events. These patients undoubtedly could no longer benefit from their discontinued study drug at 3 months. However, as presented in Table 8, their imputed values at 3 months showed an IOP reduction ranging from 5 to 9 mm Hg, indicating that these patients would still benefit significantly from their discontinued study drug. Therefore, we found these imputed values to be unreasonable. (b) (4)

As a supportive analysis, the applicant conducted the analysis of observed data only. The applicant's analysis of the observed data is an example of "while on treatment strategy" discussed in the ICH E9(R1) Addendum "Estimands and Sensitivity Analysis in Clinical Trials" ([https://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E9/E9-R1EWG\\_Step2\\_Guideline\\_2017\\_0616.pdf](https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/E9-R1EWG_Step2_Guideline_2017_0616.pdf)). We find this analysis acceptable as the majority of the dropouts were due to toxicity and no dropout was due to lack of efficacy in the PG324 group for both studies. Thus, we recommend presenting the results of this analysis along with information pertaining to the percentages of dropouts due to toxicity in the labeling. (b) (4)

Of note, the conclusions from both the primary and supportive analyses are the same.

To further examine the robustness of the observed data analysis, we performed an adaptive trimmed mean analysis (Permutt and Li: <https://www.ncbi.nlm.nih.gov/pubmed/27523396>). This analysis is an example of "composite strategy" discussed in the ICH E9(R1) Addendum. In this analysis, patients who discontinue study drug due to toxicity or lack of efficacy are not considered as having "missing data". Instead they are considered as having unfavorable efficacy outcomes (not measured by a numerical number) and are accounted for in the analysis. This analysis is equivalent to the completer analysis in the case when the treatment groups have the same number of non-adherers. The results of the adaptive trimmed analysis for Studies 301 and 302 are presented in Figure 3 and Figure 4, demonstrating superiority of PG324 over its two components in reducing IOP. The mean IOP lowering effect of PG324 was 0.8 to 2.4 mmHg greater than monotherapy with latanoprost and 2.2 to 3.6 mmHg greater than monotherapy with netarsudil.

### 5.2 Collective Evidence

Both studies had significantly higher discontinuation rates prior to Month 3 due to adverse events (AE) in the netarsudil containing groups (PG324 and netarsudil groups) compared to the

latanoprost group: 10% vs. 0% in Study 301 and 6.4% vs. 2% in Study 302 (Table 1). In Study 301, the overall discontinuation rates were 16.7% in the netarsudil containing groups and 5.5% in the latanoprost group. In Study 302, the overall discontinuation rates were 10% in the netarsudil containing groups and 5.6% in the latanoprost group.

Overall, both studies demonstrated statistically significantly higher mean IOP reductions in the PG324 group compared with its two components at the nine post-baseline time points. In Study 301, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.1 to 9.1 mmHg in the PG324 group, 4.9 to 6.1 mmHg in the netarsudil group, and 5.4 to 6.9 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.2 mmHg to -2.0 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.6 mmHg to -1.3 mmHg. (Table 2)

In Study 302, IOP reductions were observed in all three groups. The mean IOP reductions from baseline ranged from 7.0 to 8.7 mmHg in the PG324 group, 4.6 to 5.4 mmHg in the netarsudil group, and 5.5 to 6.8 mmHg in the latanoprost group. The treatment differences between PG324 and netarsudil groups ranged from -3.6 mmHg to -2.2 mmHg. The treatment differences between PG324 and latanoprost groups ranged from -2.4 to -1.5 mmHg. (Table 2)

### 5.3 Conclusions and Recommendations

In conclusion, the two pivotal studies demonstrated that Rocklatan was efficacious in reducing elevated intraocular pressure; the studies also demonstrated superiority of Rocklatan compared to its two active components: netarsudil and latanoprost.

Therefore, the statistical reviewer recommends the approval of Rocklatan for the reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

### 5.4 Labeling Recommendations

In the NDA submission, the applicant's proposed label had the following text for the clinical studies section.

***“14. CLINICAL STUDIES***

*ROCKLATAN (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% was evaluated in 2 randomized and controlled clinical trials, namely PG324-CS301 (NCT 02558400, referred to as Study 301) and PG324-CS302 (NCT 02674854, referred to as Study 302) in patients with open-angle glaucoma and ocular hypertension. Studies 301 and 302 enrolled subjects with IOP < 36 mmHg and compared IOP lowering effect of ROCKLATAN dosed once daily to individually administered netarsudil 0.02% once daily and latanoprost 0.005% once daily. The treatment duration was 12 months for Study 301 and 3 months for Study 302.*

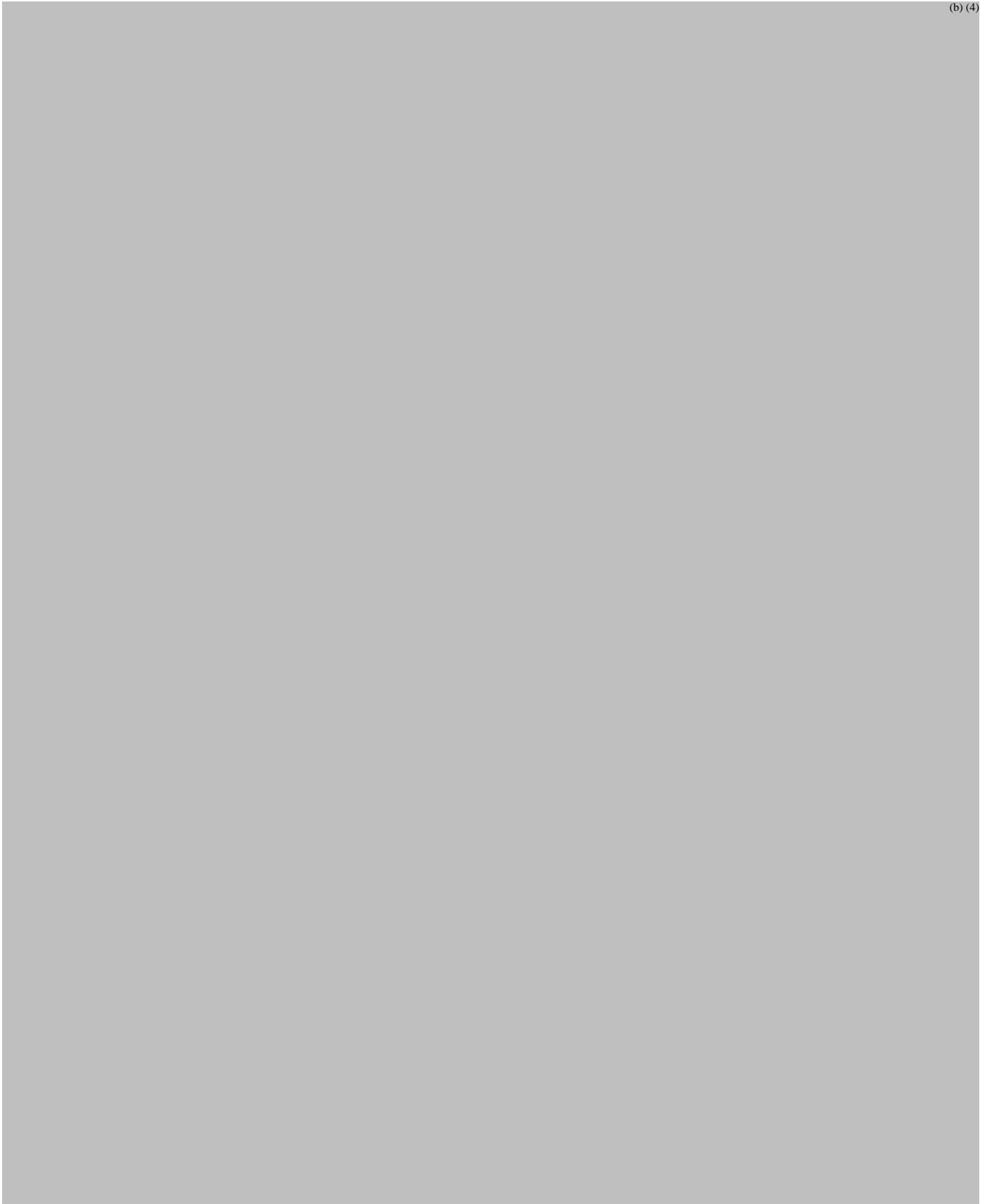
*The IOP lowering effect of ROCKLATAN was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months*

