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RESEARCH**

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Sonal D. Wadhwa, MD
NDA 208259
Rocklatan (netarsudil and latanoprost ophthalmic solution)

CLINICAL REVIEW 208259

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Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	
Established/Proper Name	Netarsudil and latanoprost ophthalmic solution
(Proposed) Trade Name	Rocklatan
Applicant	Aerie Pharmaceuticals, Inc.
Dosage Form(s)	Ophthalmic solution
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye once daily in the evening
Applicant Proposed Indication(s)/Population(s)	Patients with open-angle glaucoma or ocular hypertension
Recommendation on Regulatory Action	Recommended for approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

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Glossary

AC	advisory committee
AE	adverse event
BID	twice daily
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IOP	intraocular pressure
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NME	new molecular entity
PD	pharmacodynamics
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Netarsudil 0.02% and latanoprost 0.005% ophthalmic solution (formerly PG324, hereafter referred to as netarsudil/latanoprost) is a fixed-dose combination (FDC) of 2 FDA-approved ocular hypotensive active components, netarsudil 0.02% and latanoprost 0.005%, and has been developed by Aerie Pharmaceuticals, Inc. (Aerie) as a once-daily treatment for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 208259 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Rocklatan for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

1.3. Benefit-Risk Integrated Assessment

The data contained in this submission establishes that administration of netarsudil/latanoprost ophthalmic solution dosed once daily in the evening will lower intraocular pressure in patients in patients with open-angle glaucoma or ocular hypertension.

Studies 301 and 302 demonstrate that the IOP lowering ability of netarsudil/latanoprost ophthalmic solution is superior to either netarsudil or latanoprost alone. When looking at the Day 90 three timepoints and comparing the combination product to latanoprost alone the combination product gives an additional 1.95-2.19 mmHg IOP lowering in Study 301 and an additional 2.02-2.32 mmHg IOP lowering in Study 302. Not only is this decrease statistically significant, but the side effect profile of adding netarsudil does not add an increased risk of death as was seen in the combination prostaglandin/timolol trials.

The most common ocular adverse events for netarsudil/latanoprost are: conjunctival hyperemia, instillation site pain, corneal verticillata, conjunctival hemorrhage.

The benefit of netarsudil/latanoprost ophthalmic solution in lowering intraocular pressure outweighs the risks to patients with open-angle glaucoma or ocular hypertension.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated IOP.	Intraocular pressure establishes a direct measure of the efficacy of ocular hypotensive medications.
Current Treatment Options	There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, rho kinase inhibitors and prostaglandin analogues.	Different classes of products lower intraocular pressure by either decreasing aqueous production or increasing aqueous outflow. Additional reduction in IOP can be achieved by administering products from different classes of IOP reducing products.
Benefit	When more than one class of topical IOP lowering medication is needed, patients must wait 5-10 minutes between administering drops in the eye to prevent diluting the drug product. A combination product avoids the need to wait between drops.	The combination product demonstrated greater IOP reduction than either of the individual components given alone.
Risk and Risk Management	The adverse events previously identified in each of the individual components can be expected to occur in the combination product. No previously unseen adverse reactions are expected.	Labeling will identify the expected adverse reactions from each of components. Routine monitoring and reporting of all adverse events are expected to be adequate.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	Sec 6.1 Study endpoints
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☒	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. One of the primary risk factors is elevated IOP. The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

2.2. Analysis of Current Treatment Options

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, rho kinase inhibitors and prostaglandin analogs.

Drug Products with Approved NDAs

Pharmacologic Class/Applicant	Trade Name	Established Name
Beta-adrenergic antagonists		
Alcon	Betoptic/Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Alpha-2 agonists		
Allergan, Inc.	Alphagan/Alphagan P	brimonidine tartrate
Oral Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride

Pharmacologic Class/Applicant	Trade Name	Established Name
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Alcon	Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Valeant	Vyzulta	latanoprostene
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Rho-kinase inhibitors		
Aerie Pharmaceuticals, Inc.	Rhopressa	netarsudil
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/ timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/ timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/ pilocarpine hydrochloride
Alcon	Simbrinza	brinzolamide/brimonidine tartrate

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Netarsudil ophthalmic solution, 0.2% was approved in the US in 2017 (Rhopressa). Latanoprost ophthalmic solution, 0.005% was approved in the US in 1996 (Xalatan).

3.2. Summary of Presubmission/Submission Regulatory Activity

Type C Meeting to Discuss Clinical/Non-clinical plans	6/5/14
EOP2 Clinical/Non-clinical Meeting	3/24/15
EOP2 CMC Meeting	5/18/15
Request for Preliminary Advice-Breakthrough Therapy	5/24/16

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Type C CMC meeting	5/10/17
Pre-NDA Meeting	8/18/17

3.3. Foreign Regulatory Actions and Marketing History

Netarsudil/latanoprost is not marketed in any other country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI.

The clinical sites of Drs. Mulaney and Dubiner were inspected in review of this NDA. The clinical sites of Drs. Mulaney and Dubiner were selected for inspection as they were high enrollers in their respective studies. Based on the results of these inspections, Protocols PG324-CS301 and PG324-CS302 appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspections of both Drs. Mulaney and Dubiner was No Action Indicated (NAI).

4.2. Product Quality

Netarsudil 0.02% and latanoprost 0.005% ophthalmic solution is a topical, multidose, sterile isotonic solution at approximately pH 5. The formulation is packaged as a multi-dose product and is preserved with benzalkonium chloride. The drug product is packaged in a (b) (4) multi-dose, low-density polyethylene (LDPE) bottle fitted with a white (b) (4) polyethylene dropper tip (b) (4) and white polypropylene (PP) screw cap. The drug product is packaged in a 2.5 mL fill size (commercial and professional sample presentations).

Composition

Component	Function	Concentration	
		Quantity per mL (mg)	Quantity (% w/v)
Netarsudil mesylate	Active ingredient	0.2849 ¹	0.02
Latanoprost	Active ingredient	0.05 (b) (4)	0.005
Mannitol	(b) (4)		
Boric acid			
Benzalkonium chloride			
Sodium hydroxide			
Water for injection			

¹ 0.2849mg of netarsudil mesylate is equivalent to 0.2 mg of netarsudil.

Container and Closure System

The container closure system is one which is routinely used for administration of multi-dose ophthalmic solutions as drops. The drug product is sterile (b) (4) LDPE bottles (b) (4) dropper tip is then inserted. The bottle is closed by application of a (b) (4) screw-on white PP cap. A (b) (4) seal is shrink-wrapped over the cap and the neck of the bottle.

Bottle: (b) (4), 4 mL, LDPE, (b) (4) Bottle
Dropper: (b) (4), (b) (4) White, (b) (4) Dropper Tip, (b) (4)
Cap: (b) (4), (b) (4) White, PP, (b) (4)
Safety Seal: 31 mm. (b) (4) shrink seal

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. Clinical Pharmacology

Rhopressa (netarsudil ophthalmic solution) 0.02% (NDA 208254; approved 12/18/17)

Xalatan (latanoprost ophthalmic solution) 0.005% (NDA 020597; approved 6/5/96).

The applicant has relied on the Agency's finding of safety and effectiveness for Xalatan (latanoprost ophthalmic solution) 0.005%, NDA 020597, and specifically the current approved Xalatan prescribing information (4/10/17). Latanoprost ophthalmic solution 0.005%, is a prostaglandin F_{2α} analogue, believed to reduce IOP by increasing the outflow of aqueous humor through the uveoscleral route.

Netarsudil mesylate is a Rho kinase inhibitor developed by Aerie and is believed to reduce IOP primarily by increasing the outflow of aqueous humor through the trabecular meshwork route. The recommended dosage is one drop in the affected eye(s) once-daily in the evening.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below lists the clinical studies that were reviewed to evaluate safety and efficacy of netarsudil/latanoprost.

Table of Clinical Studies

Study Name	Study Design	Test product	Number of Subjects	Duration of Treatment	Study Status
PG324-CS201 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled study	Netarsudil 0.01% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM	298	28 days	Complete

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Study Name	Study Design	Test product	Number of Subjects	Duration of Treatment	Study Status
		Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM			
PG324-CS301 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM	718	12 months (3 months efficacy, 12 months safety) with optional 2 months observation	Complete
PG324-CS302 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Latanoprost ophthalmic solution 0.005% 1 gtt OU QD PM	750	3 months	Complete
AR-13324-CS206 Effect on trabecular outflow facility; ocular and systemic safety	Double-masked, Vehicle controlled, Paired comparison	Netarsudil ophthalmic solution 0.02% 1 gtt OU QD AM Netarsudil ophthalmic solution vehicle 1 gtt OU AM	20	7 days	Ongoing
PG324-CS303 IOP-lowering, efficacy; ocular and systemic safety	Double-masked, randomized, multi-center, active-controlled parallel study	Netarsudil 0.02% & latanoprost 0.005% ophthalmic solution 1 gtt OU QD PM Ganfort® (bimatoprost 0.03%/timolol maleate 0.5% ophthalmic solution) 1 gtt OU QD PM	472	6 months (3 months efficacy; 6 months safety)	Ongoing

5.2. Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1. The two studies which provide the main support for safety and efficacy were: Protocol PG324-CS301 which enrolled 718 subjects for the twelve-month treatment period at 58 sites in the U.S and Protocol PG324-CS302 which enrolled 750 subjects for the three-month treatment period at 60 sites in the U.S.

5.3. PG324-CS301: A prospective, double-masked, randomized, multi-center, active controlled, parallel-group 12-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution, 0.02% and Latanoprost Ophthalmic Solution, 0.005% in subjects with elevated intraocular pressure

5.3.1. Study Design

Overview and Objective

The primary objectives of this study were to evaluate the ocular hypotensive efficacy of netarsudil 0.02% and latanoprost 0.005% ophthalmic solution once daily (QD) (hereafter referred to as netarsudil/latanoprost) relative to each of its active components, netarsudil 0.02% QD, and latanoprost 0.005% QD over a 3-month period, and to evaluate the ocular and systemic safety of netarsudil/latanoprost over a 12-month period.

Trial Design

This was a 12-month, double-masked, randomized, multicenter, active-controlled, parallel-group safety and efficacy trial for the reduction of elevated IOP in subjects with a diagnosis of OAG or OHT. The efficacy of netarsudil/latanoprost in this study was assessed relative to the efficacy of each of its pharmacologically active components: netarsudil ophthalmic solution 0.02% and latanoprost ophthalmic solution 0.005%. Participating subjects attended up to 9 study visits with the option of participating in 2 additional study visits. The study duration for an enrolled subject was approximately 55 weeks from screening (Visit 1) to the last visit (Visit 9 [Day 365±7]); duration was extended by approximately 8 weeks for those subjects participating in the observational extension through Visit 11 (Day 425±7). Visit 1 was the Screening Visit and occurred up to approximately 28 days prior to Visit 2, which was the first of 2 qualification visits, the second occurring 2 to 7 days after Visit 2. After undergoing the screening visit and 2 qualification visits, eligible subjects who met eligibility criteria were enrolled and randomized at Qualification Visit #2 (Visit 3) to 1 of 3 treatment groups, with group assignment determined by a computer-generated randomization code:

- Netarsudil/latanoprost ophthalmic solution
- Netarsudil ophthalmic solution 0.02%

- Latanoprost ophthalmic solution 0.005%

Enrolled subjects returned to the investigative site at Week 2, Week 6, Month 3, Month 6, Month 9, and Month 12 for efficacy and safety assessments. Efficacy assessments focused on monitoring of IOP at 3 different times (08:00, 10:00, and 16:00 hours) during each visit; IOP assessments at Visits 7 (Month 6), 8 (Month 9), and 9 (Month 12) were not part of the primary efficacy analysis for this study. At each study visit, multiple ocular and systemic safety assessments were also conducted, including:

- Systemic safety assessments (heart rate, blood pressure, and clinical laboratory evaluations, including a panel of clinical chemistry assessments and complete blood count [hematology and differentials])
- Pregnancy testing (for women of child bearing potential)
- Ocular symptoms/adverse events
- Ocular comfort (tolerability) test
- ETDRS corrected visual acuity
- IOP
- Pupil size
- Objective findings of biomicroscopic examinations (ie. anterior segment examinations including evaluation of cornea, conjunctiva, eyelids, iris, anterior chamber and lens)
- Pachymetry and gonioscopy
- Visual field and cup-disc ratio measurements
- Dilated ophthalmoscopic examination

Following completion of the Month 12 study visit procedures, subjects were offered the opportunity to participate in the 2-month observation (i.e., non-interventional) trial extension. Subjects who agreed to participate in the extension were required to sign a new informed consent document; subjects who chose not to participate in the extension exited from the study. During the extension period, subjects did not administer any investigational or marketed ocular hypotensive product, and underwent safety and IOP assessments at Month 13 and Month 14.

