Division of Transplant and Ophthalmology Products Advisory Committee Meeting Briefing Package

for

Netarsudil ophthalmic solution 0.02% indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Sponsor: Aerie Pharmaceuticals, Inc.
2030 Main Street, Suite 1500
Irvine, CA 92614

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

Table of Contents

Introduction and Background

AR-13324 (netarsudil mesylate) is a Rho-associated protein kinase (Rho kinase) inhibitor. Rho kinase (ROCK) inhibitors represent a new class of medications proposed to lower IOP by directly increasing trabecular outflow.

Drug Established and Proposed Trade Name, Drug Class, Applicant's Proposed Indication, Dose, Regimens

Proposed Proprietary Name:	Rhopressa
Established name:	netarsudil ophthalmic solution
Sponsor:	Aerie Pharmaceuticals, Inc. 2030 Main Street, Suite 1500 Irvine, CA 92614
Pharmacologic Category:	Rho kinase inhibitor
Proposed Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosage Form and Route of Administration:	topical ophthalmic solution

State of Armamentarium for Indication

Approved drug products for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Alpha-2 agonist
apraclonidine
brimonidine tartrate
Beta adrenergic antagonists
betaxolol hydrochloride
carteolol hydrochloride
levobutanol hydrochloride
metipranolol
timolol hemihydrate
timolol maleate
Carbonic Anhydrase Inhibitors
acetazolamide
brinzolamide
dorzolamide hydrochloride
methazolamide

Cholinergic agonist
pilocarpine hydrochloride
Prostaglandin Analogues
bimatoprost
latanoprost
tafluprost
travoprost
Sympathomimetics
dipivefrin hydrochloride
Combination Products
dorzolamide hydrochloride/timolol maleate
brimonidine tartrate/timolol maleate
betaxolol hydrochloride/pilocarpine hydrochloride
brinzolamide/brimonidine
Other
unoprostone isopropyl

CMC Summary

Proprietary name	Rhopressa
Non-proprietary name	Netarsudil ophthalmic solution 0.02%
Drug substance	Netarsudil mesylate
Drug substance description	Light yellow to white powder
Description drug product	The drug product contains 0.02% netarsudil in an aqueous solution, including benzalkonium chloride (BAK) as an antimicrobial preservative.
Dosage form	Sterile, multi-dose (preserved) solution
Strength	0.02%
Sizes	2.5 mL
Drug Product Proposed Initial Expiration Dating Period	24 months
Drug Product Label Storage Conditions:	36-46°F

Description of Clinical Data Sources

Study Name	Study Design	Test product	No. of Subjects	Study Population
AR-13324-CS101	Open-label, single-arm, single-site	Netarsudil ophthalmic solution 0.02% 1 gtt OU QD AM	18	Healthy subjects
AR-13324-CS102	Double-masked, randomized, paired comparison, placebo controlled, single site	Netarsudil ophthalmic solution 0.02% 1 gtt QAM in 1 eye Vehicle 1 gtt QAM in 1 eye	11	Healthy subjects
AR-13324-CS201	Double-masked, randomized, placebo controlled, dose-response, multi-center	Netarsudil ophthalmic solution 0.01%, 0.02%, 0.04%, Vehicle 1 gtt QD AM in 1 eye	85	Subjects with elevated IOP
AR-13324-CS202	Double-masked, randomized, multi-center active controlled, dose response parallel-group	Netarsudil ophthalmic solution 0.01% and 0.02% 1 gtt OU QPM Latanoprost 0.005% 1 gtt OU QPM	224	Subjects with elevated IOP
AR-13324-CS204	Double-masked, randomized, placebo controlled study, single center	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Netarsudil ophthalmic solution placebo 1 gtt OU QPM	12	Subjects with elevated IOP
AR-13324-CS301	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Netarsudil ophthalmic solution placebo 1 gtt OU QAM Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	411	Subjects with elevated IOP
AR-13324-CS302	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Netarsudil Ophthalmic Solution Placebo 1 gtt OU QAM Netarsudil Ophthalmic Solution 0.02%	756	Subjects with elevated IOP

Study Name	Study Design	Test product	No. of Subjects	Study Population
		1 gtt OU BID Timolol Maleate Ophthalmic Solution 0.5% 1 gtt OU BID		
AR-13324-CS303	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QD PM Netarsudil ophthalmic solution placebo 1 gtt OU QD AM Netarsudil ophthalmic solution 0.02% 1 gtt OU BID Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	240 planned	Subjects with elevated IOP
AR-13324-CS304	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Netarsudil ophthalmic solution placebo 1 gtt OU QD AM Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	708	Subjects with elevated IOP
AR-13324-OBS01	Observational, prospective, targeted	None (Non-interventional)	45	Subjects from AR-1332- CS301 and AR-13324-CS302 who developed corneal deposits

Clinical Review of Efficacy

Discussion of Individual Trials

Study AR-13324-CS301: A double-masked, randomized, multi-center, active controlled, parallel, 3-month study assessing the safety and ocular hypotensive efficacy of AR-13324 ophthalmic solution, 0.02% (netarsudil) compared to timolol maleate ophthalmic solution, 0.5% in patients with elevated intraocular pressure

Study Objectives
The objectives of this study for adult subjects (18 years of age or greater) and pediatric subjects (0 to 2 years of age) were:

- To evaluate the ocular hypotensive efficacy of netarsudil ophthalmic solution, 0.02% OU QPM compared to the active comparator timolol maleate ophthalmic solution, 0.5% OU BID
- To evaluate the ocular and systemic safety of netarsudil ophthalmic solution, 0.02% OU QPM for 3 months (90 days)

This was to be a double-masked, randomized, multicenter, active-controlled, parallel-group, 3-month study to assess the ocular hypotensive efficacy and the safety of netarsudil ophthalmic solution, 0.02% OU QPM (hereafter referred to as netarsudil) compared to timolol maleate ophthalmic solution, 0.5% OU BID (AM and PM), (hereafter referred to as timolol) in adult subjects with elevated IOP. The study was also intended to enroll pediatric subjects aged 0 to 2 years.