(b) (4)

(b) (4)

*In Study*

*301 IOP reductions were maintained throughout 12 months.”*



We recommend presenting the results of the observed analysis along with information pertaining to the percentages of dropouts due to toxicity in the labeling, (b) (4)

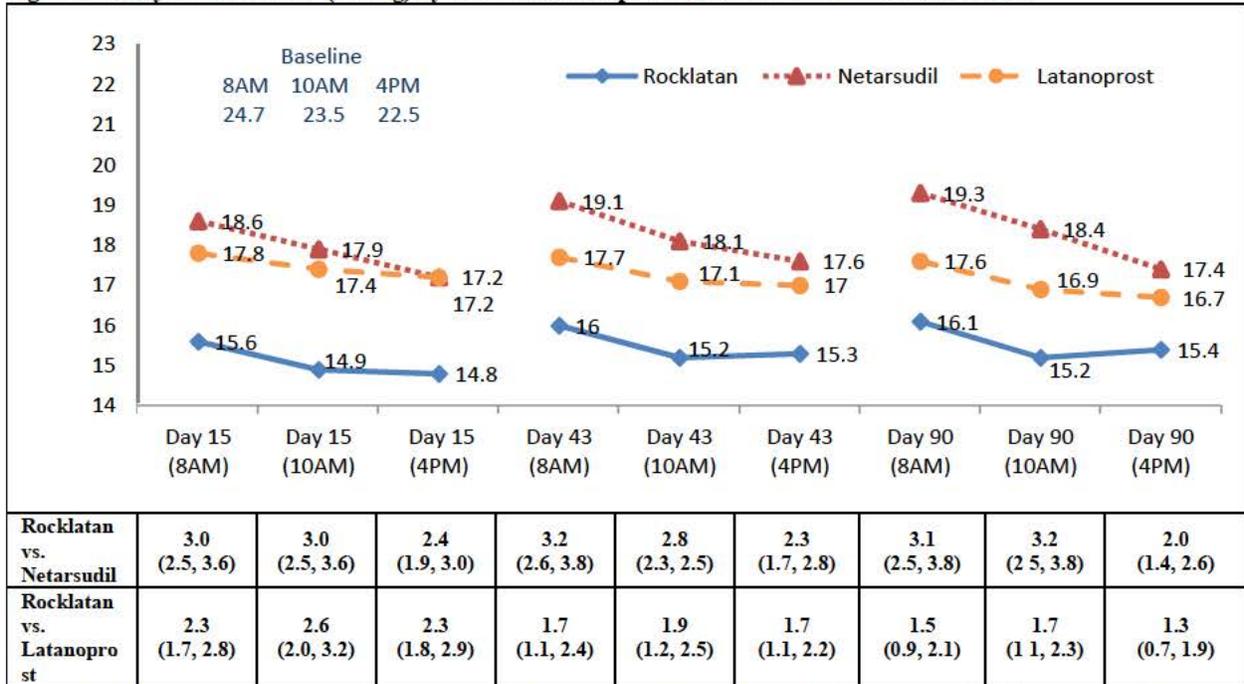
(b) (4) Of note, the conclusions from both the primary and supportive analyses are the same. The statistical review recommended the label present the study results as follows:

“ROCKLATAN (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% was evaluated in 2 randomized and controlled clinical trials, namely PG324-CS301 (NCT 02558400, referred to as Study 301) and PG324-CS302 (NCT 02674854, referred to as Study 302) in patients with open-angle glaucoma and ocular hypertension. Studies 301 and 302 enrolled subjects with IOP < 36 mmHg and compared IOP lowering effect of ROCKLATAN dosed once daily to individually administered netarsudil 0.02% once daily and latanoprost 0.005% once daily. The treatment duration was 12 months for Study 301 and 3 months for Study 302.

(b) (4)

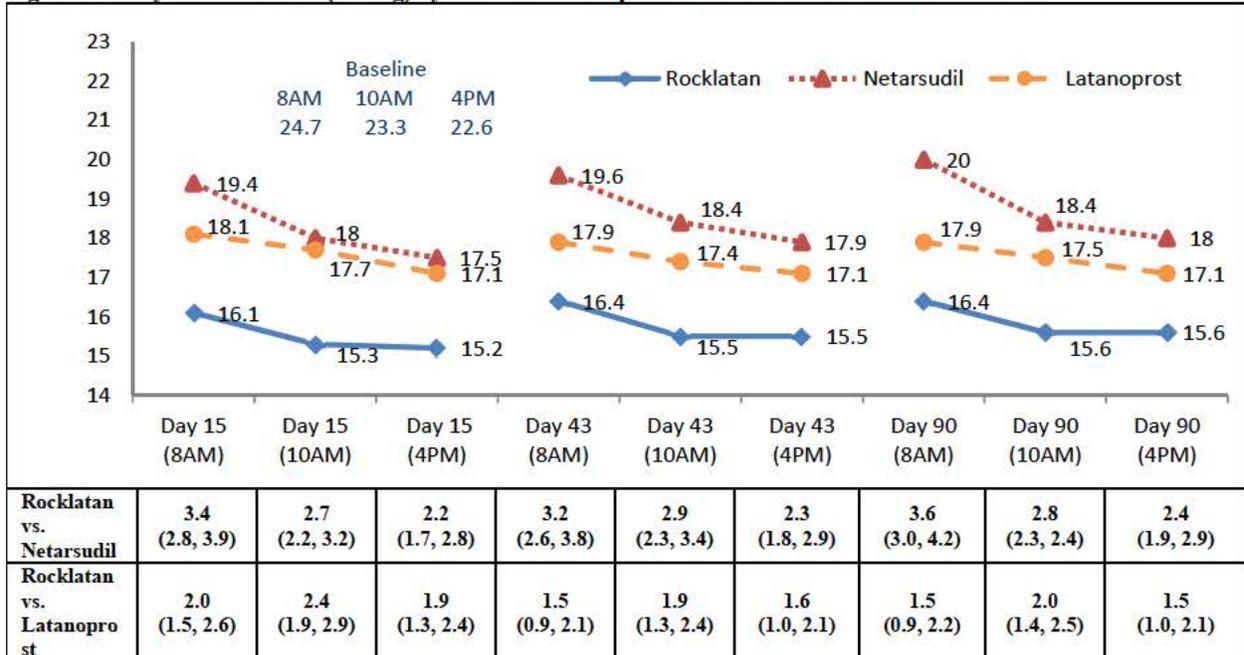
(b) (4) The average IOP lowering effect of ROCKLATAN was 1 to 3 mmHg greater than monotherapy with either netarsudil 0.02% or latanoprost 0.005% throughout 3 months (Figures 1 and 2). In Study 301 IOP reductions were maintained throughout 12 months.

**Figure 1: Study 301 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP**



The least square mean IOP at each post-baseline time point was derived using an analysis of covariance adjusted for baseline IOP and based on observed data for all randomized subjects (238 in Rocklatan group, 244 in netarsudil group, 236 in latanoprost group).

**Figure 2: Study 302 Mean IOP (mmHg) by Treatment Group and Treatment Difference in Mean IOP**



The least square mean IOP at each post baseline time point was derived using an analysis of Covariance adjusted for baseline IOP and based on observed data for all randomized subjects (245 in Rocklatan group, 255 in netarsudil group, 250 in latanoprost group).