For subjects who discontinued early from the study at any time, every possible effort was made to ensure that an exit visit was conducted which included all the required examinations listed for Visit 9 (Month 12), plus dilated ophthalmoscopy.

Inclusion Criteria

- Must be 18 years of age or older
- Diagnosis of OAG or OHT in both eyes (OAG in one eye and OHT in the fellow eye was acceptable)
- Unmedicated (post-washout) IOP >20 mmHg and <36 mmHg in both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, IOP

>17 mmHg and <36 mmHg in both eyes at 10:00 and 16:00 hours. Both eyes had to have qualified at all qualification visit time points

- BCVA + 1.0 logMAR or better by ETDRS (equivalent to 20/200 or better Snellen visual acuity in each eye)
- Be able and willing to give signed informed consent and follow study instructions

Exclusion Criteria

Ophthalmic:

- Clinically significant ocular disease (ie. 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 (ie. Grade 2 or less [Shaffer scale]; extreme narrow angle with complete or partial closure). Note: Prior laser peripheral iridotomy was NO acceptable
- IOP $\geq$ 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 (ie. 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
- Use of 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 CCT > 620 μ m in either eye at screening

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- Any abnormality preventing reliable applanation tonometry of either eye (ie. keratoconus, etc.)

Systemic:

- Clinically significant abnormalities in laboratory tests at screening
- Clinically significant systemic disease (ie. 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
- 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

Study Flow Chart

Table 3 Schedule of Events and Procedures

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 ¹²			
Inclusion/Exclusion	X	X	X	X	X																		
Washout ¹	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					
Urine Pregnancy Test ²	X											X			X			X					
Clin Labs (Chem/Hem)	X ³											X						X					
Symptoms/AEs ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Comfort Test ⁵						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 ⁶	X ⁶	X ⁶	X ⁶	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 ⁷ /Pachymetry ⁸	G/P											P											
Visual Field ⁹	X											X						X				X	
Ophthalmoscopy (dilated)	X												X					X ¹¹		X		X	
Eye-Drop Instillation Eval	X																						
Study Meds Dispensed					X			X			X			X			X						
Study Meds Collected						X ¹⁰			X ¹⁰			X ¹⁰			X ¹⁰			X ¹⁰					
Study Completed																		X ¹³				X ¹³	

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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.

- ¹. Subjects who were using ocular hypotensive medications were required undergo a minimum washout period (Table 2 for details).
- 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 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).
- ⁴. 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.
- 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 (See Protocol sections 7.1.2 to 7.1.5).
- ⁷. Gonioscopy evaluation up to 3 months prior to randomization was acceptable.
- ⁸. Pachymetry within 1 week of study visit was acceptable.
- ⁹. 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.
- ¹⁰. Collected used kit(s) dispensed during the previous visit.
- ¹¹. Ophthalmoscopy (dilated) at Visit 9.0 at 08:00; this assessment was to be performed for all non-completing subjects during the exit visit.
- ¹². Informed consent was required to be completed by the subjects before entering the extension visits.
- ¹³. Month 12 visit completed for the treatment period. Month 14 visit completed for the subjects entering the extension visits of the study.

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List of Investigators

A list of the Principle Investigator (PIs) who participated in this study is provided below.

List of Investigators			
Site Number	Investigator	Role	No. Subjects Enrolled
101	Stacey Ackerman, MD Philadelphia Eye Associates 1703 South Broad Street Philadelphia, PA 19148 USA	PI	2
102	Justus W. Thomas, MD Houston Eye Associates 22659 Highway 59 North, Suite 100 Kingwood, TX 77339 USA	PI	16
103	John F. Kozlovsky, MD Kozlovsky Delay & Winter Eye Consultants, LLC 2929 Mossrock Dr., Suite 104 San Antonio, TX 78230 USA	PI	5
104*	Jay R. Patel, MD California Eye Specialists Medical Group 2619 East Colorado Blvd., Suite 150 Pasadena, CA 91107	PI	6
105	Kent Bashford, DO Eye Center of Northern Colorado, PC 1725 East Prospect Road Fort Collins, CO 80525	PI	4
106*	Thomas Thoman Henderson, MD, F.A.C.S Eye Clinic of Austin, PLLC 3410 Far West Blvd, Suite 140 Austin, TX 78731	PI	11
107*	Fiaz Zaman, MD Houston Eye Associates 2855 Gramercy St Houston, TX 77025	PI	7
108	Joseph P. Gira, MD Ophthalmology Consultants Ltd. 12990 Manchester Rd, Suite 201 St. Louis, MO 63131	PI	5
109*	Navin Tekwani, MD Tekwani Vision Center 9911 Kennerly Rd, Suite A St. Louis, MO 63128	PI	26
110*	William J. Flynn, MD R and R Eye Research, LLC	PI	17

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	5430 Fredericksburg Rd, Suite 100 San Antonio, TX 78229		
	5430 Fredericksburg Rd, Suite 120 San Antonio, TX 78229		
111	Vickas Khemsara, MD Summit Eye Center 1710 S. Hawthorne Winston-Salem, NC 27103 PENTA Research 110 Charlois Blvd. Winston-Salem, NC 27103 3073 Trenwest Drive Winston-Salem, NC 27103	PI	4
112	Ranjan P. Malhotra, MD Ophthalmology Associates 12990 Manchester Road, Suite 200 St. Louis, MO 63131	PI	12
113	Ehsan Sadri, MD Atlantis Eyecare 7777 Edinger Ave, Suite 234 Huntington Beach, CA 92647	PI	2
114	Lawrence B. Katzen, MD Katzen Eye Care and Laser Center 901 N. Congress Ave, Suite 104 Boynton Beach, FL 33426	PI	1
115	Steven Vold, MD Vold Vision PLLC 2783 North Shiloh Drive Fayetteville, AR 72704	PI	2
117	Gary Jerkins, MD Nashville Vision Associates 4306 Harding Rd, Suite 202 Nashville, TN 37205	PI	17
118	Karen L. Klugo, MD Apex Eye 5240 E. Galbraith Rd., Suite B Cincinnati, OH 45236	PI	10
119*	Robert M. Saltzmann, MD Charlotte Eye Ear Nose & Throat Associates, PA 6035 Fairview Rd Charlotte, NC 28210	PI	12

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	400 Park Street Belmont, NC 28012 724 Aubrey Bell Drive Matthews, NC 28105		
120	Howard I. Schenker, MD Rochester Ophthalmological Group, PC 2100 S. Clinton Avenue Rochester, NY 14618	PI	28
121*	Farrell C. Tyson, MD Argus Research at Cape Coral Eye Center 4120 Del Prado Blvd. Cape Coral, FL 33904	PI	8
122*	James D. Branch, MD 224 Town Run Lane Winston Salem, NC 27101	PI	45
123*	Louis M. Alpern, MD The Cataract and Glaucoma Center 4171 N Mesa Bldg D, Ste. 100 El Paso, TX 79902	PI	19
124	Sanjay Asrani, MD Duke Eye Center 2351 Erwin Road Durham, NC 27710	PI	2
125	Jacob W. Brubaker, MD Grutzmacher, Lewis & Sierra 1515 River Park Drive, Suite 100 Sacramento, CA 95815 Northern California Research 3840 Watt Avenue Sacramento, CA 95821	PI	9
126*	William C. Christie, MD Scott & Christie and Associates, PC 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066 1101 Freeport Road Pittsburgh, PA 15238	PI	28
127*	Michael Depenbusch, MD Arizona Eye Center 604 W. Warner Rd, Suite B6 Chandler, AZ 85225	PI	13
128*	El-Roy Dixon, MD Dixon Eye Center 806 N. Jefferson Street	PI	16

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	Albany, GA 31701		
129	Eran Duzman, MD Lakeside Vision Center 4605 Barranca Pkwy, Suite 100 Irvine, CA 92604-4767	PI	4
131*	Eugene B. McLaurin, MD Total Eye Care, PA 6060 Primacy Parkway Memphis, TN 38119	PI	47
132*	Mark J. Weiss, MD Mark J. Weiss, MD, Inc 1717 South Utica Avenue, Suite 107 Tulsa, OK 74104	PI	29
133*	Matthew J. Swanic, MD AdvanceMed Clinical Research 8565 S. Eastern Avenu, Suite 102 Las Vegas, NV 89123 USA Las Vegas Eye Institute 9555 S. Eastern Avenue, Suite 260 Las Vegas, NV 89123 USA	PI	24
134	Yao Liu, MD University of Wisconsin-Madison, Department of Ophthalmology & Visual Sciences 2870 University Avenue, Suite 206 Madison, WI 53705 UW Health- University Station Clinic 2880 University Avenue Madison, WI 53705	PI	1
135	Matthew McMenemy, MD Lone Star Eye Care, PA 3515 Town Center Blvd South Sugar Land, TX 77479	PI	40
136	Brennan Greene, MD The Eye Care Institute 1536 Story Avenue Louisville, KY 40206	PI	3
138	Nicole M. Collins, OD Bergstrom Eye Research 2601 South University Drive Fargo, ND 58103	PI	4
139	Ettaleah C. Bluestein, MD Bluestein Custom Vision 2287 Henry Tecklenburg Drive Charleston, SC 29414	PI	7

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140	John S. Cohen, MD Cincinnati Eye Institute 1945 CEI Drive Cincinnati, OH 45242	PI	4
141	Sayoko Moroi, MD, PhD Kellogg Eye Center 1000 Wall Street Ann Arbor, MI 48105	PI	0
142	Damien F. Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Ave, Suite 100 Torrance, CA 90505	PI	11
143	Thomas D. LoBue, MD LoBue Laser & Eye Medical Centers, Inc. 40700 California Oaks Rd., Suite 106 Murrieta, CA 92562	PI	14
144	Andrew Mays, MD University of Alabama at Birmingham-Callahan Eye Hospital 700 South 18th Street, CEH-Suite 406 Birmingham, AL 35233 700 South 18th Street, CEH-Suite 601 Birmingham, AL 35233 700 South 18th Street, CEH-Suite 609 Birmingham, AL 35233	PI	2
145*	Brian E. Flowers, MD Ophthalmology Associates 1201 Summit Avenue Fort Worth, TX 76102	PI	5
147	Scott Han, OD The Eye Associates of Manatee, LLP 6002 Pointe West Blvd Bradenton, FL 34209	PI	2
148*	James D. Boyce, MD Orange County Ophthalmology 12665 Garden Grove Blvd. Suite 401 Garden Grove, CA 92843	PI	48
149	Raymond Fong, MD Raymond Fong Eye Center 109 Lafayette Street, 4th Floor New York, NY 10013	PI	8
150	Jodi Ian Luchs, MD South Shore Eye Care LLP 2185 Wantagh Avenue Wantagh, NY 11793	PI	5

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151*	John Nicolau, MD PI to 6May2016 San Antonio Eye Center 511 Dallas Street San Antonio, TX 78215 Kundandeep Nagi, MD PI after 6May2016 San Antonio Eye Center 511 Dallas Street San Antonio, TX 78215	PI	12
152	Lee S. Peplinski, OD Kentuckiana Institute for Eye Research Whitehouse Office Complex 1935 Bluegrass Avenue, Suite 200 Louisville, KY 10215	PI	4
153	Todd Ellsworth Daynes, MD Advanced Eye Center 1250 East 3900 South, Suite 310 Salt Lake City, UT 84124 Jean Brown Research 1045 East 3900 South Salt Lake City, UT 84124	PI	3
154*	Kevin Y. Jong, MD Houston Eye Associates 1415 North Loop West, Suite 400 Houston, TX 77008	PI	19
155*	Jay Mulaney, MD Central Florida Eye Associates 814 Griffin Road Lakeland, FL 33805	PI	50
156*	Satish Modi, MD Alterman, Modi & Wolter 23 Davis Avenue Poughkeepsie, NY 12603	PI	10
157	Mihir Parikh, MD AdvanceMed Clinical Research 4 Caraway Irvine, CA 92604 NVision 3655 Nobel Drive, Suite 130 San Diego, CA 92122	PI	6
158*	Donna Leonardo, DO Family Eye Group 2110 Harrisburg Pike # 215 Lancaster, PA 17601	PI	6

159	Bernard R. Perez, MD International Research Center 4506 Wishart Place Tampa, FL 33603	PI	2
160*	Savak Teymoorian, MD Harvard Eye Associates 24401 Calle de la Louisa, Suite 300 Laguna Hills, CA 92653	PI	16
161	Scott M. Corin, MD Advanced Eye Centers, Inc. 500 Faunce Corner Road, Suite 110 Dartmouth, MA 02747	PI	0
162	Jody Piltz-Seymour, MD 2755 Philmont Avenue Huntington Valley, PA 19006	PI	5

* Indicates the Principle Investigator also participated in the extension portion of this study.