Prior to enrollment, adult subjects were to have a Screening Visit and 2 Qualification Visits to allow for washout of ocular hypotensive medication if needed, while pediatric subjects were to have only a Baseline Visit. Subjects who met the eligibility criteria were to be randomized in a 1:1 ratio stratified by site to receive netarsudil or timolol. Subjects in this study were to be instructed to self-administer their masked medication OU BID, in the morning and evening, for 90 days. For subjects unable to self-administer the doses, a parent/guardian or caregiver was to administer the study medication. For subjects in the netarsudil group, the masked morning dose was to be placebo and the masked evening dose was to be netarsudil to maintain masking of the assigned treatment dosing schedule. Treatment assignments were to be masked to the Investigator, clinical study team, and subjects. After the start of study medication, all subjects were to have office visits at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3). A visit variation of ± 3 days was to be allowed for these 3 study visits according to the protocol. Planned enrollment was approximately 400 subjects (200 per treatment group) at approximately 40 sites in the US. Enrollment was to allow up to approximately 60 pediatric subjects 0 to 2 years of age (at least 30 per treatment group).

Efficacy was to be evaluated at study visits by IOP measurements at 08:00, 10:00, and 16:00 hours. The primary safety measures were visual acuity, pupil size (diameter), visual field testing, objective biomicroscopic and ophthalmoscopic examination, ocular tolerability as judged by a comfort test, and AEs. Other safety measures were systemic safety as measured by heart rate,

blood pressure, and clinical laboratory evaluations. Urine pregnancy tests for females of childbearing potential were to be conducted.

Inclusion Criteria

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

Specific Inclusion Criteria for Pediatric Subjects

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

Exclusion Criteria

Ophthalmic Criteria:

- Glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles. Note: Previous laser peripheral iridotomy was NOT acceptable.
- IOP $\geq$ 27 mmHg (unmedicated) in both eyes (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 combinations counted as 2 medications
- Known hypersensitivity to any component of the formulations to be used (benzalkonium chloride, etc.), topical anesthetics, or β-adrenoceptor antagonists
- Previous glaucoma intraocular surgery or glaucoma laser procedures in either eye
- Refractive surgery in either eye (ie. radial keratotomy, PRK, LASIK, corneal cross-linking)
- Ocular trauma in either eye within the 6 months prior to screening, or ocular surgery or non-refractive laser treatment within the 3 months prior to screening

- Recent or current evidence of ocular infection or inflammation in either eye. Current evidence of clinically significant blepharitis, conjunctivitis, or a history of herpes simplex or zoster keratitis at screening in either eye
- Ocular medication in either eye of any kind within 30 days of screening, with the exception of a) ocular hypotensive medications (which must have been washed out according to the provided schedule), b) lid scrubs (which may have been used prior to, but not after screening) or c) lubricating drops for dry eye (which may have been used throughout the study)
- Clinically significant ocular disease in either eye (i.e., corneal edema, uveitis, severe keratoconjunctivitis sicca) that might have interfered with the study, including glaucomatous damage so severe that washout of ocular hypotensive medications for 1 month was not judged safe (i.e., cup-to-disc ratio > 0.8, severe visual field defect)
- Central corneal thickness in either eye up to 620 μm at screening
- Any abnormality in either eye preventing reliable applanation tonometry

Systemic Criteria:

- Clinically relevant abnormalities (as determined by the Investigator) in laboratory tests at screening that may have affected the study
- Known hypersensitivity or contraindication to β-adrenoceptor antagonists (ie. chronic obstructive pulmonary disease or bronchial asthma; abnormally low blood pressure or heart rate; second or third degree heart block or CHF; severe diabetes)
- Clinically significant systemic disease (i.e., uncontrolled diabetes, myasthenia gravis, hepatic, renal, endocrine or cardiovascular disorders) that might have interfered with the study
- Participation in any investigational study within 30 days prior to screening
- Changes of systemic medication that could have had an effect on IOP within 30 days prior to screening, or anticipated during the study
- 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 postmenopausal or 3 months postsurgical sterilization. All females of childbearing potential must have had a negative urine pregnancy test result at the screening examination and must not have intended to become pregnant during the study

Specific Exclusion Criteria for Pediatric Subjects

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

Medication Administration

Subjects, or a parent/guardian or caregiver where applicable, were to administer the assigned masked study medication to both eyes twice daily, once in the morning and once in the evening, for 90 days. One drop of study medication was to be instilled to each eye during dosing; for pediatric subjects, this was to be to the lower cul-de-sac of each eye. Subjects were to be instructed to take the morning dose from the bottle marked AM and the evening dose from the bottle marked PM. Subjects in the timolol group were to instill timolol maleate ophthalmic

solution, 0.5% BID for both the morning and evening doses in a masked fashion. Subjects in the netarsudil group received placebo QD for the morning dose and netarsudil ophthalmic solution, 0.02% QD for the evening dose in a masked fashion

Identity of Investigational Products

Netarsudil ophthalmic solution 0.02% used in this study was a sterile, isotonic, buffered aqueous solution containing netarsudil (0.02%), boric acid, mannitol, water for injection, and preserved with BAK (0.015%). The product formulation was adjusted to approximately pH 5. Lot 221011 was used in the study.