”

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

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

### Key Inclusion Criteria:

- 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 < 36 mmHg in both eyes at 2 qualification visits (8am), 2 to 7 days apart. At the second qualification visit, IOP > 17 mmHg and < 36 mmHg in both eyes at 10am and 4pm. Both eyes had to have qualified at all qualification visit time points
- Best 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:

#### Ophthalmic

- Clinically significant ocular disease (e.g., corneal edema, uveitis, severe keratoconjunctivitis sicca) which might have interfered with interpretation of the study efficacy endpoints or with safety assessments, including subjects with glaucomatous damage so severe that washout of ocular hypotensive medications (if needed) for 1 month was not judged safe as it would put the subject at risk for further vision loss
- Pseudoexfoliation or pigment dispersion component glaucoma, history of angle closure glaucoma, or narrow angles (i.e., Grade 2 or less [Shaffer scale]; extreme narrow angle with complete or partial closure). Note: Prior laser peripheral iridotomy was NOT acceptable
- Intraocular pressure  $\geq 36$  mmHg (unmedicated) in either eye at any time point (individuals who were excluded for this criterion were not allowed to attempt requalification), or use of more than 2 ocular hypotensive medications within 30 days of screening. Note: Fixed dose combination medications, for the purpose of this exclusion criterion, was counted as one medication
- Known hypersensitivity to any component of the formulation, to latanoprost, or to topical anesthetic
- Previous glaucoma intraocular surgery, including SLT or ALT in either eye
- Refractive surgery in either eye (e.g., radial keratotomy, PRK, LASIK, corneal cross-linking, etc.)
- 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, keratitis, or conjunctivitis. Additionally, current evidence or history of herpes simplex or zoster keratitis in either eye at screening was excluded
- Used ocular medication in either eye of any kind within 30 days of screening and throughout the study, 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), c) lubricating drops for dry eye (which may have been used throughout the study), or d) non-corticosteroid or non-vasoconstrictor-containing allergy drops and allergy drops that do not have a redness reliever effect as prescribed by the Investigator
- Mean central corneal thickness greater than 620  $\mu\text{m}$  in either eye at screening
- Any abnormality preventing reliable applanation tonometry of either eye (e.g., keratoconus, etc.)

**Systemic:**

- Clinically significant abnormalities in laboratory tests at screening
- Clinically significant systemic disease (e.g., uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) which might have interfered with the study
- Participation in any investigational study within 60 days prior to screening Schedule of assessments for Studies 301 and 302 are presented in the following table.
- Systemic medication that could have had a substantial effect on IOP within 30 days prior to screening, or anticipated during the study, including any corticosteroid-containing containing drug regardless of route of administration
- Women of childbearing potential who were pregnant, nursing, planning a pregnancy, or not using a medically acceptable form of birth control. An adult woman was considered to be of childbearing potential unless she was 1 year post-menopausal or 3 months post-surgical sterilization. All females of childbearing potential had to have a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study

Schedule of assessments for Studies 301 and 302 are presented in the following table.

**Table 26: Study 301 Schedule of Assessments**

Day/Week/Month	Screen	Qual #1	Qual #2 D1		Post D1 Treatment Period Assessment															Extension Period		
					W2 (D15±3)			W6 (D43±3)			M3, M6 (D90±3, D180±7)			M9 (D270±7)			M12 (D365±7)			M13 (D395±7)	M14 (D425±7)	
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0,7.0	6.1,7.1	6.2,7.2	8.0	8.1	8.2	9.0	9.1	9.2	10	11
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16	08	10	16	08	10	16	08	08
Informed Consent	X																				X <sup>12</sup>	
Inclusion/Exclusion	X	X	X	X	X																	
Washout <sup>1</sup>	X																					
Demography	X																					
Medical/Ophthalmic Hx	X	X	X																			
Concomitant Meds	X	X	X			X			X			X			X			X			X	X
HR/BP	X	X	X			X			X			X			X			X			X	X
Urine Pregnancy Test <sup>2</sup>	X											X			X			X				
Clin Labs (Chem/Hem)	X <sup>3</sup>											X						X				
Symptoms/AEs <sup>4</sup>	X	X	X	X	X	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			X				
Visual Acuity (ETDRS)	X	X	X			X			X			X			X			X			X	X
Pupil Size			X									X						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	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X	X
Gonioscopy <sup>7</sup> /Pachymetry <sup>8</sup>	G/P											P										
Visual Field <sup>9</sup>	X											X						X				X
Ophthalmoscopy (dilated)	X													X				X <sup>11</sup>		X		X
Eye-Drop Instillation Eval	X																					
Study Meds Dispensed					X			X			X			X			X					
Study Meds Collected						X <sup>10</sup>			X <sup>10</sup>			X <sup>10</sup>			X <sup>10</sup>			X <sup>10</sup>				X <sup>13</sup>
Study Completed																		X <sup>13</sup>				X <sup>13</sup>

Abbreviations: Screen, screening; Qual, qualification; D, day; W, week; M, month; Hx, History; Meds, medications; HR/BP, heart rate/blood pressure; Clin Labs (Chem/Hem), Clinical Labs (Chemistry/Hematology); G, gonioscopy; P, pachymetry; Eval, evaluation.

- Subjects who were using ocular hypotensive medications were required undergo a minimum washout period (Table 2 for details).
- Urine pregnancy test for women of childbearing potential was required.
- For subjects who were unable or unwilling to have blood drawn for clinical labs at Visit 1 (Screening), the blood sample could be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs were available for that subject prior to Visit 3 (Qualification Visit #2).
- Ocular symptoms: Subjects were queried at each visit "How are you feeling?" and treatment emergent AEs beginning at Visit 3 (Qualification Visit #2) 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 hour for study drug visits, subjects were queried "Did you experience any discomfort when placing the drops in your eyes?"
- Individuals returning at an unscheduled visit within 1 week were required to only remeasure IOP in both eyes (See Protocol sections 7.1.2 to 7.1.5).
- Gonioscopy evaluation up to 3 months prior to randomization was acceptable.
- Pachymetry within 1 week of study visit was acceptable.
- Entry visual field evaluation up to 3 months prior to randomization was acceptable. Visual field collection were required to meet the requirement for automated threshold visual field assessment (e.g., 30-2 or 24-2 Humphrey) and reliability.
- Collected used kit(s) dispensed during the previous visit.
- Ophthalmoscopy (dilated) at Visit 9.0 at 08:00: this assessment was to be performed for all non-completing subjects during the exit visit.
- Informed consent was required to be completed by the subjects before entering the extension visits.
- Month 12 visit completed for the treatment period. Month 14 visit completed for the subjects entering the extension visits of the study.

Source: Table 3 of Study 301 Report.