Primary Efficacy Endpoint

The primary efficacy outcome was the comparison of netarsudil/latanoprost ophthalmic solution relative to each of its active components (netarsudil 0.02% and latanoprost 0.005%) for mean IOP within a treatment group at 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits.

Secondary Efficacy Endpoints

- 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 mean 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 mean diurnal IOP at each post-treatment visit
- Percentages of subjects achieving pre-specified levels of mean, mean change, and percent mean change in mean diurnal IOP at each post-treatment visit

Observation Period Efficacy Variables (Timepoints Month 13 and Month 14)

- Percentage of subjects with IOP value returning to the time-matched baseline at each visit in the observational period. Return to baseline is defined as a difference of ≤ 1 mmHg between measured IOP and time-matched baseline IOP (baseline – measured)
- Mean IOP at each visit in the observational period
- Mean change in IOP from time-matched baseline at each visit in the observational period
- Mean change in IOP from medicated baseline at each visit in the observational period

Statistical Analysis Plan

The primary analysis of the primary outcome employed an ANCOVA model with mean IOP at the given visit (Week 2, Week 6, and Month 3) and time point (08:00, 10:00, and 16:00 hours) as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the ITT population with multiple imputation techniques (i.e., Monte-Carlo Markov Chain [MCMC]) applied to impute missing data. Each time point within each visit was modeled separately. The least squares (LS) mean differences (netarsudil/latanoprost – comparator) between netarsudil/latanoprost ophthalmic solution and each of latanoprost ophthalmic solution 0.005% and netarsudil ophthalmic solution 0.02% were tested. The 2-sided p-values and associated 95% confidence intervals were presented.

Interim Analysis

When all subjects completed 3 months of treatment, Aerie's biostatistical representative unmasked the study to analyze the 3-month efficacy and safety data. No other study personnel other than the statistician, SAS programmers, VP, Clinical Research and Medical Affairs, Chief Scientific Officer and Information Systems Manager were unmasked to the individual subject treatment assignments and demographic information to perform the 3-month efficacy and safety data analysis and further exploratory data analysis as necessary. This was the primary efficacy analysis of the study and therefore no alpha adjustment for this interim analysis was implemented.

A second interim analysis was conducted when all subjects had completed 12 months on treatment. The interim database lock was planned so that primary safety and efficacy data could be analyzed, while providing additional time for subjects completing the study, as described in Amendments 3 and 4 to the protocol. This was the primary analysis of the safety data. Masking was maintained for subjects, Investigators, and site staff, but as for the 3-month interim data base lock, Aerie and data management personnel were unmasked in order to perform the safety data analysis.

Analysis of the data from subjects who participated in the observational extension to the study were analyzed when all subjects had exited from the extension, and those data were analyzed separately from the 12 months safety and efficacy data.

Protocol Amendments

Amendment 1 (6/24/15), included minor clarifications on procedures, correction of typographical errors, and correct application of the inclusion criteria by study visit.

Amendment 2 (4/12/16), included clarifications on procedures, correction of typographical errors, correct application of the inclusion criteria by study visit, and other minor clarifications.

Amendment 3 (1/5/17), included an extension to the study by adding 2 additional observational visits after Month 12. Minor changes to pagination and punctuation were also made.

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Amendment 4 (6/12/17), included the addition of an interim database lock when all subjects had completed 12 months treatment; this interim database lock was planned so that primary safety and efficacy data could be analyzed, while providing additional time for subjects completing the study to enter into the study extension described in Amendment 3. Additional wording changes were documented.

5.3.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs)

Financial Disclosure

See Financial Disclosure Template in Section 12.2. of this review.

Patient Disposition

Study PG324-CS301: Subject Disposition

Population	Netarsudil 0.02%/Latanoprost 0.005% QD	Netarsudil 0.02% QD	Latanoprost 0.005% QD
Safety	238	243	237
Intent to Treat (ITT)	238	244	236
Per Protocol (PP)	195	203	195

	Month 3		Month 12		Month 3		Month 12	
Study Completion	Month 3	Month 12	Month 3	Month 12	Month 3	Month 12	Month 3	Month 12
Completed	201	159	201	148	223	203		
Discontinued	37	79	43	96	13	33		
Reason for Subject Discontinuation								
Adverse Event	25	47	23	53	0	4		
Withdrawal of Consent	4	13	4	9	4	8		
Non-compliant	0	0	1	1	1	3		
Lost to Follow-up	1	5	3	5	1	4		
Lack of Efficacy	0	0	5	13	1	1		
Disallowed Concurrent Medication	1	6	4	7	2	5		
Investigator Decision	2	2	0	2	0	0		
Protocol Violation	4	6	1	3	4	8		
Death	0	0	0	1	0	0		
Other	0	0	2	2	0	0		

Study PG324-CS301: Demographics (Randomized Patients)

Characteristic	Netarsudil 0.02%/Latanoprost 0.005% QD N=238	Netarsudil 0.02% QD N=244	Latanoprost 0.005% QD N=236
Study eye diagnosis			
POAG	173	187	181
OHT	65	57	55
Sex			
Male	104	108	100
Female	134	136	136
Age (years)			
Mean	64.4	64.6	65.4
Range	18, 88	27, 91	22, 89
Race			
Asian	7	6	10
Black or African-American	69	70	67
White	162	167	157
Multiple	0	1	2
Other	0	0	0
Ethnicity			
Hispanic or Latino	30	32	30
Not Hispanic or Latino	208	212	206
Iris color of study eye			
Blue/Grey/Green	68	73	62
Brown	141	137	154
Hazel	29	34	20

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

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Efficacy Results – Primary Endpoint

Study PG324-CS301: Mean Study Eye IOP (mmHg) By Visit (Baseline Adjusted ANCOVA, ITT Population with MCMC)

Day and Time	Mean IOP Netar/Lat N=238	Mean IOP Netar N=244	Mean IOP Lat N=236	Mean Difference from Netarsudil	95% CI	Mean Difference From Latanoprost	95% CI
Day 15							
08:00	15.62	18.62	17.84	-3.00	(-3.57, -2.43)	-2.22	(-2.79, -1.65)
10:00	14.83	17.83	17.41	-3.00	(-3.60, -2.39)	-2.58	(-3.18, -1.98)
16:00	14.81	17.21	17.17	-2.39	(-2.92, -1.87)	-2.36	(-2.88, -1.83)
Day 43							
08:00	15.98	19.01	17.69	-3.04	(-3.65, -2.43)	-1.71	(-2.35, -1.07)
10:00	15.28	17.97	17.11	-2.68	(-3.26, -2.10)	-1.83	(-2.42, -1.24)
16:00	15.41	17.50	17.03	-2.09	(-2.67, -1.51)	-1.62	(-2.21, -1.03)
Day 90							
08:00	16.31	19.00	17.64	-2.69	(-3.34, -2.03)	-1.32	(-1.93, -0.72)
10:00	15.31	18.00	16.93	-2.69	(-3.37, -2.00)	-1.62	(-2.27, -0.98)
16:00	15.47	17.26	16.73	-1.79	(-2.42, -1.16)	-1.26	(-1.806 -0.66)

Note: The ANCOVA model has treatment as a factor and baseline as a covariate, where baseline refers to data from Visit 3 (Day 1) at the corresponding time point.

Reviewer's Comments:

The primary endpoint of this study was the comparison of netarsudil/latanoprost ophthalmic solution relative to each of its active components (netarsudil 0.02% and latanoprost 0.005%) for mean IOP within a treatment group at 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits using baseline adjusted ANCOVA and ITT with MCMC. This analysis demonstrated statistical superiority ($p < 0.01$) of netarsudil/latanoprost ophthalmic solution dosed QD relative to both of its individual components in the ITT population at all 9 timepoints from Week 2 through Month 3, meeting the criteria for success.

Efficacy Results – Secondary and other relevant endpoints

Study PG324-CS301: Mean Eye IOP (mmHg) By Visit (ITT With LOCF)

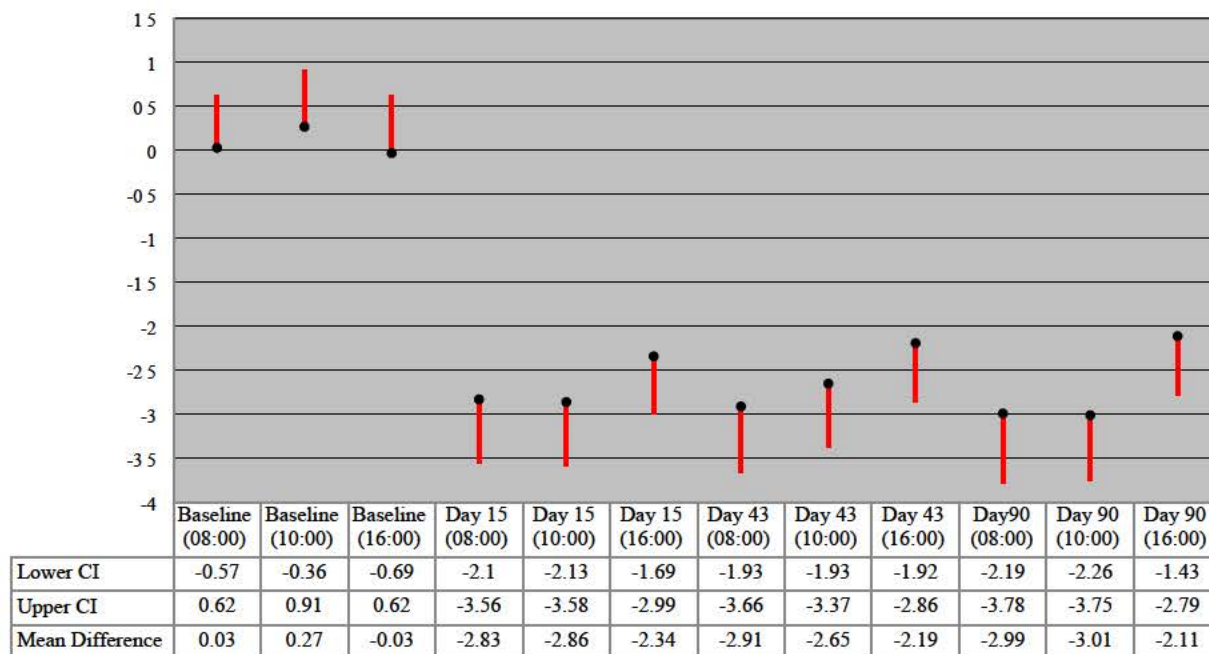
Day and Time	Mean IOP Netar/Lat N=238	Mean IOP Netar N=244	Mean IOP Lat N=236	Mean Diff From Net	95% CI P-value	Mean Diff From Lat	95% CI P-value
Day 1							
08:00	24.84	24.81	24.59	0.03	(-0.57, 0.62) 0.9244	0.25	(-0.31, 0.81) 0.3853
10:00	23.72	23.45	23.43	0.27	(-0.36, 0.91) 0.4009	0.29	(-0.34, 0.92) 0.3686
16:00	22.59	22.63	22.43	-0.03	(-0.69, 0.62) 0.9169	0.16	(-0.47, 0.79) 0.6130
Day 15							
08:00	15.92	18.75	17.80	-2.83	(-3.56, -2.10) <0.0001	-1.88	(-2.54, -1.21) <0.0001
10:00	15.15	18.00	17.43	-2.86	(-3.58, -2.13) <0.0001	-2.29	(-2.94, -1.63) <0.0001
16:00	15.07	17.41	17.20	-2.34	(-2.99, -1.69) <0.0001	-2.13	(-2.73, -1.52) <0.0001
Day 43							
08:00	16.27	19.18	17.69	-2.91	(-3.66, -1.93) <0.0001	-1.42	(-2.31, -1.03) <0.0001
10:00	15.26	18.25	17.24	-2.65	(-3.37, -1.93) <0.0001	-1.64	(-2.28, -1.00) <0.0001
16:00	15.63	17.82	17.10	-2.19	(-2.86, -1.92) <0.0001	-1.48	(-2.11, -0.85) <0.0001
Day 90							
08:00	16.50	19.49	17.62	-2.99	(-3.78, -2.19) <0.0001	-1.11	(-1.78, -0.45) 0.0010
10:00	15.55	18.56	17.00	-3.01	(-3.75, -2.26) <0.0001	-1.48	(-2.11, -0.85) <0.0001
16:00	15.66	17.76	16.83	-2.11	(-2.79, -1.43) <0.0001	-1.18	(-1.80, -0.55) 0.0002