Netarsudil ophthalmic solution placebo was a sterile, isotonic, buffered aqueous solution containing boric acid, mannitol, water for injection, and preserved with BAK (0.015%). The product formulation was adjusted to approximately pH 5. Lot 220991 was used in the study.

Timolol maleate ophthalmic solution, 0.5% was supplied as a commercially available generic product. Timolol maleate ophthalmic solution, 0.5% used in this study was a sterile, isotonic, buffered, aqueous solution of timolol maleate. Each mL contained 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients in the formulation are monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and Water for Injection. BAK 0.01% was present as a preservative. Lots 233640F and 229526F were used in the study.

The container-closure system used for netarsudil and placebo was chosen to be similar to the timolol commercial product presentation. The labels from the commercial bottles of timolol were removed and the product bottles were labeled with investigational labels with the study salient information. The product for each individual treatment assignment was packaged into identical subject packers that contained subject kits to cover the intended duration of treatment; each subject kit contained 2 bottles: either placebo (AM) and netarsudil ophthalmic solution 0.02% (PM), or 2 timolol maleate ophthalmic solution, 0.5% bottles (labeled AM and PM). To assist the subject in selecting the correct bottle for AM and PM dosing, the bottle labels were color-coded to suitably distinguish the bottles for AM and PM dosing and also included the word “AM” or “PM” in clearly identifiable font size on the labels. The products were to be stored refrigerated (36°F-46°F) in a secure location until they were provided to the subjects. The subjects were to be instructed that, after the bottle was opened, the product could be kept at room temperature (up to 77°F) for the intended duration of use and was not to be frozen.

Table 3 Schedule of Visits and Procedures for Adult Subjects

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

Table 3 Notes:
Qualifying IOP: At Qualification #1 and/or # 2, individuals who did NOT meet the requirements for minimum qualifying IOPs (IOP > 20 mmHg) could return for up to 2 additional qualification visits within 1 week of failing the first. Subjects who had IOP ≥ 27 mmHg (in both eyes) at Qualification #1 or #2 were not allowed to return.
Early Discontinuation: Visit 6 Procedures were to be completed.
Dosing: Investigational staff were to instruct subjects (or parent/guardian or caregiver) to administer their masked medication at home in both eyes between 07:30 and 08:30 hours (7:30 am and 8:30 am) and between 20:00 and 22:00 hours (8 pm and 10 pm) except during site visits. During site visits subjects brought medication to the office and self-administered the AM dose 30 minutes AFTER the first IOP measurement.
Visit requirements: IOP measurements at all visits were to be made within (±) one half hour of the protocol-specified times of 08:00, 10:00, and 16:00 hours with the exception of the screening visit.
Visit window: Allowable visit variation on post-qualification visits was ± 3 days.

Table 3 Footnotes:
1 Subjects currently using ocular hypotensive medications must have undergone a minimum washout period.
2 Urine pregnancy test for women of childbearing potential.
3 Symptoms: Subjects were queried at each visit "How are you feeling?" and treatment-emergent AEs were documented on the AE case report form (CRF). Additional symptoms reported after screening and before randomization were documented on the medical history CRF.
4 Comfort test: At 08:00 hours for on study drug visits, subjects were queried "Did you experience any discomfort when placing the drops in your eyes?"
5 Gonioscopy and entry visual field evaluation up to 3 months prior to randomization was acceptable. Visual field must have met the requirement for automated threshold visual field (e.g., 30-2 or 24-2 Humphrey) and reliability.
6 Pachymetry within 1 week of screening was acceptable.
7 Used kit(s) dispensed during the previous visit were collected at 08:00 hours (after the AM dosing).

Primary Efficacy Variable

For adult subjects, the primary efficacy outcome was to be the mean IOP at 08:00, 10:00, and 16:00 hours at the Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90) visits.

Secondary Efficacy Variables

Secondary efficacy endpoints included mean change from baseline IOP at each post-treatment time point, mean percent change from diurnally adjusted baseline IOP at each time point, and mean diurnal and change from baseline diurnal IOP at each post-treatment visit.

Analysis Populations

Four analysis populations were defined:

- The randomized population was to include all subjects who were randomized to treatment. Baseline variables and demographic characteristics were to be summarized for this population.
- The Intent-to-Treat (ITT) population was to include all randomized subjects who received at least 1 dose of study medication. This was to be the secondary population for efficacy analyses and was to be used to summarize a subset of efficacy variables. The ITT population was to summarize subjects according to their randomization assignment for purpose of analysis.
- The Per Protocol (PP) population was a subset of the ITT population and was to include subjects (and their visits) who did not have major protocol violations likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. This was to be the primary population for efficacy analyses and was to be used to summarize all efficacy variables. The PP population was to summarize subjects as treated for purpose of analysis.
- The safety population was to include all randomized subjects who received at least 1 dose of study medication and was to be used to summarize safety variables. The safety population was to summarize subjects as treated for purpose of analysis.

Separate analysis populations were to be defined for subjects 0 to 2 years old and for subjects 18 years of age and older; however, no pediatric subjects were enrolled.

Primary Efficacy Endpoint Analysis Methods

The primary analysis of the primary outcome was to be completed using individual 2-sample 95% t-distribution CIs for each comparison at each time point (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3) using the PP population. If the upper limits of the 95% CIs for the difference (netarsudil – timolol) were within 1.5 mmHg at all time points and within 1.0 mmHg at a majority of time points (at least 5 of 9), then the null hypothesis was to be rejected in favor of the alternative hypothesis and netarsudil was to be considered clinically non-inferior to timolol. The 2-sample t-test was to be used to test whether the difference equals 0. Analyses were to be performed primarily on the PP population using observed data only (without imputation).