**Table 27: Study 302 Schedule of Assessments**

Day/Week/Month	Screen	Qual. #1	Qual. #2 Day 1			W2 (Day 15±3)			W6 (Day 43±3)			M3 (Day 90±3)		
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													
Med/Ophthalmic History	X	X	X											
Concomitant Meds	X	X	X			X			X			X		
HR/BP	X	X	X			X			X			X		
Urine Pregnancy Test <sup>2</sup>	X											X		
Clin Labs	X <sup>3</sup>											X		
Symptoms/AEs <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test <sup>5</sup>						X			X			X		
Visual Acuity(ETDRS)	X	X	X			X			X			X		
Pupil size			X									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
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specular Microscopy	X											X		
Gonioscopy <sup>7</sup> / Pachymetry <sup>8</sup>	G/P											P		
Visual Field <sup>9</sup>	X											X		

Day/Week/Month	Screen	Qual. #1	Qual. #2 Day 1			W2 (Day 15±3)			W6 (Day 43±3)			M3 (Day 90±3)		
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
Ophthalmoscopy(dilated) <sup>10</sup>	X											X <sup>10</sup>		X
Eye-Drop Instillation Eval	X													
Study Meds Dispensed					X			X			X			
Collect Study Meds						X <sup>11</sup>			X <sup>11</sup>			X <sup>11</sup>		
Study Completed														X

Abbreviations: W, week; M, month; Med/Ophthalmic Hist, Medical/Ophthalmic History; HR/BP, heart rate/blood pressure; Clin Labs, Clinical Labs (Chemistry/Hematology); G, gonioscopy; P, pachymetry; AE, adverse event; ETDRS, early treatment diabetic retinopathy study; IOP, intraocular pressure

1. Subjects using ocular hypotensive medications were required to undergo a minimum washout period (see Table 2).
2. Urine pregnancy test for women of childbearing potential was required.
3. For subjects who were unable or unwilling to have blood drawn for clinical labs at screening (Visit 1), the blood sample may have been drawn at Qualification Visit #1 (Visit 2) so long as the results of the clinical labs were available for that subject prior to Qualification Visit #2 (Visit 3).
4. Ocular symptoms: Subjects were queried at each visit “How are you feeling?” and treatment emergent AEs beginning at Qualification Visit #2 (Visit 3) were documented on the AE form. Additional symptoms reported after screening and before randomization were documented on the medical history form.
5. Comfort test: At 08:00 hour for study drug visits, subjects were queried “Did you experience any discomfort when placing the drops in your eyes?”
6. Individuals returning at an unscheduled visit within 1 week were required to only remeasure IOP in both eyes
7. Gonioscopy evaluation up to 3 months prior to randomization was acceptable.
8. Pachymetry within one week of Screening was acceptable.
9. Entry visual field evaluation up to 3 months prior to randomization was acceptable. Visual field collection had to meet the requirement for automated threshold visual field assessment (e.g., 30-2 or 24-2 Humphrey) and reliability.
10. Ophthalmoscopy (dilated) at day 90 (Visit 6.0): this assessment was performed for all non-completing subjects during the exit visit.
11. Collect used kit(s) dispensed during the previous visit. Collection of used kit(s) may have occurred anytime during this visit. Subjects who failed to return their used study medication as requested at their next study visit may have returned it at the following study visit.

Source: Table 3 of Study 302 Report.

## Appendix 2: The Applicant's SAS code for the Primary Analysis

For the primary efficacy analysis, the following information was provided in the applicant's SAP:

“The following SAS code will be used for multiple imputations using the Monte-Carlo Markov Chain method, where a separate model will be fit for each time point at each visit.

```
proc mi data = indata seed = 48669 out = outdata1;  
  mcmc initial = em;  
  var trt01pn baseline IOP;  
run;
```

where

- *indata* is the name of the input dataset
- *outdata* is the name of the output dataset
- *trt01pn* is the name of the treatment group variable in numeric format
- *baseline* captures the baseline IOP for the given time point
- *IOP* is the name of the IOP measure.

Five complete data sets will be generated from the above code. Each complete data set will be used to analyze this primary efficacy endpoint separately using analysis of variance. Then, the SAS procedure MIANALYZE will be used to analyze the results from the 5 complete data sets to generate a combined inference. The following SAS code will be used:

```
ods output diffs = outdata2;  
proc mixed data = outdata1;  
  class trt01pn;  
  model IOP=trt01pn baseline;  
  lsmeans trt01pn / cl pdiff;  
  by _Imputation_;  
run;  
proc sort data=outdata2;  
  by trt01pn _trt01pn;  
run;  
ods output ParameterEstimates = outdata3;  
proc mianalyze data = outdata2 alpha = 0.05;  
  by trt01pn _trt01pn;  
  class trt01pn _trt01pn;  
  modeleffects estimate;  
  stderr stderr;  
run;
```

where

- *IOP* is the name of the IOP measure
- *trt01pn* is the name of the treatment group variable in numeric format
- *outdata2* is the name of the output dataset that contains the statistical results of the differences between treatment groups

- *outdata3* is the name of the output dataset that contains summary and inferential statistics.”

### Appendix 3: Selected Supportive Analyses Results

**Table 28: Baseline Adjusted ANCOVAs for Study Eye IOP (mmHg) at Each Post-Dose Time Point (ITT MCMC)**

	Study 301			Study 302		
	Rocklatan n = 238	Netarsudil n = 244	Latanoprost n = 236	Rocklatan n = 245	Netarsudil n = 255	Latanoprost n = 250
Mean Baseline IOP						
8am	24.8	24.8	24.6	24.7	24.7	24.8
10am	23.7	23.5	23.4	23.3	23.4	23.2
4pm	22.6	22.6	22.4	22.4	22.8	22.6
Day 15, 8am						
Mean IOP	15.6	18.6	17.8	16.1	19.4	18.1
Difference from Rocklatan		-3.0	-2.2		-3.3	-2.0
95% 2-sided CI		(-3.6, -2.4)	(-2.8, -1.7)		(-3.9, -2.8)	(-2.6, -1.5)
Day 15, 10am						
Mean IOP	14.8	17.8	17.4	15.3	17.9	17.7
Difference from Rocklatan		-3.0	-2.6		-2.6	-2.4
95% 2-sided CI		(-3.6, -2.4)	(-3.2, -2.0)		(-3.2, -2.1)	(-2.9, -1.8)
Day 15, 4pm						
Mean IOP	14.8	17.2	17.2	15.3	17.4	17.1
Difference from Rocklatan		-2.4	-2.4		-2.2	-1.8
95% 2-sided CI		(-2.9, -1.9)	(-2.9, -1.8)		(-2.7, -1.7)	(-2.3, -1.3)
Day 43, 8am						
Mean IOP	16.0	19.1	17.7	16.4	19.5	17.9
Difference from Rocklatan		-3.2	-1.7		-3.1	-1.5
95% 2-sided CI		(-3.8, -2.6)	(-2.4, -1.1)		(-3.7, -2.5)	(-2.1, -0.9)
Day 43, 10am						
Mean IOP	15.2	18.1	17.1	15.5	18.4	17.4
Difference from Rocklatan		-2.9	-1.9		-2.8	-1.9
95% 2-sided CI		(-3.3, -2.1)	(-2.5, -1.3)		(-3.4, -2.3)	(-2.4, -1.3)
Day 43, 4pm						
Mean IOP	15.3	17.6	17.0	15.6	17.9	17.1
Difference from Rocklatan		-2.3	-1.7		-2.3	-1.5
95% 2-sided CI		(-2.8, -1.7)	(-2.2, -1.1)		(-2.8, -1.7)	(-2.1, -1.0)
Day 90, 8am						
Mean IOP	16.0	19.0	17.7	16.5	19.8	18.0
Difference from Rocklatan		-3.0	-1.7		-3.3	-1.5
95% 2-sided CI		(-3.7, -2.4)	(-2.4, -1.1)		(-3.9, -2.7)	(-2.1, -0.9)
Day 90, 10am						
Mean IOP	15.3	18.0	17.1	15.6	18.3	17.5
Difference from Rocklatan		-2.7	-1.8		-2.7	-2.0
95% 2-sided CI		(-3.3, -2.1)	(-2.4, -1.2)		(-3.3, -2.1)	(-2.5, -1.4)

Day 90, 4pm						
Mean IOP	15.4	17.5	17.0	15.6	17.9	17.1
Difference from Rocklatan		-2.1	-1.6		-2.2	-1.5
95% 2-sided CI		(-2.7, -1.5)	(-2.2, -1.0)		(-2.8, -1.7)	(-2.1, -0.9)

<sup>1</sup> Difference from PG324, and 2-sided CIs were based on an ANCOVA comparing PG324 with netarsudil 0.02% QD and latanoprost 0.005% QD. The ANCOVA model has treatment as a factor and baseline IOP as a covariate, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.1 of Study 301 Report and Table 14.2.1.1.1 of Study 302 Report.