Reviewer's Comments:

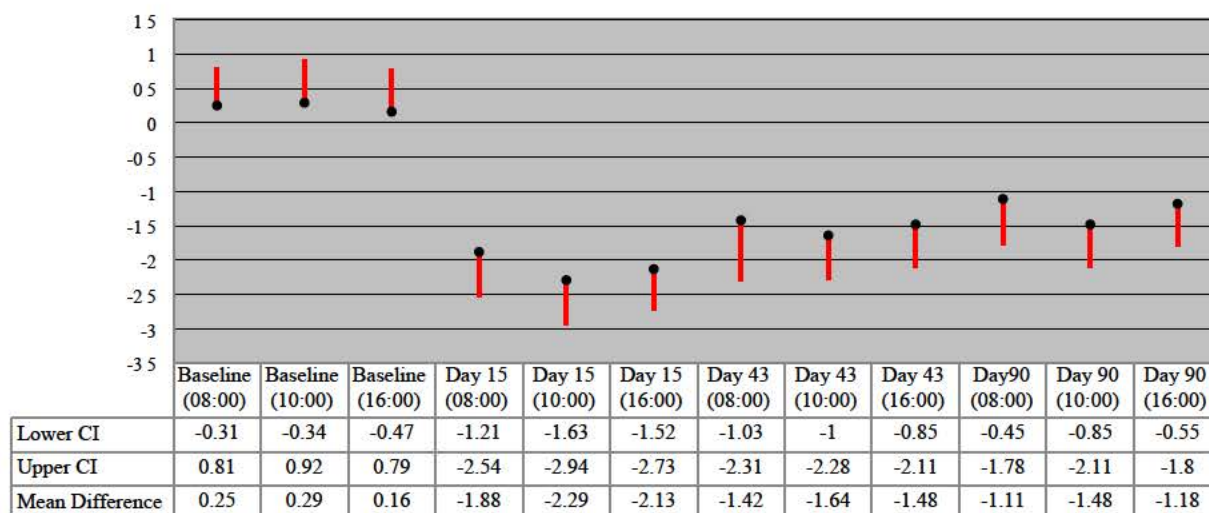
Looking at the primary endpoint with actual mean IOP (without ANCOVA modeling) and ITT with LOCF baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90.

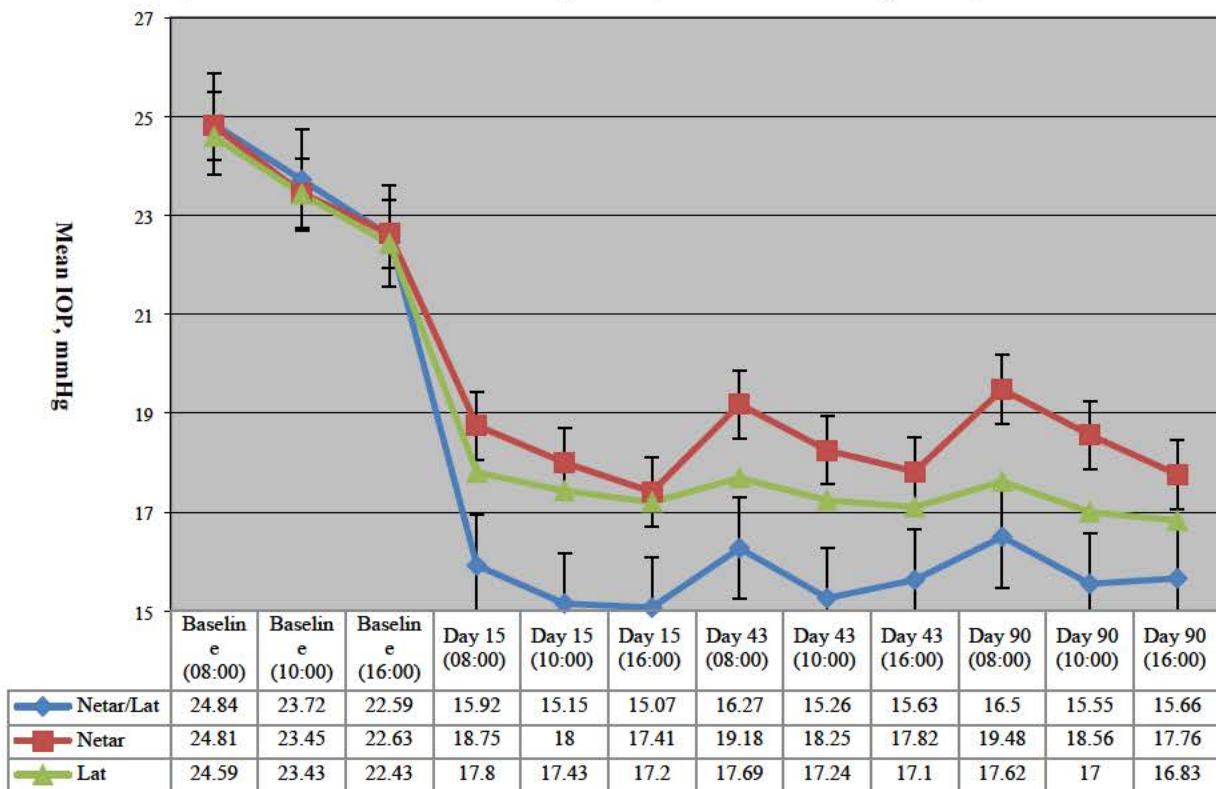
**Study PG324-CS301: Mean Difference Netarsudil/Latanoprost and Netarsudil With 95% Confidence Intervals
ITT With LOCF**



**Study PG324-CS301: Mean Difference Netarsudil/Latanoprost and Latanoprost With 95% Confidence Intervals
ITT With LOCF**



Study PG324-CS301: Mean IOP Comparison (ITT with LOCF Population)



Study PG324-CS301: Mean Eye IOP (mmHg) Study Eye By Visit (PP With Observed Data)

Day and Time	Mean IOP Netar/Lat	Mean IOP Netar	Mean IOP Lat	Mean Dif From Netar	95% CI P-value	Mean Diff From Lat	95% CI P-value
Day 1							
08:00	24.89 N=195	24.93 N=203	24.68 N=195	-0.04	(-0.70, 0.62) 0.91	0.22	(-0.041, 0.84) 0.49
10:00	23.65 N=195	23.52 N=203	23.50 N=195	0.14	(-0.57, 0.84) 0.70	0.15	(-0.55, 0.85) 0.67
16:00	22.55 N=195	22.69 N=203	22.42 N=195	-0.14	(-0.87, 0.58) 0.70	0.12	(-0.58, 0.83) 0.73
Day 15							
08:00	15.82 N=190	18.74 N=201	17.82 N=194	-2.92	(-3.69, -2.14) <0.01	-2.00	(-2.89, -1.48) <0.01
10:00	14.95 N=191	17.84 N=197	17.44 N=193	-2.89	(-3.66, -2.12) <0.01	-2.49	(-3.19, -1.79) <0.01
16:00	14.88 N=190	17.34 N=203	17.04 N=192	-2.45	(-3.14, -1.77) <0.01	-2.16	(-2.78, -1.54) <0.01
Day 43							
08:00	16.03 N=180	19.33 N=191	17.51 N=189	-3.30	(-4.12, -2.36) <0.01	-1.48	(-2.15, -0.81) <0.01
10:00	15.38 N=178	18.10 N=187	17.06 N=189	-2.71	(-3.49, -1.94) <0.01	-1.68	(-2.34, -1.02) <0.01
16:00	15.37 N=177	17.75 N=178	16.84 N=189	-2.38	(-3.09, -1.66) <0.01	-1.47	(-2.10, -0.83) <0.01
Day 90							
08:00	16.15 N=169	19.38 N=173	17.52 N=188	-3.22	(-4.12, -2.33) <0.01	-1.37	(-2.06, -0.67) <0.01
10:00	15.35 N=166	18.32 N=171	16.89 N=188	-2.97	(-3.81, -2.12) <0.01	-1.54	(-2.19, -0.88) <0.01
16:00	15.37 N=166	17.61 N=171	16.59 N=188	-2.24	(-3.03, -1.46) <0.01	-1.22	(-1.95, -0.52) <0.01

Reviewer's Comments:

Looking at the primary endpoint with actual mean IOP (without ANCOVA modeling) and PP with observed data baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90. Therefore, the PP with observed data is similar to the ITT with LOCF analysis.

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Dose/Dose Response

There was only one dose of netarsudil/latanoprost in this study.

Durability of Response

Netarsudil is intended to treat a chronic condition.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

None.

Reviewer's Comment:

The primary endpoint of this study was met; netarsudil/latanoprost was statistically superior to each of its active components in reducing IOP at all time points (08:00, 10:00, and 16:00 hours) at Week 2, Week 6, and Month 3. Netarsudil/latanoprost achieved greater IOP reductions than netarsudil by -1.8 to -3.0 mmHg ($p < 0.001$) and latanoprost by -1.3 to -2.6 mmHg ($p < 0.001$) at all 9 post-dose time points. The primary efficacy analysis was conducted on the ITT population with ANCOVA modeling with missing data imputed using the MCMC method.

The results were duplicated using actual mean IOP without ANCOVA modeling with both ITT with LOCF and PP with Observed data analyses.

5.4. PG324-CS302: A prospective, double-masked, randomized, multi-center, active controlled, parallel-group, 3-month study assessing the safety and ocular hypotensive efficacy of PG324 Ophthalmic Solution compared to AR-13324 Ophthalmic Solution 0.02% and latanoprost ophthalmic solution 0.005% in subjects with elevated intraocular pressure

5.4.1. Study Design

Overview and Objective – Same as PG324-CS301 except -302 was only a 3 month study

Trial Design – Same as first 3 months of PG324-CS301 without systemic safety assessment and includes corneal endothelial cell counts (ECCs) in both eyes by specular microscopy (at selected sites).

Inclusion Criteria/Exclusion Criteria Identical to Study PG324-CS301.