Study AR-13324-CS302: A double-masked, randomized, multi-center, active-controlled, parallel, 12-month study assessing the safety and ocular hypotensive efficacy of AR-13324 (netarsudil) Ophthalmic Solution, 0.02% QD and BID compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure

Study Objectives:
The objectives of this study for adult and pediatric subjects (0 to 2 years of age) were:

- To evaluate the ocular hypotensive efficacy of netarsudil ophthalmic solution 0.02% dosed QD and netarsudil ophthalmic solution 0.02% dosed BID compared to the active comparator Timolol maleate ophthalmic solution 0.5% over a 3 month period
- To evaluate the ocular and systemic safety of netarsudil ophthalmic solution 0.02% dosed QD and BID for 12 months

This was a double-masked, randomized, multicenter, active-controlled, parallel-group, 12-month study to assess the ocular hypotensive efficacy and the safety of netarsudil ophthalmic solution 0.02% dosed OU QPM (hereafter referred to as netarsudil QD) and netarsudil ophthalmic solution 0.02% dosed OU BID (hereafter referred to as netarsudil BID) compared to timolol maleate ophthalmic solution 0.5% dosed OU BID (hereafter referred to as timolol) in adult subjects with elevated IOP. The study was also intended to enroll pediatric subjects aged 0 to 2 years old.

Prior to enrollment, adult subjects had a Screening Visit and 2 Qualification Visits to allow for washout of ocular hypotensive medication while pediatric subjects were to have only a Baseline Visit. Subjects who met the eligibility criteria were to be randomized in a 1:1:1 ratio, stratified by site, to receive netarsudil QD, netarsudil BID, or timolol. For subjects in the netarsudil QD treatment group, the morning dose was to be netarsudil ophthalmic solution placebo (vehicle) and the masked evening dose was to be netarsudil QD to maintain masking of the assigned treatment dosing schedule. Therefore, all subjects in the study were to dose BID in order to maintain masking in the study. Treatment assignments were to be masked to the Investigator, clinical study team, and subjects. Subjects were instructed to self-administer their masked medication OU BID in the morning (AM) and evening (PM), for 365 days, with IP bottles labeled "AM" to be used for AM dosing and IP bottles labeled "PM" for PM dosing. For pediatric or adult subjects unable to self-administer the doses, a parent/guardian or caregiver was to administer the study medication. After the start of study medication, all subjects were to have office visits at Day 15 (Week 2), Day 43 (Week 6), Day 90 (Month 3), Day 180 (Month 6), Day 270 (Month 9), and Day 365 (Month 12). A visit variance of ± 3 days was to be allowed for the Week 2 and Week 6 study visits while subsequent study visits had an allowed visit variance of ± 5 days. Planned enrollment was approximately 756 subjects (252 subjects per treatment group) at approximately 60 sites in the US. Enrollment was intended to allow up to approximately 60 pediatric subjects 0 to 2 years of age (approximately 20 subjects per treatment group).

Efficacy was to be evaluated at study visits by IOP measurements at 08:00, 10:00, and 16:00 hours at baseline (Day 1), Week 2, Week 6, and Month 3. The primary safety measures were visual acuity, pupil size, visual field testing, objective biomicroscopic and ophthalmoscopic examination, ocular tolerability as judged by a comfort test, ECC by specular microscopy, and treatment emergent AEs (TEAEs). Other safety measures were systemic safety as measured by

heart rate, blood pressure, clinical laboratory evaluations; and urine pregnancy test (for females of childbearing potential).

Inclusion/Exclusion Criteria were identical to Study AR-13324-CS301.

Medication Administration was identical to Study AR-13324-CS301.

Identity of Investigation Products

The same investigational drug products from Study AR-13324-CS301 were used in this study: netarsudil 0.02% (Lot Numbers 221011 and 228501), netarsudil ophthalmic solution placebo (Lot Numbers 220991 and 230271), and timolol maleate ophthalmic solution 0.5% (Lot Numbers 233640F, 229526F, and 233643F).

Study Schedule

9.5.1.3 Schedule of Events

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

At Qualification #1 and/or # 2, individuals who did NOT meet the requirements for minimum qualifying IOPs (IOP >20 mmHg) could return for up to 2 additional qualification visits within 1 week of failing the first. Those that were ≥ 27 mmHg (in both eyes) at Qualification #1 or #2 were not allowed to return.
HR/BP = heart rate/blood pressure; G = gonioscopy, P = pachymetry. Early Discontinuation: Visit 9 Procedures to be completed
Dosing: Investigational staff were to instruct patients (or parent/guardian) to administer their masked medication at home in both eyes between 07:30 – 08:30 hours (7:30am and 8:30am) and 20:00 – 22:00 hours (8pm and 10pm) except during site visits. During site visits subjects were to bring medication to the office and self-administer the AM dose 30 minutes AFTER the first IOP measurement.
Visit requirements: IOP measurements at all visits were to be made within (+/-) one half hour of the protocol specified times of 08:00, 10:00 and 16:00 hours with the exception of the screening visit.
Visit window: Allowable visit variation on post-qualification visits with the first 3 months was ± 3 days Subsequent visits have ± 5 day variance.

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

Primary Efficacy Variable

The primary efficacy outcome was the mean IOP for subjects with baseline IOP > 20 mmHg (08:00 hours) and < 25 mmHg (at 08:00, 10:00, and 16:00 hours) in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits.