**Table 29: Baseline Adjusted ANCOVAs for Study Eye IOP (mmHg) at Each Post-Dose Time Point (ITT LOCF)**

	Study 301			Study 302		
	Rocklatan n = 238	Netarsudil n = 244	Latanoprost n = 236	Rocklatan n = 245	Netarsudil n = 255	Latanoprost n = 250
Mean Baseline IOP						
8am	24.8	24.8	24.6	24.7	24.7	24.8
10am	23.7	23.5	23.4	23.3	23.4	23.2
4pm	22.6	22.6	22.4	22.4	22.8	22.6
Day 15, 8am						
Mean IOP	15.9	18.7	17.9	16.3	19.5	18.2
Difference from Rocklatan		-2.9	-2.0		-3.2	-1.9
95% 2-sided CI		(-3.4, -2.3)	(-2.6, -1.4)		(-3.8, -2.6)	(-2.5, -1.3)
Day 15, 10am						
Mean IOP	15.1	18.1	17.5	15.5	18.1	17.7
Difference from Rocklatan		-3.0	-2.4		-2.5	-2.2
95% 2-sided CI		(-3.6, -2.4)	(-3.1, -1.8)		(-3.1, -2.0)	(-2.7, -1.6)
Day 15, 4pm						
Mean IOP	15.1	17.4	17.3	15.5	17.6	17.2
Difference from Rocklatan		-2.3	-2.2		-2.1	-1.6
95% 2-sided CI		(-2.9, -1.8)	(-2.8, -1.7)		(-2.6, -1.6)	(-2.2, -1.1)
Day 43, 8am						
Mean IOP	16.2	19.1	17.8	16.7	19.7	17.9
Difference from Rocklatan		-2.9	-1.6		-3.0	-1.3
95% 2-sided CI		(-3.6, -2.3)	(-2.2, -1.0)		(-3.6, -2.4)	(-1.9, -0.7)
Day 43, 10am						
Mean IOP	15.5	18.3	17.3	15.8	18.5	17.4
Difference from Rocklatan		-2.8	-1.8		-2.7	-1.7
95% 2-sided CI		(-3.4, -2.2)	(-2.4, -1.2)		(-3.3, -2.1)	(-2.2, -1.1)
Day 43, 4pm						
Mean IOP	15.6	17.8	17.2	15.8	18.0	17.2
Difference from Rocklatan		-2.2	-1.6		-2.2	-1.4
95% 2-sided CI		(-2.7, -1.6)	(-2.1, -1.0)		(-2.7, -1.6)	(-1.9, -0.8)
Day 90, 8am						
Mean IOP	16.4	19.5	17.7	16.7	20.1	18.0
Difference from Rocklatan		-3.0	-1.3		-3.4	-1.3
95% 2-sided CI		(-3.6, -2.4)	(-1.9, -0.7)		(-4.0, -2.8)	(-1.9, -0.7)
Day 90, 10am						

Mean IOP	15.4	18.6	17.1	15.8	18.6	17.6
Difference from Rocklatan		-3.2	-1.6		-2.8	-2.0
95% 2-sided CI		(-3.8, -2.5)	(-2.3, -1.0)		(-3.3, -2.2)	(-2.3, -1.2)
Day 90, 4pm						
Mean IOP	15.6	17.7	16.9	15.9	18.2	17.2
Difference from Rocklatan		-2.1	-1.3		-2.4	-1.3
95% 2-sided CI		(-2.7, -1.5)	(-1.8, -0.7)		(-2.9, -1.8)	(-1.8, -0.8)

<sup>1</sup> Difference from PG324, and 2-sided CIs were based on an ANCOVA comparing PG324 with netarsudil 0.02% QD and latanoprost 0.005% QD. The ANCOVA model has treatment as a factor and baseline IOP as a covariate, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.3 of Study 301 Report and Table 14.2.1.1.3 of Study 302 Report

**Table 30: Baseline Adjusted ANCOVAs for Study Eye IOP (mmHg) at Each Post-Dose Time Point (ITT BOCF)**

	Study 301			Study 302		
	Rocklatan n = 238	Netarsudil n = 244	Latanoprost n = 236	Rocklatan n = 245	Netarsudil n = 255	Latanoprost n = 250
Mean Baseline IOP						
8am	24.8	24.8	24.6	24.7	24.7	24.8
10am	23.7	23.5	23.4	23.3	23.4	23.2
4pm	22.6	22.6	22.4	22.4	22.8	22.6
Day 15, 8am						
Mean IOP	15.9	18.7	17.9	16.3	19.5	18.2
Difference from Rocklatan		-2.9	-2.0		-3.2	-1.9
95% 2-sided CI		(-3.4, -2.3)	(-2.6, -1.4)		(-3.8, -2.6)	(-2.5, -1.3)
Day 15, 10am						
Mean IOP	15.1	18.1	17.5	15.5	18.1	17.7
Difference from Rocklatan		-3.0	-2.4		-2.5	-2.2
95% 2-sided CI		(-3.6, -2.4)	(-3.1, -1.8)		(-3.1, -2.0)	(-2.7, -1.6)
Day 15, 4pm						
Mean IOP	15.1	17.4	17.3	15.5	17.6	17.2
Difference from Rocklatan		-2.3	-2.2		-2.1	-1.6
95% 2-sided CI		(-2.9, -1.8)	(-2.8, -1.7)		(-2.6, -1.6)	(-2.2, -1.1)
Day 43, 8am						
Mean IOP	16.6	19.5	17.9	16.8	19.7	18.1
Difference from Rocklatan		-2.9	-1.4		-2.9	-1.3
95% 2-sided CI		(-3.6, -2.3)	(-2.0, -0.7)		(-3.6, -2.3)	(-1.9, -0.7)
Day 43, 10am						
Mean IOP	15.9	18.6	17.4	15.9	18.5	17.5
Difference from Rocklatan		-2.6	-1.4		-2.6	-1.9
95% 2-sided CI		(-3.2, -2.0)	(-2.0, -0.8)		(-3.2, -2.1)	(-2.2, -1.1)
Day 43, 4pm						
Mean IOP	16.0	18.0	17.3	15.9	18.0	17.3
Difference from Rocklatan		-2.0	-1.2		-2.1	-1.5
95% 2-sided CI		(-2.6, -1.4)	(-1.8, -0.6)		(-2.7, -1.5)	(-2.0, -0.8)
Day 90, 8am						
Mean IOP	17.4	20.1	18.0	17.1	20.4	18.3

Difference from Rocklatan 95% 2-sided CI		-2.8 (-3.5, -2.1)	-0.6 (-1.3, 0.1)		-3.3 (-3.9, -2.6)	-1.2 (-1.8, -0.5)
Day 90, 10am						
Mean IOP	16.6	19.3	17.2	16.3	18.9	17.8
Difference from Rocklatan 95% 2-sided CI		-2.7 (-3.4, -2.1)	-0.6 (-1.3, 0.1)		-2.6 (-3.2, -2.0)	-1.5 (-2.1, -1.0)
Day 90, 4pm						
Mean IOP	16.6	18.3	17.0	16.3	18.5	17.4
Difference from Rocklatan 95% 2-sided CI		-1.7 (-2.4, -1.1)	-0.6 (-1.1, 0.2)		-2.2 (-2.7, -1.6)	-1.1 (-1.7, -0.6)

<sup>1</sup> Difference from PG324, and 2-sided CIs were based on an ANCOVA comparing PG324 with netarsudil 0.02% QD and latanoprost 0.005% QD. The ANCOVA model has treatment as a factor and baseline IOP as a covariate, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Table 14.2.1.1.4 of Study 301 Report and Table 14.2.1.1.4 of Study 302 Report.