Study Flow Chart

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 ¹	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 ²	X											X		
Clin Labs	X ³											X		
Symptoms/AEs ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test ⁵						X			X			X		
Visual Acuity(ETDRS)	X	X	X			X			X			X		
Pupil size			X									X		
IOP	X	X ⁶	X ⁶	X ⁶	X ⁶	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 ⁷ / Pachymetry ⁸	G/P											P		
Visual Field ⁹	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) ¹⁰	X											X ¹⁰		X
Eye-Drop Instillation Eval	X													
Study Meds Dispensed					X			X			X			
Collect Study Meds						X ¹¹			X ¹¹			X ¹¹		
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.

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List of Investigators

A list of the Principle Investigator (PIs) who participated in this study is provided below.

List of Investigators			
Site Number	Investigator	Role	No. Subjects Enrolled
201	Eugene B. McLaurin, MD Total Eye Care, PA 6060 Primacy Parkway, Suite 200 Memphis, TN 38119	Principal Investigator	21
202	Matthew G. McMenemy, MD Lone Star Eye Care, P.A. 3515 Town Center Boulevard South Sugar Land, TX 77479	Principal Investigator	11
203	Howard I. Schenker, MD Rochester Ophthalmological Group, PC 2100 S. Clinton Avenue Rochester, NY 14618	Principal Investigator	31
204	Navin Tekwani, MD Tekwani Vision Center 9911 Kennerly Road Suite A St. Louis, MO 63128	Principal Investigator	8
205	James D. Boyce, MD Orange County Ophthalmology 12665 Garden Grove Blvd, Suite 401 Garden Grove, CA 92843	Principal Investigator	24
206	James D. Branch, MD James D. Branch, MD 224 Town Run Lane NW Winston-Salem, NC 27101	Principal Investigator	22
207	Mark J. Weiss, MD Mark J. Weiss, MD, Inc. 1717 S Utica Avenue, Suite 107 Tulsa, OK 74104	Principal Investigator	12

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208	William J. Flynn, MD R and R Eye Research, LLC. 5430 Fredericksburg Rd, Suite 120 San Antonio, TX 78229	Principal Investigator	3
209	Savak Teymoorian, MD Harvard Eye Associates 24401 Calle de la Louisa, Suite 300 Laguna Hills, CA 92653	Principal Investigator	9
210	Emil A. Stein, MD Emil A. Stein, MD, Ltd. 7730 West Cheyenne Ave., Suite 103 Las Vegas, NV 89129	Principal Investigator	18
213	Kenneth Sall, MD Sall Research Medical Center 11423 187 th Street, Suite 200 Artesia, CA 90701	Principal Investigator	41
214	Louis M. Alpern, MD The Cataract & Glaucoma Center 4171 N. Mesa Bldg. D, Suite 100 El Paso, TX 79902	Principal Investigator	10
215	Matthew J. Swanic, MD AdvanceMed Clinical Research 8565 S. Eastern Avenue, Suite 102 Las Vegas, NV 89123	Principal Investigator	14
216	William C. Christie, MD Scott & Christie and Associates, PC - 105 Brandt Drive, Suite 201 Cranberry Township, PA 16066 - 1101 Freeport Road Pittsburgh, PA 15238	Principal Investigator	16
218	Frank J. Grady, MD Brazosport Eye Institute/Frank J. Grady & Associates 103 Parking Way Lake Jackson, TX 77566	Principal Investigator	8
219	Henry McQuirter, OD Eye Specialty Group 825 Ridge Lake Blvd. Memphis, TN 38120	Principal Investigator	25

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220	El-Roy Dixon, MD Dixophthal, PC dba Dixon Eye Care 806 N. Jefferson Street Albany, GA 31701	Principal Investigator	17
221	Kevin Y. Jong, MD Houston Eye Associates 1415 North Loop West, Suite 400 Houston, TX 77008	Principal Investigator	19
222	Gregg J. Berdy, MD Ophthalmology Associates 12990 Manchester Road, #200 St. Louis, MO 63131	Principal Investigator	11
223	David Keith Harper PENTA Research at Cabarrus Eye Center 201 LePhillip Ct. NE Concord, NC 28025	Principal Investigator	6
224	Charles J. Crane, MD Northern New Jersey Eye Institute PA 71 Second Street South Orange, NJ 07079	Principal Investigator	6
225	Raymond Fong, MD Raymond Fong MDPC 109 Lafayette Street 4 th Floor New York, NY 10013	Principal Investigator	3
226	Mohammad Ali Haider Senior Health Services 2932 Breckenridge Ln, Suite 5 Louisville, KY 40220	Principal Investigator	13
227	A.W. Rifkind, MD A.W. Rifkind 826 Main St. E. Hamilton, Ontario, Canada L8M 1L6	Principal Investigator	7
228	Harvey Dubiner, MD Clayton Medical Center 1000 Corporate Center Dr. Suite 120 Morrow, GA 30260	Principal Investigator	34

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229	Gary Jerkins, MD Nashville Vision Associates 4306 Harding Rd., Suite 202 Nashville, TN 37205	Principal Investigator	13
230	Iqbal (Ike) K. Ahmed, MD Prism Eye Institute 3200 Erin Mills Parkway, Unit #1 Millway Plaza Mississauga, Ontario, Canada L5L 1W8	Principal Investigator	1
231	Ronald E.P. Frenkel, MD East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL 34994	Principal Investigator	5
232	William R. Beck, MD Heartland Research Associates, LLC 700 Medical Center Drive, Suite 210 Newton, KS 67114	Principal Investigator	8
233	Sherif M. El-Harazi, MD Lugene Eye Institute 1510 South Central Avenue, Suite 300 Glendale, CA 91204	Principal Investigator	31
234	Carla Bourne, MD USF Eye Institute 13217 Magnolia Drive Tampa, FL 33612	Principal Investigator	4
235	Damien F. Goldberg, MD Wolstan & Goldberg Eye Associates 23600 Telo Ave., Suite 100 Torrance, CA 90505	Principal Investigator	8
236	Justus W. Thomas, MD Houston Eye Associates 22659 Highway 59 North, Suite #100 Kingwood, TX 77339	Principal Investigator	8
237	Jacob W. Brubaker, MD Grutzmacher & Lewis, A Medical Corporation 1515 River Park Drive, Suite 100 Sacramento, CA 95815	Principal Investigator	5

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238	Julie Tsai, MD Julie Tsai, MD 343 West Houston Street, Suite 109 San Antonio, TX 78205	Principal Investigator	16
239	Jonathan I. Macy, MD Macy Eye Center 8653 W. Third Street, Suite 360W Los Angeles, CA 90048	Principal Investigator	3
240	Sebastien Gagné Institut de l'oeil des Laurentides 4800 Ambroise-Lafortune Boisbriand, QC, Canada, J7H 1S6	Principal Investigator	1
241	L. Wayne Freeman, MD Eye Physicians of Long Beach 3325 Palo Verde Ave. Long Beach, CA 90808	Principal Investigator	8
242	Gerald B. Walman, MD Walman Eye Center 10615 W. Thunderbird Blvd., Suite D180 Sun City, AZ 85351	Principal Investigator	13
243	Lesya Shuba, MD QEII Health Sciences Centre Dept. of Ophthalmology and Visual Sciences Eye Care Centre 1276 South Park St., 2 nd Floor Centennial Bld. Halifax, NS, Canada B3H 2Y9	Principal Investigator	3
244	Keith Skolnick, MD Fort Lauderdale Eye Institute 850 South Pine Island Road, Suite A100 Plantation, FL 33324	Principal Investigator	0
245	Fiaz Zaman, MD Houston Eye Associates 2855 Gramercy St Houston, TX 77025	Principal Investigator	10
246	Rajesh Shetty, MD Florida Eye Research Center 11512 Lake Mead Ave, Suite 534 Jacksonville, FL 32256	Principal Investigator	13

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247	Michael Stiles, MD Stiles Eyecare Excellence and Glaucoma Institute 7200 W. 129 th Street Overland Park, KS 66213	Principal Investigator	3
248	Da-Thuy Van, DO The Eye Clinic of Texas, an affiliate of Houston Eye Associates 1100 Gulf Freeway, Suite 114 League City, TX 77573	Principal Investigator	14
249	Mark Lesk, MD Hospital Maisonneuve-Rosemont 5415 Boulv de L' Assomption Montreal, Quebec, Canada H1T 2M4	Principal Investigator	3
250	Andrew Gardner Logan, MD Andrew Gardner Logan dba Logan Ophthalmic Research, LLC 7401 N. University Drive, Suite 201 Tamarac, FL 33321	Principal Investigator	25
251	Marjorie Carbonneau, MD Hotel-Dieu de Sherbrooke 580 rue Bowen Sud Sherbrooke, Quebec, Canada J1G 2E8	Principal Investigator	3
252	David T. Douglass, OD Eye Center Northeast 955 Broadway Bangor, ME 04401	Principal Investigator	17
253	Douglas G. Day, MD Coastal Research Associates, LLC 11205 Alpharetta Highway, Suite J3 Roswell, GA 30076	Principal Investigator	20
254	Philip Lee Shettle, DO Shettle Eye Research, Inc. 13113 66 th Street N. Largo, FL 33773	Principal Investigator	14
255	Jose F. Cardona, MD Indago Research and Health Center, Inc. 3700 W 12 th Ave., Suite 300 Hialeah, FL 33012	Principal Investigator	15

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256	David L. Wirta, MD Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	Principal Investigator	25
257	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way Petaluma, CA 94954	Principal Investigator	9
258	Thomas Richard Walters, MD Texan Eye, PA / Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731	Principal Investigator	21
259	Bradley Kwapiszkeski, MD Heart of America Eye Care, P.A. 8901 W. 74 th St Shawnee Mission, KS 66204	Principal Investigator	8
260	Pankajkumar Gopaldas Shah, MD DCT- Shah Research, LLC dba Discovery Clinical Trials 1506 E. Griffin Pkwy Mission, TX 78572	Principal Investigator	7
261	Blake Simmons, OD., FAAO Vision Institute 320 East Fontanero Street, Suite 201 Colorado Springs, CO 80907	Principal Investigator	4
262	Michael E. Tepedino, MD Cornerstone Eye Care 1400 East Hartley Drive High Point, NC 27262	Principal Investigator	22
263	Marlene R. Moster, MD Ophthalmic Partners of Pennsylvania, PC 100 Presidential Blvd., Suite 200 Bala Cynwyd, PA 19004	Principal Investigator	1

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Primary Efficacy Variable - same as Study PG324-CS301

Statistical Analysis Plan -same as Study PG324-CS301

Protocol Amendments

The SAP, Version 1.0 dated 12/30/16 included no changes to the analyses planned in the protocol. The clinical protocol was amended once on 4/8/16, in order to clarify the storage instructions for IP, and to also clarify the procedure (both eyes) and certification by a reading center for specular microscopy.

5.4.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs)

Financial Disclosure

See Financial Disclosure Template in Section 12.2. of this review.