Secondary Efficacy Variables

Mean IOP for subjects with baseline IOP > 20 mmHg (08:00 hours) and < 27 mmHg (08:00, 10:00, and 16:00 hours) in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 Visits.

Additionally, the following endpoints were to be summarized for both populations of subjects (i.e., maximum baseline IOP < 25 mmHg and < 27 mmHg):

- Mean change from baseline IOP at each post-treatment time point
- Mean percent change from diurnally adjusted baseline IOP at each time point
- Mean diurnal and change from baseline diurnal IOP at each post-treatment visit
- Sub-group analyses based upon pre-study characteristics such as demographics, unmedicated baseline IOP, and pre-study ocular hypotensive medications

Analysis Populations

The four analysis population definitions (randomized, ITT, PP, and safety) were identical to Study AR-13324-CS301.

Primary Efficacy Endpoint Analysis Methods

The primary analysis of the primary outcome was completed using individual 2-sample 95% t-distribution confidence intervals for each comparison at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits). This was done with observed data only for the PP population having maximum baseline IOP > 20 mmHg (08:00 hours) and < 25 mmHg (08:00, 10:00, and 16:00 hours) in the study eye. The primary efficacy analysis was completed in a hierarchical fashion to preserve alpha, first testing netarsudil QD to timolol, and secondarily testing netarsudil BID to timolol if netarsudil QD demonstrated clinical non-inferiority. The study was to be considered a success and clinical non-inferiority of netarsudil QD concluded if the upper limit of the 95% CIs around the difference in mean IOP values (netarsudil QD – timolol) was within 1.5 mmHg at all time points through Month 3 and within 1.0 mmHg at a majority of the time points (at least 5 of 9 time points) through Month 3. If clinical non-inferiority was concluded for netarsudil QD, then netarsudil BID was tested against timolol in a hierarchical fashion. Clinical non-inferiority for netarsudil ophthalmic solution 0.02% BID was concluded if the upper limit of the 95% CIs around the difference in mean IOP values (netarsudil BID – timolol) was within 1.5 mmHg at all time points through Month 3 and was within 1.0 mmHg at a majority of time points (at least 5 of 9 time points) through Month 3.

Interim Analysis

Two interim analyses were prospectively planned for this study. When all subjects completed the first 3 months of treatment or had prematurely discontinued from the study within the first 3 months of treatment, the Sponsor's biostatistical representative unmasked the study to analyze the 3-month efficacy and safety data. No study personnel other than the statistician, SAS programmers, Aerie VP Clinical Research and Medical Affairs, Aerie Chief Scientific Officer and an Aerie Information Systems Manager were unmasked to the individual subject treatment assignments and demographic information to perform the 3-month efficacy and safety data analysis. For Aerie personnel, access to individual subject treatment assignments was exclusively to conduct further exploratory data analysis. This first interim analysis was the primary efficacy analysis of the study and therefore no alpha adjustment for this interim analysis was implemented. This first interim analysis was to be completed at an overall 2-sided alpha of 5%, with each of the pairwise comparisons of netarsudil (QD and BID) to timolol completed at a 2-sided alpha of 5% (2-sided 95% CI). First netarsudil QD was tested versus timolol, then in a hierarchical fashion testing netarsudil BID versus timolol was tested only if netarsudil QD showed non-inferiority to timolol. For the efficacy interim analyses, analyses were to be limited to data available through 3 months of treatment. Additionally, key adverse event summaries were to be limited to data available through 3 months.

Once at least 100 subjects in each of the netarsudil QD and timolol treatment arms completed the 12-month visit, a second interim analysis for safety was planned, but not completed. Continuing efforts were made to keep Sponsor and CRO staff, Investigators and their staff, and enrolled subjects masked to the individual subject assignments for remaining enrolled subjects as they continued to be evaluated for safety through 12 months of treatment.

Changes in the Planned Statistical Analysis

Several protocol amendments and a consequent updated Statistical Analysis Plan were prepared during the study that changed the original planned statistical analyses. Important changes were made in Amendments #2, #4, #5 and #7 as summarized in table below.

Table 6 Important Changes in Statistical Analysis

Protocol Amendment	Item Changed	From	To
Amendment #2	Primary efficacy outcome	Mean change from baseline IOP at the following time points: 08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits.	Mean IOP at the following time points: 08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits.
Amendment #4	Inclusion/exclusion criteria	N/A	Third and fourth qualification visits: "If only one eye has an IOP > 17 mmHg, it must be the same eye that met qualification requirements at Visit 2.
Amendment #5	Primary efficacy outcome and analysis population	Mean IOP for all PP subjects	Mean IOP for PP subjects with baseline IOP > 20 mmHg (08:00 h) and < 24 mmHg (08:00, 10:00, and 16:00 h) in the study eye
	Secondary efficacy endpoint added	N/A	Mean IOP for subjects with baseline IOP > 20 mmHg (08:00 h) and < 27 mmHg (08:00, 10:00, and 16:00 h) in the study eye at the following time points: 08:00, 10:00, and 16:00 h at the Week 2, Week 6, and Month 3 Visits.
	Added additional subgroup analyses	N/A	Sub-group analyses based upon pre-study characteristics such as demographics, unmedicated baseline IOP, and pre-study ocular hypotensive medications will be completed to further investigate the efficacy measures.
	Sample size	690/study; 230/treatment group	879/study; 293/treatment group
	Testing of primary efficacy variable	at a 2-sided 0.025 significance level to maintain an overall alpha level of 0.05 using Bonferroni correction. Two-sided 97.5% confidence intervals will be reported unless otherwise specified	hierarchical manner at a 2-sided 0.05 significance level with AR-13324 QD tested for non-inferiority to Timolol first. Subsequently, only if non-inferiority has been demonstrated for AR-13324 QD, then AR-13324 BID will be tested for non-inferiority to Timolol. This hierarchical approach will allow maintenance of an overall alpha
Amendment #7	Primary efficacy outcome	mean IOP for subjects with baseline IOP > 20 mmHg (08:00 h) and < 24 mmHg (08:00, 10:00, and 16:00 h) in the study eye	mean IOP for subjects with baseline IOP > 20 mmHg (08:00 h) and < 25 mmHg (08:00, 10:00, and 16:00 h) in the study eye
	Additional analyses	for both populations of subjects (< 24 mmHg and < 27 mmHg)	both populations of subjects (< 25 mmHg and < 27 mmHg)
	Sample size	879/study; 293/treatment group	Approximately 756/study; 252/treatment group to obtain approximately 122 per protocol subjects per treatment group completing through Month 3