**Table 31: Mean Study Eye IOP (mmHg) at Each Post-Dose Time Point (ITT MMRM)**

	Study 301			Study 302		
	Rocklatan n = 238	Netarsudil n = 244	Latanoprost n = 236	Rocklatan n = 245	Netarsudil n = 255	Latanoprost n = 250
Mean Baseline IOP						
8am	24.8	24.8	24.6	24.7	24.7	24.8
10am	23.7	23.5	23.4	23.3	23.4	23.2
4pm	22.6	22.6	22.4	22.4	22.8	22.6
Day 15, 8am						
n	231	241	234	238	252	246
Mean IOP	15.5	18.4	17.6	15.7	19.0	17.7
Difference from Rocklatan 95% 2-sided CI		-3.0 (-3.6, -2.4)	-2.1 (-2.7, -1.5)		-3.4 (-4.0, -2.8)	-2.1 (-2.6, -1.5)
Day 15, 10am						
n	232	236	232	236	249	247
Mean IOP	14.9	17.8	17.4	15.4	18.1	17.7
Difference from Rocklatan 95% 2-sided CI		-2.9 (-3.6, -2.3)	-2.5 (-3.1, -1.8)		-2.8 (-3.3, -2.2)	-2.4 (-2.9, -1.8)
Day 15, 4pm						
n	231	237	231	235	248	247
Mean IOP	15.1	17.5	17.3	15.5	17.9	17.4
Difference from Rocklatan 95% 2-sided CI		-2.4 (-3.0, -1.9)	-2.3 (-2.8, -1.7)		-2.4 (-2.9, -1.9)	-1.9 (-2.4, -1.4)
Day 43, 8am						
n	221	227	226	234	248	242
Mean IOP	15.8	18.9	17.4	16.1	19.3	17.5
Difference from Rocklatan 95% 2-sided CI		-3.1 (-3.8, -2.4)	-1.6 (-2.3, -1.0)		-3.2 (-3.8, -2.6)	-1.5 (-2.1, -0.9)
Day 43, 10am						
n	217	223	225	233	247	242
Mean IOP	15.4	18.2	17.2	15.6	18.5	17.4
Difference from Rocklatan		-2.7	-1.7		-2.9	-1.9

95% 2-sided CI		(-3.4, -2.1)	(-2.4, -1.1)		(-3.5, -2.4)	(-2.4, -1.3)
<b>Day 43, 4pm</b>						
n	216	223	225	232	247	241
Mean IOP	15.7	17.9	17.2	15.8	18.3	17.4
Difference from Rocklatan		-2.3	-1.5		-2.5	-1.6
95% 2-sided CI		(-2.9, -1.7)	(-2.1, -0.9)		(-3.1, -1.9)	(-2.2, -1.1)
<b>Day 90, 8am</b>						
n	204	205	223	223	231	236
Mean IOP	16.0	19.2	17.4	16.1	19.7	17.6
Difference from Rocklatan		-3.2	-1.3		-3.7	-1.6
95% 2-sided CI		(-3.9, -2.5)	(-2.0, -0.7)		(-4.3, -3.0)	(-2.2, -0.9)
<b>Day 90, 10am</b>						
n	200	200	223	222	228	236
Mean IOP	15.4	18.5	16.9	15.7	18.6	17.6
Difference from Rocklatan		-3.1	-1.5		-3.0	-1.9
95% 2-sided CI		(-3.8, -2.5)	(-2.2, -0.9)		(-3.5, -2.4)	(-2.5, -1.3)
<b>Day 90, 4pm</b>						
n	200	198	223	221	228	236
Mean IOP	15.7	17.9	16.9	15.9	18.5	17.4
Difference from Rocklatan		-2.2	-1.2		-2.6	-1.6
95% 2-sided CI		(-2.8, -1.6)	(-1.8, -0.6)		(-3.1, -2.1)	(-2.1, -1.0)

\* Difference from PG324 and two-sided CIs are based on an MMRM comparing PG324 QD with Netarsudil 0.02% QD and Latanoprost 0.005% QD. The MMRM model has treatment, visit, timepoint, treatment\*visit, treatment\*timepoint, visit\*timepoint, and treatment\*visit\*timepoint as factors, baseline as a covariate, and subjects as the repeated random factor using an unstructured covariance matrix.

Source: Table 14.2.3 of Study 301 Report and Table 14.2.3 of Study 302 Report

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

Table 32: Study 301 Mean IOP Subgroup Analyses by Gender, Age, and Race

Sub group	Day	Time	Mean IOP						Treatment Difference (95% CI) <sup>†</sup>	
			8am		10am		4pm		PG324 vs. Netarsudil	PG324 vs. Latanoprost
			N	IOP	N	IOP	N	IOP		
<b>Female</b>	<b>15</b>	<b>8am</b>	128	15.7	136	18.3	134	17.8	-2.6 (-3.4, -1.9)	-2.1 (-2.9, -1.4)
		<b>10am</b>	129	15.1	135	17.7	132	17.4	-2.7 (-3.5, -1.9)	-2.3 (-3.1, -1.5)
		<b>4pm</b>	128	14.9	135	17.2	131	17.3	-2.3 (-3.0, -1.6)	-2.3 (-3.0, -1.6)
<b>Male</b>	<b>15</b>	<b>8am</b>	103	15.5	105	19.0	100	17.8	-3.6 (-4.4, -2.7)	-2.4 (-3.3, -1.5)
		<b>10am</b>	103	14.6	101	18.0	100	17.5	-3.5 (-4.4, -2.5)	-2.9 (-3.8, -2.0)
		<b>4pm</b>	103	14.7	102	17.3	100	17.0	-2.6 (-3.4, -1.8)	-2.4 (-3.2, -1.5)
<b>Female</b>	<b>43</b>	<b>8am</b>	122	16.0	130	18.9	129	17.8	-2.9 (-3.8, -2.1)	-1.9 (-2.7, -1.0)
		<b>10am</b>	119	15.5	130	18.1	128	17.3	-2.6 (-3.4, -1.9)	-1.9 (-2.7, -1.1)
		<b>4pm</b>	118	15.6	130	17.7	128	17.0	-2.1 (-2.8, -1.3)	-1.5 (-2.2, -0.7)
<b>Male</b>	<b>43</b>	<b>8am</b>	99	15.9	97	19.4	97	17.5	-3.5 (-4.4, -2.6)	-1.6 (-2.5, -0.7)
		<b>10am</b>	98	15.0	93	18.2	97	16.9	-3.2 (-4.1, -2.3)	-1.9 (-2.8, -1.0)
		<b>4pm</b>	98	15.0	93	17.5	97	16.9	-2.5 (-3.4, -1.7)	-1.9 (-2.8, -1.1)
<b>Female</b>	<b>90</b>	<b>8am</b>	108	16.2	119	18.9	127	17.6	-2.6 (-3.5, -1.8)	-1.4 (-2.2, -0.5)
		<b>10am</b>	107	15.5	114	17.9	127	16.9	-2.4 (-3.2, -1.5)	-1.4 (-2.2, -0.6)
		<b>4pm</b>	107	15.7	112	17.0	127	16.7	-1.4 (-2.1, -0.6)	-1.0 (-1.8, -0.2)
<b>Male</b>	<b>90</b>	<b>8am</b>	96	16.0	86	19.8	96	17.6	-3.8 (-4.8, -2.9)	-1.6 (-2.5, -0.7)