Study PG324-CS302: Subject Disposition

Population	Netar/Lat	Netarsudil 0.02%	Latanoprost 0.005%
Safety	244	255	251
Intent to Treat (ITT)	245	255	250
Per Protocol (PP)	217	228	226

Study Completion			
Completed	221	228	236
Discontinued	24	27	14
Reason for Subject Discontinuation			
Adverse Event	17	15	5
Withdrawal of Consent	1	5	4
Non-compliant	1	0	1
Lost to Follow-up	1	0	2
Lack of Efficacy	0	3	0
Disallowed Concurrent Medication	2	2	0
Protocol Violation	1	1	2
Death	0	1	0
Other	1	0	0

Study PG324-CS302: Demographics (Randomized Patients)

Characteristic	Netarsudil 0.02%/Latanoprost 0.005% QD N=245	Netarsudil 0.02% QD N=255	Latanoprost 0.005% QD N=250
Study eye diagnosis			
POAG	172	187	171
OHT	72	68	79
Sex			
Male	93	102	106
Female	152	153	144
Age (years)			
Mean	64.2	64.5	64.3
Range	18, 88	22, 93	24, 99
Race			
Asian	7	11	6
Black or African-American	74	76	79
White	161	165	163
American Indian or Native Alaskan	0	0	1
Multiple	2	3	0
Other	1	0	1
Ethnicity			
Hispanic or Latino	45	48	55
Not Hispanic or Latino	200	207	195
Iris color of study eye			
Blue/Grey/Green	49	48	52
Brown	172	185	174
Hazel	24	22	24

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

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Efficacy Results – Primary Endpoint

Study PG324-CS302: Mean Study Eye IOP (mmHg) By Visit (Baseline Adjusted ANCOVA, ITT Population with MCMC)

Day and Time	Mean IOP Netar/Lat N=245	Mean IOP Netar N=255	Mean IOP Lat N=250	Mean Diff from Netar	95% CI P-value	Mean Diff from Lat	95% CI P-value
Day 15							
08:00	16.06	19.38	18.07	-3.31	(-3.86, -2.76) <0.001	-2.01	(-2.56, -1.46) <0.001
10:00	15.31	17.94	17.66	-2.64	(-3.16, -2.11) <0.001	-2.35	(-2.88, -1.83) <0.001
16:00	15.27	17.43	17.07	-2.16	(-2.68, -1.65) <0.001	-1.80	(-2.31, -1.29) <0.001
Day 43							
08:00	16.43	19.54	17.90	-3.11	(-3.70, -2.25) <0.001	-1.47	(-2.06, -0.87) <0.001
10:00	15.53	18.36	17.40	-2.83	(-3.40, -2.26) <0.001	-1.87	(-2.42, -1.31) <0.001
16:00	15.56	17.85	17.08	-2.29	(-2.84, -1.73) <0.001	-1.52	(-2.06, -0.98) <0.001
Day 90							
08:00	16.45	19.75	17.95	-3.30	(-3.90, -2.70) <0.001	-1.50	(-2.90, -0.92) <0.001
10:00	15.57	18.25	17.53	-2.68	(-3.27, -2.09) <0.001	-1.96	(-2.50, -1.42) <0.001
16:00	15.63	17.85	17.13	-2.22	(-2.79, -1.65) <0.001	-1.50	(-2.06, -0.94) <0.001

Note: The ANCOVA model has treatment as a factor and baseline as a covariate, where baseline refers to data from Visit 3 (Day 1) at the corresponding time point.

Reviewer's Comments:

The primary endpoint of this study was the comparison of netarsudil/latanoprost ophthalmic solution relative to each of its active components (netarsudil 0.02% and latanoprost 0.005%) for mean IOP within a treatment group at 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 study visits using baseline adjusted ANCOVA and ITT with MCMC. This analysis demonstrated statistical superiority of netarsudil/latanoprost ophthalmic solution dosed QD relative to both of its individual components at all 9 timepoints from Week 2 through Month 3, meeting the criteria for success.

Efficacy Results – Secondary and other relevant endpoints

Study PG324-CS302: Mean Eye IOP (mmHg) in Study Eye By Visit (ITT With LOCF)

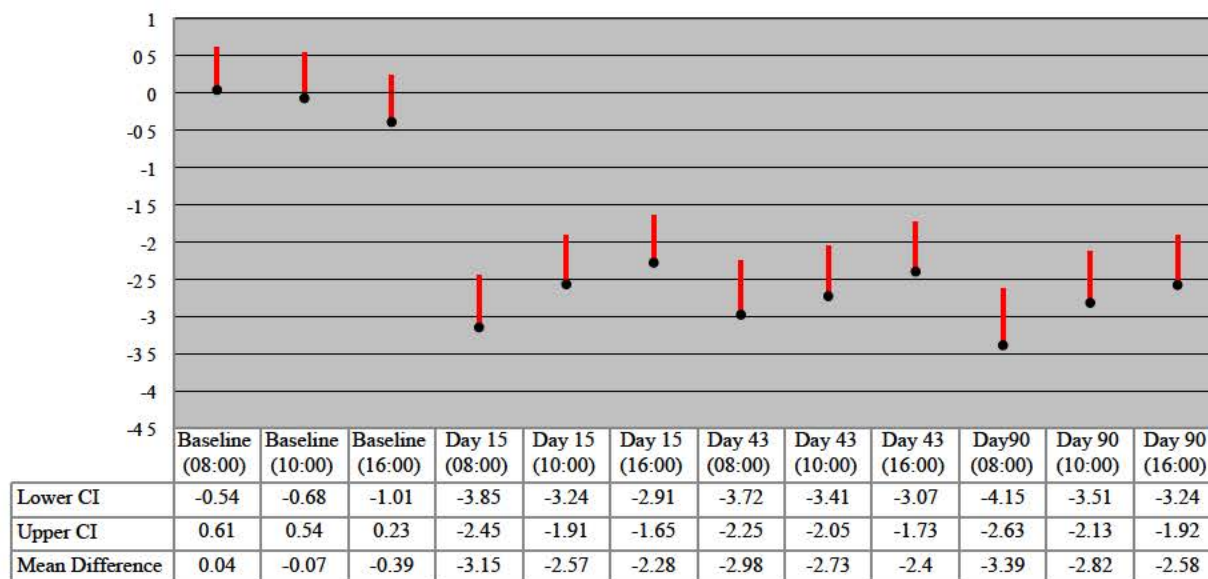
Day and Time	Mean IOP Netar/Lat N=245	Mean IOP Netar N=255	Mean IOP Lat N=250	Mean Diff from Netar	95% CI P-value	Mean Diff from Lat	95% CI P-value
Day 1							
08:00	24.69	24.66	24.75	0.04	(-0.54, 0.61) 0.90	-0.05	(-0.64, 0.54) 0.86
10:00	23.33	23.40	23.23	-0.07	(-0.68, 0.54) 0.82	0.11	(-0.49, 0.70) 0.72
16:00	22.37	22.76	22.59	-0.39	(-1.01, 0.23) 0.22	-0.22	(-0.83, 0.39) 0.48
Day 15							
08:00	16.27	19.42	18.18	-3.15	(-3.85, -2.45) <0.001	-1.91	(-2.54, -1.29) <0.001
10:00	15.55	18.12	17.65	-2.57	(-3.24, -1.91) <0.001	-2.11	(-2.71, -1.50) <0.001
16:00	15.41	17.69	17.16	-2.28	(-2.91, -1.65) <0.001	-1.74	(-2.33, -1.15) <0.001
Day 43							
08:00	16.64	19.63	17.96	-2.98	(-3.72, -2.25) <0.001	-1.32	(-1.99, -0.65) <0.001
10:00	15.77	18.50	17.39	-2.73	(-3.41, -2.05) <0.001	-1.73	(-2.39, -1.07) <0.001
16:00	15.65	18.05	17.16	-2.40	(-3.07, -1.73) <0.001	-1.50	(-1.93, -0.64) <0.001
Day 90							
08:00	16.69	20.08	18.05	-3.39	(-4.15, -2.63) <0.001	-1.36	(-2.02, -0.71) <0.001
10:00	15.84	18.66	17.53	-2.82	(-3.51, -2.13) <0.001	-1.69	(-2.32, -1.06) <0.001
16:00	15.74	18.32	17.16	-2.58	(-3.24, -1.92) <0.001	-1.42	(-2.02, -0.81) <0.001

Reviewer's Comments:

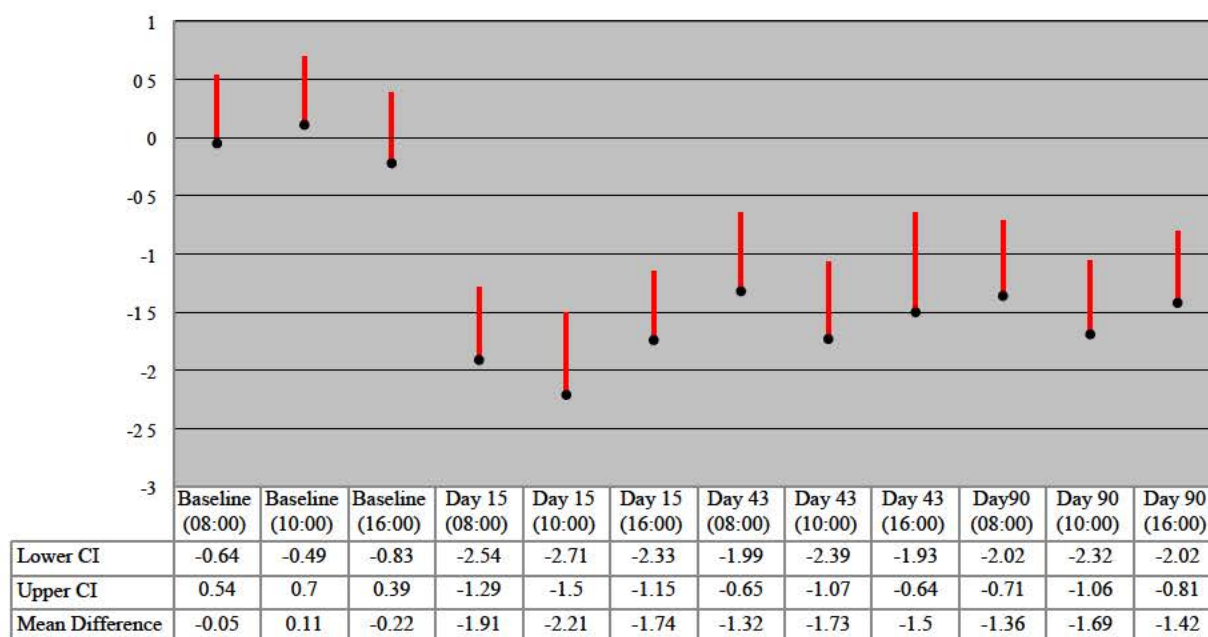
Looking at the primary endpoint with actual mean IOP (without ANCOVA modeling) and ITT with LOCF baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90.

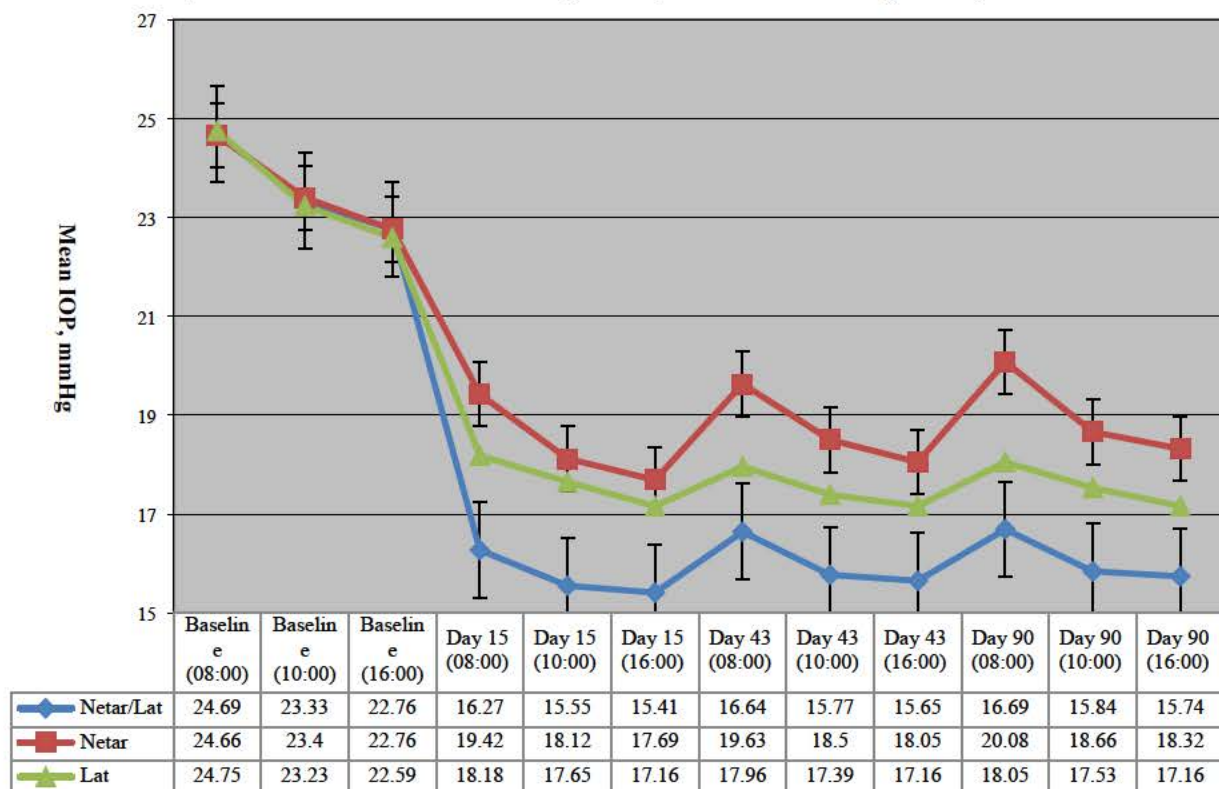
**Study PG324-CS302: Mean Difference Netarsudil/Latanoprost and Netarsudil With 95% Confidence Intervals
ITT With LOCF**