Demographics and Disposition

Study AR-13324-CS301: Demographics (Randomized Patients)

Characteristic	**Netarsudil 0.02% QD N=202**	**Timolol 0.5% BID N=209**
Study eye diagnosis		
POAG	134 (66%)	136 (65%)
OHT	68 (34%)	73 (35%)
Sex		
Male	88 (44%)	73 (35%)
Female	114 (56%)	136 (65%)
Age (years)		
Mean	65.8	64.2
Range	20, 96	26, 90
Race		
Asian	2 (1%)	4 (2%)
Black or African-American	43 (21%)	51 (24%)
White	157 (78%)	153 (73%)
Other	0	1 (1%)
Ethnicity		
Hispanic or Latino	27 (13%)	28 (13%)
Not Hispanic or Latino	175 (87%)	181 (87%)
Iris color of study eye		
Blue/Grey/Green	71 (35%)	54 (26%)
Brown	107 (53%)	141(67%)
Hazel	24 (12%)	14 (7%)

Study AR-13324-CS302: Demographics (Randomized Patients)

Characteristic	**Netarsudil 0.02% QD N=251**	**Netarsudil 0.02% BID N=254**	**Timolol 0.5% BID N=251**
Study eye diagnosis			
POAG	167 (67%)	158 (62%)	171 (68%)
OHT	84 (33%)	96 (38%)	80 (32%)
Sex			
Male	103 (41%)	89 (35%)	101 (40%)
Female	148 (59%)	165 (65%)	150 (60%)
Age (years)			
Mean	65.83	64.1	63.0
Range	14, 86	18, 92	11, 88
Race			
Asian	2 (0.8%)	6 (2%)	6 (2%)
Black or African- American	69 (27%)	69 (27%)	76 (30%)
Native American	2 (0.8%)	0	0
White	178 (71%)	177 (70%)	166 (66%)
Other	0	2 (0.8%)	3 (1%)
Ethnicity			
Hispanic or Latino	41 (16%)	43 (17%)	42 (17%)
Not Hispanic or Latino	210 (83%)	211 (83%)	209 (83%)
Iris color of study eye			
Blue/Grey/Green	60 (24%)	57 (22%)	69 (27%)
Brown	155 (62%)	169 (67%)	165 (66%)
Hazel	35 (14%)	28 (11%)	17 (7%)
Other	1 (0.4%)	0	0

Study AR-13324-CS301: Analysis Population

Population	**netarsudil 0.02%**	**Timolol 0.5%**
Safety	203*	208
Intent to Treat (ITT)	202	209
Per Protocol (PP)	182	188

* For the treatment assignments, ITT use was assigned as randomized subjects; Safety and PP use was assigned as treated subjects. Several subjects incorrectly received treatment with IP other than that to which they were randomized.

Study AR-13324-CS301: Subject Disposition (ITT Population)

Number of Randomized Subjects	**netarsudil 0.02% N=202**	**Timolol 0.5% N=209**
Study Completion		
Completed	171 (85%)	196 (95%)
Discontinued	31 (15%)	13 (6%)
Reason for Subject Discontinuation		
Adverse Event	20 (10%)	4 (2%)
Withdrawal of Consent	3 (1%)	2 (1%)
Non-compliant	0	1 (0.5%)
Lost to Follow-up	0	1 (0.5%)
Lack of Efficacy	3 (1%)	0
Investigator Decision	2 (1%)	0
Protocol Violation	3 (1%)	5 (2%)

Study AR-13324-CS302: Analysis Populations

Population	netarsudil 0.02% QD	netarsudil 0.02% BID	Timolol 0.5% BID
Safety	251	253	251
Intent to Treat (ITT)	251	253	251
Per Protocol (PP)	206	209	217

Study AR-13324-CS302: Subject Disposition (ITT Population)

Number of Randomized Subjects	netarsudil 0.02% QD N=251	netarsudil 0.02% BID N=254	Timolol 0.5% BID N=251
Study Completion			
Completed Month 3	205 (82%)	153 (60%)	237 (94%)
Discontinued Prior to Month 3	46 (18%)	101 (40%)	14 (6%)
Completed Month 12	146 (58%)	86 (34%)	204 (81%)
Discontinued Prior to Month 12	105 (42%)	168 (66%)	47 (19%)
Reason for Subject Discontinuation			
Adverse Event	71 (28%)	132 (52%)	15 (6%)
Withdrawal of Consent	9 (4%)	13 (5%)	9 (4%)
Non-compliant	3 (1%)	1 (0.4%)	3 (1%)
Lost to Follow-up	1 (0.4%)	3 (1%)	0
Lack of Efficacy	10 (4%)	4 (2%)	2 (0.8%)
Disallowed Concurrent Medication	2 (0.8%)	2 (1%)	5 (2%)
Investigator Decision	1 (0.4%)	2 (1%)	2 (1%)
Protocol Violation	4 (2%)	6 (2%)	10 (4%)
Death	2 (0.8%)	0	0
Other	2 (0.8%)	5 (2%)	1 (0.4%)

Netarsudil ophthalmic solution 0.02% BID was not well tolerated. Forty (40) percent of patients discontinued within the first 3 months of treatment.