		<b>10am</b>	93	14.9	86	19.0	96	16.8	-4.1 (-5.1, -3.2)	-1.9 (-2.8, -1.0)
		<b>4pm</b>	93	15.1	86	17.9	96	16.7	-2.9 (-3.7, -2.0)	-1.6 (-2.5, -0.8)
<b>Age</b>										
<b>&lt; 65</b>	<b>15</b>	<b>8am</b>	104	14.7	103	17.1	92	17.0	-2.3 (-3.1, -1.5)	-2.3 (-3.1, -1.5)
		<b>10am</b>	104	14.9	102	17.8	92	17.3	-2.9 (-3.7, -2.1)	-2.4 (-3.2, -1.6)
		<b>4pm</b>	104	14.7	103	17.1	92	17.0	-2.3 (-3.1, -1.5)	-2.3 (-3.1, -1.5)
<b>&gt; 65</b>	<b>15</b>	<b>8am</b>	127	14.9	134	17.4	139	17.2	-2.5 (-3.2, -1.8)	-2.3 (-3.0, -1.6)
		<b>10am</b>	127	15.2	134	18.0	139	17.6	-2.8 (-3.5, -2.1)	-2.4 (-3.1, -1.7)
		<b>4pm</b>	127	14.9	134	17.4	139	17.2	-2.5 (-3.2, -1.8)	-2.3 (-3.0, -1.6)
<b>&lt; 65</b>	<b>43</b>	<b>8am</b>	101	15.6	101	19.1	91	17.6	-3.5 (-4.4, -2.6)	-2.0 (-2.9, -1.1)
		<b>10am</b>	100	14.8	101	18.1	90	17.1	-3.2 (-4.1, -2.4)	-2.3 (-3.2, -1.4)
		<b>4pm</b>	100	14.9	101	17.5	90	17.0	-2.6 (-3.4, -1.8)	-2.1 (-3.0, -1.3)
<b>&gt; 65</b>	<b>43</b>	<b>8am</b>	120	16.3	126	19.1	135	17.8	-2.9 (-3.7, -2.1)	-1.5 (-2.3, -0.7)
		<b>10am</b>	117	15.6	122	18.2	135	17.1	-2.6 (-3.4, -1.8)	-1.6 (-2.3, -0.8)
		<b>4pm</b>	116	15.7	122	17.4	135	16.9	-2.0 (-2.8, -1.2)	-1.3 (-2.0, -0.5)
<b>&lt; 65</b>	<b>90</b>	<b>8am</b>	96	15.7	97	19.3	89	17.4	-3.6 (-4.5, -2.7)	-1.7 (-2.6, -0.7)
		<b>10am</b>	95	15.0	96	18.3	89	16.6	-3.4 (-4.3, -2.5)	-1.7 (-2.6, -0.7)
		<b>4pm</b>	95	15.2	95	17.4	89	16.6	-2.3 (-3.1, -1.4)	-1.4 (-2.2, -0.5)
<b>&gt; 65</b>	<b>90</b>	<b>8am</b>	108	16.5	108	19.2	134	17.7	-2.7 (-3.6, -1.9)	-1.2 (-2.1, -0.4)
		<b>10am</b>	105	15.4	104	18.4	134	17.0	-3.0 (-3.8, -2.1)	-1.6 (-2.4, -0.8)
		<b>4pm</b>	105	15.6	103	17.4	134	16.8	-1.8 (-2.6, -1.0)	-1.2 (-2.0, -0.4)
<b>Race</b>										
<b>Caucasian</b>	<b>15</b>	<b>8am</b>	158	15.4	165	18.2	156	17.8	-2.8 (-3.5, -2.1)	-2.4 (-3.1, -1.7)
		<b>10am</b>	158	14.5	161	17.3	154	17.5	-2.8 (-3.5, -2.1)	-3.0 (-3.7, -2.2)
		<b>4pm</b>	158	14.6	162	16.9	153	17.3	-2.3 (-2.9, -1.6)	-2.6 (-3.3, -2.0)
<b>Other</b>	<b>15</b>	<b>8am</b>	73	16.0	76	19.5	78	17.9	-3.5 (-4.5, -2.5)	-1.8 (-2.8, -0.8)
		<b>10am</b>	74	15.6	75	19.1	78	17.3	-3.5 (-4.6, -2.5)	-1.8 (-2.8, -0.7)
		<b>4pm</b>	73	15.2	75	-2.8	78	-1.7	-2.8 (-3.8, -1.9)	-1.7 (-2.7, -0.8)
<b>Caucasian</b>	<b>43</b>	<b>8am</b>	149	15.8	154	18.7	150	17.7	-3.0 (-3.7, -2.2)	-1.9 (-2.6, -1.1)
		<b>10am</b>	146	14.9	152	17.7	149	17.0	-2.8 (-3.5, -2.1)	-2.1 (-2.8, -1.4)
		<b>4pm</b>	145	15.0	152	17.4	149	16.9	-2.3 (-3.0, -1.6)	-1.9 (-2.6, -1.2)
<b>Other</b>	<b>43</b>	<b>8am</b>	72	16.3	73	20.0	76	17.8	-3.6 (-4.7, -2.6)	-1.4 (-2.5, -0.4)
		<b>10am</b>	71	15.9	71	19.1	76	17.3	-3.2 (-4.2, -2.2)	-1.4 (-2.4, -0.4)
		<b>4pm</b>	71	15.9	71	18.1	76	17.1	-2.2 (-3.2, -1.2)	-1.2 (-2.2, -0.2)
<b>Caucasian</b>	<b>90</b>	<b>8am</b>	135	16.2	137	18.7	148	17.7	-2.5 (-3.3, -1.8)	-1.6 (-2.3, -0.8)
		<b>10am</b>	131	15.1	135	17.9	148	16.9	-2.8 (-3.6, -2.0)	-1.8 (-2.6, -1.1)
		<b>4pm</b>	131	15.3	134	17.2	148	16.8	-1.9 (-2.6, -1.2)	-1.5 (-2.2, -0.8)
<b>Other</b>	<b>90</b>	<b>8am</b>	69	16.1	68	20.4	75	17.4	-4.3 (-5.4, -3.3)	-1.3 (-2.3, -0.2)
		<b>10am</b>	69	15.4	65	19.3	75	16.7	-3.9 (-5.0, -2.8)	-1.3 (-2.3, -0.3)
		<b>4pm</b>	69	15.7	64	17.9	75	16.6	-2.3 (-3.3, -1.3)	-0.9 (-1.9, 0.1)

<sup>1</sup> Difference from PG324, and 2-sided CIs were based on an ANCOVA comparing PG324 with netarsudil 0.02% QD and latanoprost 0.005% QD using observed data. The ANCOVA model had treatment as a factor, baseline IOP and corresponding baseline characteristics (gender, or age category, or race) as covariates, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Tables 14.2.6.4, 14.2.6.5, and 14.2.6.6 of Study 301 tables.