**Study PG324-CS302: Mean Difference Netarsudil/Latanoprost and Latanoprost With 95% Confidence Intervals
ITT With LOCF**



Study PG324-CS302: Mean IOP Comparison (ITT with LOCF Population)



Study PG324-CS302: Mean Eye IOP (mmHg) in Study Eye By Visit (PP With Observed Data)

Day and Time	Mean IOP Netar/Lat	Mean IOP Netar	Mean IOP Lat	Mean Diff from Netar	95% CI P-value	Mean Diff from Lat	95% CI P-value
Day 1							
08:00	24.71 N=217	24.59 N=228	24.79 N=226	0.12	(-0.50, 0.73) 0.71	-0.08	(-0.71, 0.54) 0.79
10:00	23.33 N=217	23.33 N=228	23.26 N=226	0	(-0.64, 0.64) 0.998	0.08	(-0.56, 0.71) 0.81
16:00	22.42 N=217	22.70 N=228	22.60 N=226	-0.27	(-0.93, 0.38) 0.41	-0.17	(-0.82, 0.47) 0.60
Day 15							
08:00	16.10 N=213	19.29 N=226	17.99 N=222	-3.19	(-3.91, -2.47) <0.001	-1.89	(-2.52, -1.25) <0.001
10:00	15.34 N=211	18.05 N=226	17.52 N=223	-2.71	(-3.40, -2.03) <0.001	-2.19	(-2.81, -1.56) <0.001
16:00	15.22 N=210	17.61 N=225	16.99 N=223	-2.39	(-3.04, -1.74) <0.001	-1.77	(-2.38, -1.16) <0.001

Day and Time	Mean IOP Netar/Lat	Mean IOP Netar	Mean IOP Lat	Mean Diff from Netar	95% CI P-value	Mean Diff from Lat	95% CI P-value
Day 43							
08:00	16.40 N=210	19.53 N=224	17.73 N=219	-3.12	(-3.88, -2.36) <0.001	-1.33	(-2.01, -0.65) <0.001
10:00	15.57 N=209	18.41 N=223	17.29 N=219	-2.85	(-3.55, -2.14) <0.001	-1.72	(-2.36, -1.08) <0.001
16:00	15.47 N=208	18.05 N=223	17.10 N=218	-2.57	(-3.27, -1.88) <0.001	-1.62	(-2.27, -0.98) <0.001
Day 90							
08:00	16.46 N=204	19.91 N=211	17.87 N=215	-3.46	(-4.23, -2.69) <0.001	-1.42	(-2.09, -0.74) <0.001
10:00	15.68 N=204	18.43 N=209	17.32 N=216	-2.75	(-3.46, -2.03) <0.001	-1.64	(-2.29, -1.00) <0.001
16:00	15.60 N=203	18.15 N=209	17.04 N=216	-2.55	(-3.22, -1.88) <0.001	-1.44	(-2.05, -0.83) <0.001

Reviewer's Comments:

Looking at the primary endpoint with actual mean IOP (without ANCOVA modeling) and PP with observed data, the baseline mean IOP of the three treatment groups is similar. The 95% confidence intervals cross zero at all time points measured at baseline.

The mean IOP of the fixed combination is numerically lower than the individual components at all time points measured at Day 15, Day 43, and Day 90. In addition, the mean difference between the fixed combination and netarsudil is statistically significant at all time points at Day 15, Day 43, and Day 90.

Therefore, the PP with observed data is similar to the ITT with LOCF analysis.

Dose/Dose Response

There was only one dose of netarsudil/latanoprost in this study.

Durability of Response

Rocklatan is intended to treat a chronic condition.

Persistence of Effect

Not applicable.

Additional Analyses Conducted on the Individual Trial

None.

Reviewer's Comment:

The primary endpoint of this study was met; netarsudil/latanoprost was statistically superior to

each of its active components in reducing IOP at all time points (08:00, 10:00, and 16:00 hours) at Week 2, Week 6, and Month 3. Netarsudil/latanoprost achieved greater IOP reductions than netarsudil by -2.2 to -3.3 mmHg ($p < 0.001$) and latanoprost by -1.8 to -2.4 mmHg ($p < 0.001$) at all 9 post-dose time points. The primary efficacy analysis was conducted on the ITT population with ANCOVA modeling with missing data imputed using the MCMC method.

The results were duplicated using actual mean IOP without ANCOVA modeling with both ITT with LOCF and PP with Observed data analyses

6. Integrated Review of Effectiveness

6.1. Assessment of Efficacy Across Trials

6.1.1. Primary Endpoints

The primary efficacy endpoint for studies 301 and 302, mean IOP measured at multiple time points achieved their primary endpoint.

6.1.2. Subpopulations

The following subgroups were analyzed: prior prostaglandin use, age, race, or gender. There were no notable differences in either study in any of the subgroups analyzed.

6.1.3. Dose and Dose-Response

Only one dose of Rocklatan was studied.

6.2. Additional Efficacy Considerations

6.2.1. Considerations on Benefit in the Postmarket Setting

Study PG324-CS301:

Observational Period

Following completion of the 12-month treatment and evaluation period, subjects were offered the opportunity to continue for an additional 2 months in a non-interventional, observation extension trial.

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Study PG324-CS301: Mean IOP and Mean Change in the Observation Period by Visit (Observation Period Efficacy Population)

	Netarsudil/Latanoprost	Netarsudil	Latanoprost
Medicated Baseline	16.29 N=26	18.71 N=24	17.39 N=36
Month 13	20.71 N=26	21.23 N=24	21.90 N=35
Month 13 Change From Medicated Baseline	4.42	2.52	4.43
Month 14	20.65 N=26	20.85 N=24	22.58 N=36
Month 14 Change From Medicated Baseline	4.37	2.15	5.19

Reviewer's Comment:

At Month 14 change in mean IOP was smallest for netarsudil (2.15 mmHg) and largest for latanoprost (5.19 mmHg), with netarsudil/latanoprost falling in between (4.37 mmHg).

6.2.2. Other Relevant Benefits

There are no other relevant benefits for this drug product.

6.3. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of netarsudil/latanoprost ophthalmic solution dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

7. Review of Safety

7.1. Safety Review Approach

The main support for safety is from 2 clinical studies (Studies PG324-CS301 and PG324-CS302).

7.2. Review of the Safety Database

7.2.1. Overall Exposure

Study PG324-CS301: Exposure to Study Medication by Treatment Group (Safety Population)

	Netarsudil/Latanoprost QD N=244	Netarsudil QD N=243	Latanoprost QD N=237
Days of Exposure			
Mean (sd)	275.7	266.2	330.4

Study PG324-CS302: Exposure to Study Medication by Treatment Group (Safety Population)

	Netarsudil/Latanoprost QD N=244	Netarsudil QD N=255	Latanoprost QD N=251
Days of Exposure			
Mean (sd)	84.9	85.2	87.7

7.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat. The safety population included primarily subjects with open-angle glaucoma or ocular hypertension

7.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

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7.3.2. Categorization of Adverse Events

Adverse events were summarized by the number and percentage of subjects with TEAEs by treatment group, SOC, and PT using version 19.0 of the MedDRA coding dictionary.

7.3.3. Routine Clinical Tests

See section 8.4.6

7.4. Safety Results

7.4.1. Deaths

Study PG324-CS301: One death was reported during the study. Subject (b) (6) died presumably from atherosclerotic and hypertensive cardiovascular disease after 252 days on treatment (netarsudil).

Study PG324-CS302: One death was reported during the study. Subject (b) (6) suffered a fatal cardiac arrest after 47 days on treatment (netarsudil).

7.4.2. Serious Adverse Events

Study PG324-CS301: Serious Treatment Emergent AEs (Safety Population)

	Netarsudil/Latanoprost QD N=238	Netarsudil QD N=243	Latanoprost QD N=237
Any TE SAE	5	10	10
Neoplasms			
Bladder CA	0	1	0
Breast CA	1	0	0
Gastric CA recurrent	0	0	1
Intraductal proliferative breast lesion	0	1	0
Ovarian adenoma	0	0	1
Prostate CA recurrent	0	0	1
GI disorders			
Abdominal pain	1	0	0
GI hemorrhage	0	1	0
Impaired gastric emptying	0	1	0
Lower GI hemorrhage	0	0	1
Cardiac disorders			
MI	0	0	2

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	Netarsudil/Latanoprost QD N=238	Netarsudil QD N=243	Latanoprost QD N=237
Coronary artery stenosis	0	1	0
Infections			
Cellulitis	0	1	0
Pneumonia	1	0	0
Sepsis	0	0	1
Nervous system disorders			
Carotid artery stenosis	1	0	0
Metabolic encephalopathy	0	0	1
Syncope	0	0	1
Injury			
Fall	0	0	1
Femoral neck fracture	0	0	1
Respiratory disorders			
Bronchitis chronic	0	1	0
Pulmonary embolism	0	0	1
Vascular disorders			
Arteriosclerosis	0	1	0
DVT	0	0	1
HTN	0	1	0
Blood disorders			
Anemia	1	0	0
Hepatobiliary disorders			
Cholecystitis	1	0	0
Metabolism disorders			
Hypoglycemia	0	1	0
Musculoskeletal disorders			
Osteoarthritis	0	0	1
Pregnancy conditions			
Abortion spontaneous	0	1	0

Reviewer's Comment:

Study PG324-CS301: There were 32 SAEs reported from 25 subjects. Six SAEs (5 subjects) were in the netarsudil/latanoprost treatment group and 12 SAEs (10 subjects) were in the netarsudil group. The remaining 14 SAEs (10 subjects) were reported in the latanoprost group. All SAEs reported during the treatment period were non-ocular SAEs.

Study PG324-CS302: Serious Treatment Emergent AEs (Safety Population)

	Netarsudil/Latanoprost QD N=244	Netarsudil N=255	Latanoprost QD N=251
Any TE SAE	2	6	5
Cardiac disorders			
A fib	1	2	0
CHF	0	1	1
Cardiac arrest	0	1	0
CAD	1	0	0
Infections			
Bronchitis	0	1	0
Device related infection	0	0	1
Pneumonia	0	0	1
Eye disorders			
Retinal detachment	0	0	1
Hepatobiliary disorders			
Acute cholecystitis	0	0	1
Nervous system disorders			
Vertebral artery stenosis	0	1	0
Psychiatric disorders			
Mental status change	1	0	0
Mediastinal disorders			
Pulmonary embolism	0	1	0

Reviewer's Comment:

Study PG324-CS302: A total of 13 subjects reported a total of 15 SAEs. Two of the subjects reporting 3 SAEs were in the netarsudil/latanoprost treatment group, and a total of 6 subjects in the netarsudil group reported 7 SAEs; the remaining 5 SAEs were reported by 5 subjects in the latanoprost group. One of the 15 SAEs reported was coded to an eye disorder, a retinal detachment in a subject treated with latanoprost.