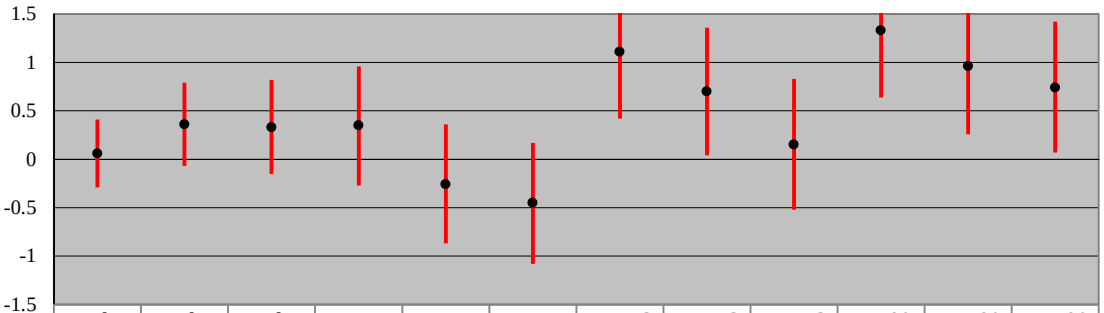
Study AR-13324-CS301 Primary Endpoint:
The primary efficacy outcome was the mean IOP at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) visits.

The primary analysis of the primary outcome was completed using individual 2-sample 95% t-distribution CIs for each comparison at each time point (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3) using the PP population. If the upper limits of the 95% CIs for the difference (netarsudil – timolol) in mean IOP were within 1.5 mmHg at all time points and within 1.0 mmHg at a majority of time points (at least 5 of 9), then the null hypothesis was to be rejected in favor of the alternative hypothesis and netarsudil was to be considered clinically non-inferior to timolol. Secondarily, the 2-sample t-test was used to test whether the difference equals 0. Analyses were performed primarily on the PP population using observed data only (without imputation).

Study AR-13324-CS301: Study eye IOP (mmHg) by visit
(PP Population With Observed Data-Baseline IOP<27)

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

Study AR-13324-CS301: Difference in Mean IOP
PP Population (Baseline IOP<27)



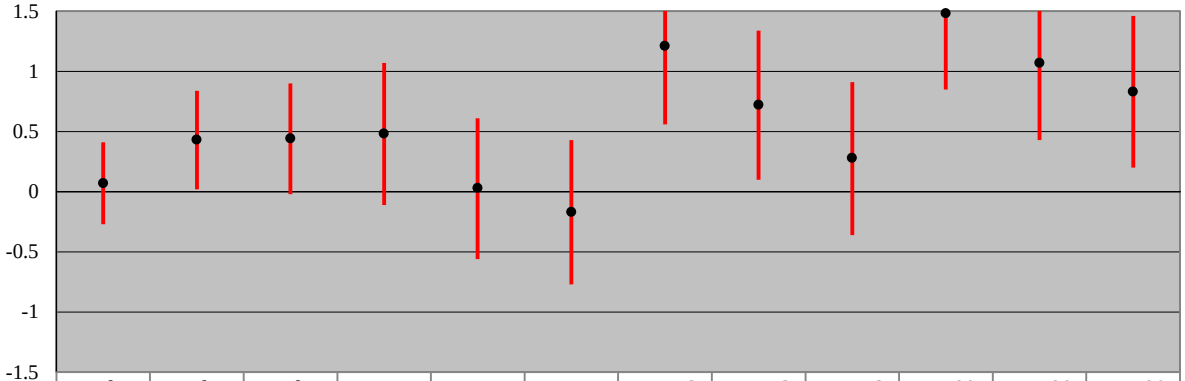
	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.29	-0.07	-0.15	-0.27	-0.87	-1.08	0.42	0.04	-0.52	0.64	0.26	0.07
Upper CI	0.41	0.79	0.82	0.96	0.36	0.17	1.8	1.36	0.83	2.03	1.66	1.42
Mean Difference	0.06	0.36	0.33	0.35	-0.26	-0.45	1.11	0.7	0.15	1.33	0.96	0.74

The PP population did not demonstrate non-inferiority of netarsudil ophthalmic solution 0.02% dosed QD to timolol maleate ophthalmic solution 0.5% dosed BID (baseline IOP < 27 mmHg). The upper 95% confidence limit for the differences in mean IOP was within 1.5 mmHg at 6 of the 9 time points and within 1.0 mmHg at 4 of the 9 time points; therefore it did not meet the pre-specified criteria for non-inferiority.