**Table 33: Study 302 Mean IOP Subgroup Analyses by Gender, Age, and Race**

Sub group	Day	Time	Mean IOP						Treatment Difference (95% CI) <sup>1</sup>	
			N	IOP	N	IOP	N	IOP	PG324 vs. Netarsudil	PG324 vs. Latanoprost
<b>Female</b>	<b>15</b>	<b>8am</b>	148	16.3	150	19.5	141	18.2	-3.2 (-3.9, -2.5)	-1.9 (-2.6, -1.1)
		<b>10am</b>	146	15.5	150	18.0	142	17.7	-2.5 (-3.2, -1.8)	-2.2 (-2.9, -1.5)
		<b>4pm</b>	145	15.6	149	17.6	142	17.3	-2.0 (-2.7, -1.4)	-1.7 (-2.4, -1.1)
<b>Male</b>	<b>15</b>	<b>8am</b>	90	15.6	102	19.2	105	18.0	-3.6 (-4.5, -2.7)	-2.3 (-3.2, -1.5)

Female	43	10am	90	14.9	99	17.9	105	17.6	-3.1 (-3.9, -2.2)	-2.7 (-3.6, -1.9)
		4pm	90	14.7	99	17.3	105	16.8	-2.6 (-3.4, -1.8)	-2.1 (-2.9, -1.3)
		8am	144	16.9	149	19.8	139	17.9	-2.9 (-3.7, -2.2)	-1.0 (-1.8, -0.2)
		10am	143	15.8	149	18.5	139	17.4	-2.7 (-3.5, -2.0)	-1.6 (-2.3, -0.9)
Male	43	4pm	143	15.8	149	18.1	138	17.4	-2.4 (-3.1, -1.7)	-1.6 (-2.4, -0.9)
		8am	90	15.7	99	19.3	103	17.9	-3.6 (-4.6, -2.6)	-2.2 (-3.2, -1.3)
		10am	90	15.1	98	18.2	103	17.4	-3.1 (-4.0, -2.2)	-2.3 (-3.2, -1.4)
Female	90	4pm	89	15.2	98	17.5	103	16.8	-2.3 (-3.2, 1.4)	-1.6 (-2.4, -0.7)
		8am	135	16.7	135	20.1	135	17.9	-3.4 (-4.2, -2.6)	-1.2 (-2.0, -0.4)
		10am	134	15.7	132	18.5	135	17.5	-2.8 (-3.5, -2.1)	-1.8 (-2.5, -1.1)
		4pm	134	15.8	132	18.2	135	17.0	-2.3 (-3.1, -1.7)	-1.2 (-1.9, -0.5)
Male	90	8am	88	15.8	96	19.7	101	17.9	-3.9 (-4.8, -2.9)	-2.1 (-3.0, -1.1)
		10am	88	15.3	96	18.2	101	17.5	-2.9 (-3.8, -2.1)	-2.2 (-3.0, -1.3)
		4pm	87	15.3	96	17.7	101	17.3	-2.4 (-3.2, -1.6)	-2.0 (-2.9, -1.2)
<b>Age</b>										
< 65	15	8am	116	16.1	108	19.5	111	18.5	-3.5 (-4.3, -2.7)	-2.4 (-3.3, -1.6)
		10am	114	15.2	105	18.1	111	18.1	-2.9 (-3.7, -2.1)	-2.9 (-3.7, -2.1)
		4pm	113	15.4	105	17.4	110	17.4	-2.1 (-2.8, -1.3)	-2.1 (-2.8, -1.3)
> 65	15	8am	122	16.0	144	19.3	135	17.7	-3.3 (-4.1, -2.5)	-1.7 (-2.5, -0.9)
		10am	122	15.3	144	17.9	136	17.3	-2.6 (-3.3, -1.9)	-2.0 (-2.7, -1.3)
		4pm	122	15.1	143	17.5	137	16.8	-2.4 (-3.1, -1.7)	-1.7 (-2.4, -1.0)
< 65	43	8am	114	16.4	106	19.9	107	18.3	-3.5 (-4.4, -2.6)	-1.9 (-2.8, -1.0)
		10am	113	15.5	106	18.5	107	17.7	-3.0 (-3.8, -2.2)	-2.2 (-3.0, -1.4)
		4pm	112	15.4	106	17.9	107	17.8	-2.5 (-3.3, -1.7)	-2.4 (-3.2, -1.6)
> 65	43	8am	120	16.4	142	19.4	135	17.6	-2.9 (-3.8, -2.1)	-1.2 (-2.0, -0.3)
		10am	120	15.5	141	18.3	135	17.1	-2.8 (-3.5, -2.0)	-1.6 (-2.4, -0.8)
		4pm	120	15.7	141	17.9	134	16.6	-2.2 (-2.9, -1.4)	-0.9 (-1.7, -0.2)
< 65	90	8am	110	16.4	100	19.9	106	18.2	-3.5 (-4.4, -2.6)	-1.8 (-2.7, -1.0)
		10am	110	15.6	98	18.5	106	17.8	-2.9 (-3.7, -2.1)	-2.3 (-3.0, -1.5)
		4pm	110	15.9	98	17.9	106	17.4	-2.1 (-2.9, -1.3)	-1.6 (-2.3, -0.8)
> 65	90	8am	113	16.4	131	20.0	130	17.7	-3.6 (-4.5, -2.8)	-1.3 (-2.1, -0.5)
		10am	112	15.6	130	18.3	130	17.3	-2.8 (-3.5, -2.0)	-1.7 (-2.5, -1.0)
		4pm	111	15.3	130	18.0	130	16.8	-2.7 (-3.4, -2.0)	-1.6 (-2.3, -0.8)
<b>Race</b>										
Caucasian	15	8am	156	15.8	162	19.4	159	18.2	-3.6 (-4.2, -2.9)	-2.4 (-3.1, -1.7)
		10am	154	15.1	160	17.7	160	18.0	-2.6 (-3.3, -2.0)	-2.8 (-3.5, -2.2)
		4pm	154	15.3	159	17.5	160	17.4	-2.2 (-2.8, -1.6)	-2.1 (-2.8, -1.5)
Other	15	8am	82	16.5	90	19.5	87	17.8	-3.0 (-4.0, -2.1)	-1.3 (-2.2, -0.4)
		10am	82	15.5	89	18.4	87	17.1	-2.9 (-3.8, -2.0)	-1.6 (-2.5, -0.7)
		4pm	81	15.2	89	17.5	87	16.5	-2.3 (-3.2, -1.5)	-1.3 (-2.2, -0.5)
Caucasian	43	8am	152	16.3	160	19.6	156	18.0	-3.3 (-4.0, -2.6)	-1.7 (-2.5, -0.9)
		10am	152	15.4	159	18.3	156	17.7	-2.9 (-3.6, -2.2)	-2.3 (-3.0, -1.6)
		4pm	152	15.5	159	17.9	156	17.3	-2.4 (-3.1, -1.7)	-1.8 (-2.5, -1.1)
Other	43	8am	82	16.6	88	19.5	86	17.7	-3.0 (-4.0, -2.0)	-1.1 (-2.1, -0.1)
		10am	81	15.8	88	18.6	86	16.9	-2.9 (-3.8, -1.9)	-1.1 (-2.1, -0.2)
		4pm	80	15.6	88	17.8	85	16.8	-2.2 (-3.2, -1.3)	-1.2 (-2.1, -0.3)
Caucasian	90	8am	145	16.4	149	20.1	150	18.1	-3.7 (-4.4, -2.9)	-1.7 (-2.4, -0.9)
		10am	144	15.5	146	18.5	151	17.5	-3.0 (-3.6, -2.3)	-1.9 (-2.6, -1.3)
		4pm	144	15.7	146	18.0	151	17.1	-2.4 (-3.0, -1.7)	-1.4 (-2.1, -0.8)
Other	90	8am	78	16.3	82	19.8	86	17.6	-3.4 (-4.5, -2.4)	-1.3 (-2.3, -0.3)
		10am	78	15.6	82	18.2	85	17.6	-2.6 (-3.5, -1.7)	-2.0 (-2.9, -1.1)
		4pm	77	15.4	82	17.9	85	17.2	-2.5 (-3.4, -1.6)	-1.7 (-2.6, -0.9)

<sup>1</sup> Difference from PG324, and 2-sided CIs were based on an ANCOVA comparing PG324 with netarsudil 0.02% QD and latanoprost 0.005% QD using observed data. The ANCOVA model had treatment as a factor, baseline IOP and corresponding baseline characteristics (gender, or age category, or race) as covariates, where baseline IOP refers to the IOP data from Visit 3 (Day 1) for the corresponding time point.

Source: Tables 14.2.6.4, 14.2.6.5, and 14.2.6.6 of Study 302 tables.

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/s/  
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YUNFAN DENG  
02/08/2019 03:09:56 PM

YAN WANG  
02/08/2019 03:17:33 PM  
I concur.