7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study PG324-CS301: Subject Disposition

Number of Randomized Subjects	Netarsudil 0.02%/Latanoprost 0.005% QD N=238		Netarsudil 0.02% QD N=244		Latanoprost 0.005% QD N=236	
Study Completion	Month 3	Month 12	Month 3	Month 12	Month 3	Month 12
Completed	201	159	201	148	223	203
Discontinued	37	79	43	96	13	33
Reason for Subject Discontinuation						
Adverse Event	25	47	23	53	0	4
Withdrawal of Consent	4	13	4	9	4	8
Non-compliant	0	0	1	1	1	3
Lost to Follow-up	1	5	3	5	1	4
Lack of Efficacy	0	0	5	13	1	1
Disallowed Concurrent Medication	1	6	4	7	2	5
Investigator Decision	2	2	0	2	0	0
Protocol Violation	4	6	1	3	4	8
Death	0	0	0	1	0	0
Other	0	0	2	2	0	0

Study PG324-CS302: Subject Disposition

Number of Randomized Subjects	Netarsudil 0.02%/Latanoprost 0.005% QD N=245		Netarsudil 0.02% QD N=255		Latanoprost 0.005% QD N=250	
Study Completion						
Completed	221		228		236	
Discontinued	24		27		14	
Reason for Subject Discontinuation						
Adverse Event	17		15		5	
Withdrawal of Consent	1		5		4	
Non-compliant	1		0		1	
Lost to Follow-up	1		0		2	
Lack of Efficacy	0		3		0	
Disallowed Concurrent Medication	2		2		0	
Protocol Violation	1		1		2	
Death	0		1		0	
Other	1		0		0	

7.4.4. Significant Adverse Events

See Section 8.4.2.

7.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Studies -301 and -302: Ocular TEAEs Occurring at an Incidence of $\geq 1\%$ (Safety Population)

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
	CS301	CS302	CS301	CS302	CS301	CS302
	N=238	N=244	N=243	N=255	N=237	N=251
Any TEAE	197	171	190	161	128	109
Eye disorders						
Conjunctival hyperemia	150	133	125	109	52	56
Conjunctival hemorrhage	31	21	44	28	3	2
Corneal verticillata	42	32	33	25	0	0
Eye pruritis	27	10	22	1	3	2
Punctate keratitis	12	5	18	9	10	4
Lacrimation increased	17	8	20	8	1	0
Visual acuity reduced	13	12	13	8	6	3
Vision blurred	11	12	15	8	3	4
Blepharitis	15	4	8	6	5	1
Eye irritation	11	4	7	6	3	1
Erythema of eyelid	10	8	9	5	1	3
Conjunctivitis allergic	8	2	11	3	0	0
Conjunctival edema	9	3	7	3	1	1
Eyelid edema	6	8	9	6	2	3
Dry eye	6	1	3	3	6	3
Meibomian gland dysfunction	5		5		2	
Eye pain	4	3	6	5	0	4
FBS in eyes	4	7	5	1	1	2
Cataract	1		6		2	
Chalazion	5		3		0	
Conjunctival disorder	3		3		2	
Eyelid pruritis	5		3		0	
Miosis	2		2		3	
Vitreous detachment	2		2		3	
Photophobia	4		1		1	
Corneal deposits	5		0		0	
Eyelid margin crusting	4	3	1	3	0	0
Corneal opacity	1		3		0	
General disorders						
Instillation site pain	55	42	60	23	18	15
Instillation site discomfort	10	15	7	16	3	2
Instillation site erythema	10	10	5	6	1	4
Instillation site FBS	0		6		3	
Peripheral swelling	0		0		3	
Infections						
Conjunctivitis	1		4		1	
Investigations						
Vital dye staining cornea present	8	10	7	14	3	7

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
	CS301	CS302	CS301	CS302	CS301	CS302
	N=238	N=244	N=243	N=255	N=237	N=251
IOP increased	0		4		1	
Nervous system disorders						
VF defect	5		3		1	
Skin disorders						
Dermatitis contact	7		3		0	

Reviewer's Comment:

The Agency sent an IR to the Applicant stating that corneal disorders in Study 302 should be specified as they were in Study 301. The Applicant responded to the IR SDN-17 (1/31/19) stating:

Table 16 in both PG324-CS301 and PG324-CS302 CSRs are similar in design. The main reason for the apparent difference is that in Study PG324-CS302 the 2 Verbatim Terms “distortion of specular microscopy corneal endothelial cell morphology” and “endothelial cell pleomorphism” were mapped to the Preferred Term (PT) “corneal disorder”, whereas in Study PG324-301 the Verbatim Term “corneal anterior basement membrane changes” was mapped to the PT “corneal disorder”. However, there was only 1 subject in the latanoprost arm with “corneal anterior basement membrane changes”, which is not shown in Table 16 because of the 1% incidence cut-off. There were no treatment-emergent adverse events (TEAEs) regarding endothelial cell morphology or pleomorphism in Study PG324-CS301 and no basement membrane changes in Study PG324-CS302. The PT “corneal disorder” was used in both studies, because it was most relevant for mapping the endothelial cell morphology/pleomorphism and basement membrane changes using MedDRA Version 19.0. Furthermore, in Study PG324-302 there were 3 subjects with TEAEs mapped to the PT “corneal opacity”, 1 subject in the PG324 arm and 2 subjects in the netarsudil arm, which are also below the 1% incidence cut-off used in Table 16.

This response is acceptable. Only Study -302 evaluated endothelial cell count.

Studies -301 and -302: Non-Ocular TEAEs Occurring at an Incidence of $\geq 1\%$ (Safety Population)

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
	CS301	CS302	CS301	CS302	CS301	CS302
	N=238	N=244	N=243	N=255	N=237	N=251
Any TEAE	197	171	190	161	128	109
Infections						
Upper respiratory tract infection	1	3	5	1	6	0
Nasopharyngitis	7		3		1	
Bronchitis	4	0	3	3	3	2

	Netarsudil 0.02% /Latanoprost 0.005%		Netarsudil 0.02%		Latanoprost 0.005%	
Sinusitis	2		5		3	
Influenza	0		2		5	
UTI	0		1		3	
Investigations						
Blood triglycerides increased	2	3	4	1	3	0
Blood glucose increased	1		4		1	
Blood pressure increased	0		0		4	
Nervous system disorders						
HA	4	1	1	8	2	0
Injury						
Fall	0		0		3	
Respiratory disorders						
Nasal congestion	3		0		1	
Vascular disorders						
HTN	2	1	5	3	5	1
Metabolism disorders						
Type 2 DM	1		3		1	

7.4.6. Laboratory Findings

Study PG324-CS301: Clinical laboratory assessments were collected at Screening and at the 08:00 time point of Months 3, 6, and 12 (exit visit). The numbers of subjects with clinical chemistry values out of the normal range were comparable across treatment groups at the end of the study.

The population enrolled in this study reported a high incidence of hypertension overall (66.6%). Approximately, one-third of the overall subject population had hypercholesterolemia (38.4%) or Type 2 diabetes mellitus (31.6%) as part of their medical history.

Urine pregnancy testing was required for females of child-bearing potential. Of the approximately 6% of female subjects who were considered to be of child-bearing potential, 1 subject (b) (6) in the netarsudil group reported a pregnancy during the study. The pregnancy resulted in a miscarriage, which was reported as an SAE.

Study PG324-CS302: Clinical laboratory assessments were collected at Screening and at the 08:00 time point of Month 3 (exit visit). The numbers of subjects with clinical chemistry values out of the normal range were comparable across treatment groups at the end of the study.

The population enrolled in this study reported a high incidence of hypertension (68.3% overall). Approximately a third of the overall subject population had hypercholesterolemia (30.1%) or type 2 diabetes mellitus (28.1%) as part of their medical history.

Urine pregnancy testing was required for females of child-bearing potential. Of the approximately 7% of female subjects who were considered to be of child-bearing potential, none reported a pregnancy during the study.

7.4.7. Vital Signs

In both Studies PG324-CS301 and PG324-CS302 heart rate and blood pressure were collected at screening, baseline, and each on-treatment visit (at 08:00 hours). Minimal changes were observed during the study at any time point for any treatment group in either heart rate or blood pressure.

7.4.8. Electrocardiograms (ECGs)

Not performed.

7.4.9. QT

Not applicable.

7.4.10. Immunogenicity

Not applicable.

7.5. Analysis of Submission-Specific Safety Issues

None.

7.5.1. Endothelial Cell Counts

Study PG324-CS302: Endothelial Cell Counts

	Netarsudil 0.02%/Latanoprost 0.005% QD N=244	Netarsudil 0.02% QD N=255	Latanoprost 0.005% QD N=251
Baseline cell density (cells/mm ²)	2464 N=160	2506 N=172	2448 N=160
Mean change from baseline in cell density at Day 90 (Completers only)	8.8 N=122	17.95 N=137	-0.4 N=145

Reviewer's Comment:

There were no clinically significant changes in corneal endothelial cell density at Month 3.

7.6. Specific Safety Studies/Clinical Trials

Not applicable.

7.7. Additional Safety Explorations

7.7.1. Human Carcinogenicity or Tumor Development

Because of the low expected absorption of netarsudil and latanoprost in topical preparations, no carcinogenicity studies were conducted.

7.7.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

7.7.3. Pediatrics and Assessment of Effects on Growth

In the 4/5/15, End of Phase 2 meeting the Sponsor stated that the Phase 3 clinical protocols for netarsudil 0.02% and latanoprost 0.005% ophthalmic solution would include subjects 18 years of age and older, with the acknowledgement that the risks associated with prostaglandin analogues (i.e., permanent darkening of iris, skin discoloration and loss of orbital fat) may not be appropriate for pediatric patients. Therefore, the Sponsor proposed to seek a waiver in the pediatric study plan (PSP) for inclusion of subjects 0-17 years of age in the Phase 3 studies. On 6/10/15, the Sponsor submitted a Pediatric Study Plan which described plans to request a full waiver of pediatric studies. In a 8/28/15, Advice Letter, the Agency agreed to the PSP.

7.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Rocklatan is a non-narcotic and does not have abuse potential.

7.8. Safety in the Postmarket Setting

7.8.1. Safety Concerns Identified Through Postmarket Experience

On 8/28/18, a 4 month safety update was submitted. Since the submission of NDA 208259, no new information affecting the safety, effectiveness, or proposed labeling of the drug product, Rocklatan™, have been identified either in the literature or in the ongoing clinical studies. As of 7/13/18, approximately (b) (4) samples of 2.5 ml bottles and (b) (4) prescriptions of 2.5 ml bottles of Rhopressa® have been distributed in the United States. For this period, post-marketing reports from spontaneous sources received through pharmacovigilance activities identified a total of 105 adverse events related to Rhopressa®, of which 76 (72%) were related to the eyes. The most frequent AEs observed were expected ocular AEs: conjunctival hyperemia was reported in 22 cases (29%) followed by 10 cases of vision blurred (13%), 3 cases (4%) of conjunctival

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hemorrhage and 3 cases (4%) of visual acuity reduced. Unexpected/unlisted ocular AEs reported in more than 1 subject included 4 cases (5%) of IOP increase, 4 cases (5%) of eye pain, 3 cases (4%) of diabetic macular edema, and 2 cases each (3%) of visual impairment, vitreous floaters, transient blindness, eye irritation and eye discharge.

7.8.2. Expectations on Safety in the Postmarket Setting

None.

7.8.3. Additional Safety Issues From Other Disciplines

None.

7.9. Integrated Assessment of Safety

The safety database contained in this submission establishes the relative safety of netarsudil/latanoprost ophthalmic solution dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

8. Advisory Committee Meeting and Other External Consultations

There were no issues identified in the review of the application that were thought to benefit from an Advisory Committee discussion.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

See labeling recommendations in the draft revised package insert attached to the end of this review. This labeling is DRAFT.

9.2. Nonprescription Drug Labeling

No Medication Guide, patient package insert, or instructions for use is recommended.

10. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

11. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

12. Appendices

12.1. References

An independent literature review was not conducted for this application.

12.2. Financial Disclosure

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Covered Clinical Study (Name and/or Number): CS301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>58</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator <u>1</u> Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>58</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Investigator (b) (6) (Study -301) held significant equity interest defined as > \$50,000.00.

This was an adequate and well-controlled, double masked clinical trial.

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Covered Clinical Study (Name and/or Number): CS302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>60</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>60</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This was an adequate and well-controlled, double masked clinical trial.

11 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SONAL D WADHWA
03/05/2019 09:05:33 AM

WILLIAM M BOYD
03/05/2019 09:38:18 AM