Study AR-13324-CS301: Study eye IOP (mmHg) by visit (ITT with LOCF Population)

Day and Time	Mean IOP netarsudil QD N=202	Mean IOP Timolol BID N=209	Mean Difference Between netarsudil and Timolol	95% CI
Baseline (Visit 3)				
08:00	23.41	23.34	0.07	(-0.27, 0.41)
10:00	22.30	21.87	0.43	(0.02, 0.84)
16:00	21.84	21.40	0.44	(-0.02, 0.90)
Day 15				
08:00	18.81	18.33	0.48	(-0.11, 1.07)
10:00	17.54	17.51	0.03	(-0.56, 0.61)
16:00	17.50	17.68	-0.17	(-0.77, 0.43)
Day 43				
08:00	19.46	18.26	1.21	(0.56, 1.86)
10:00	18.22	17.50	0.72	(0.10, 1.34)
16:00	18.07	17.79	0.28	(-0.36, 0.91)
Day 90				
08:00	19.97	18.48	1.48	(0.85, 2.12)
10:00	19.03	17.96	1.07	(0.43, 1.71)
16:00	18.68	17.85	0.83	(0.20, 1.46)

Study AR-13324-CS301: Difference in Mean IOP ITT with LOCF Population (Baseline IOP<27)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.27	0.02	-0.02	-0.11	-0.56	-0.77	0.56	0.1	-0.36	0.85	0.43	0.2
Upper CI	0.41	0.84	0.9	1.07	0.61	0.43	1.86	1.34	0.91	2.12	1.71	1.46
Mean Difference	0.07	0.43	0.44	0.48	0.03	-0.17	1.21	0.72	0.28	1.48	1.07	0.83

The ITT population (N = 411 subjects) was similar in size to the PP population (N = 370 subjects), and the degree of change from diurnally adjust baseline values at each of the 9 observation time points at Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) was also similar. As with the PP population, netarsudil did not demonstrate non-inferiority to timolol in the ITT population.

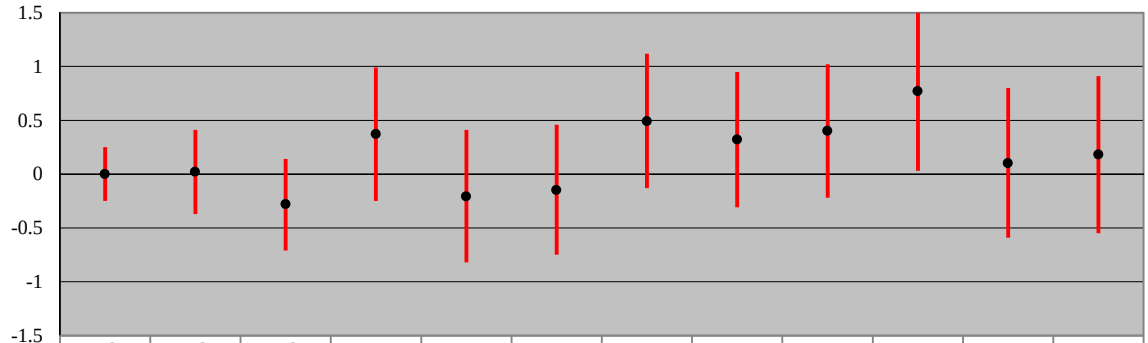
Study AR-13324-CS302 Primary Endpoint:
The primary efficacy outcome was the mean IOP for subjects with baseline IOP > 20 mmHg (08:00 hours) and **< 25 mmHg** (at 08:00, 10:00, and 16:00 hours) in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits.

The primary analysis of the primary outcome was completed using individual 2-sample 95% t-distribution confidence intervals for each comparison at each time point (08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits). This was done with observed data only for the PP population having maximum baseline IOP > 20 mmHg (08:00 hours) and < 25 mmHg (08:00, 10:00, and 16:00 hours) in the study eye. The primary efficacy analysis was completed in a hierarchical fashion to preserve alpha, first testing netarsudil QD to timolol, and secondarily testing netarsudil BID to timolol if netarsudil QD demonstrated clinical non-inferiority. The study was to be considered a success and clinical non-inferiority of netarsudil QD concluded if the upper limit of the 95% CIs around the difference in mean IOP values (netarsudil QD – timolol) was within 1.5 mmHg at all time points through Month 3 and within 1.0 mmHg at a majority of the time points (at least 5 of 9 time points) through Month 3. If clinical non-inferiority was concluded for netarsudil QD, then netarsudil BID was tested against timolol in a hierarchical fashion. Clinical non-inferiority for netarsudil ophthalmic solution 0.02% BID was concluded if the upper limit of the 95% CIs around the difference in mean IOP values (netarsudil BID – timolol) was within 1.5 mmHg at all time points through Month 3 and was within 1.0 mmHg at a majority of time points (at least 5 of 9 time points) through Month 3.

Study AR-13324-CS302: Study eye IOP (mmHg) by visit
(PP Population with Observed Data with Baseline IOP <25 MmHg)

Day and Time	Mean IOP netarsudil 0.02% QD	Mean IOP netarsudil 0.02% BID	Mean IOP Timolol 0.5% BID	Mean Difference Timolol-netarsudil 0.02% QD	95% CI	Mean Difference Timolol-netarsudil 0.02% BID	95% CI
Baseline							
08:00	22.54 N=129	22.55 N=132	22.54 N=142	0	(-0.25, 0.25)	0.01	(-0.24, 0.26)
10:00	21.29 N=129	21.27 N=132	21.27 N=142	0.02	(-0.37, 0.41)	-0.01	(-0.40, 0.38)
16:00	20.43 N=129	20.56 N=132	20.71 N=142	-0.28	(-0.71, 0.14)	-0.15	(-0.58, 0.29)
Day 15							
08:00	18.07 N=127	17.21 N=122	17.69 N=142	0.37	(-0.25, .99)	-0.48	(-1.19, 0.22)
10:00	16.72 N=126	16.35 N=120	16.93 N=141	-0.21	(-0.82, 0.41)	-0.57	(-1.24, 0.09)
16:00	16.68 N=126	15.65 N=118	16.83 N=141	-0.15	(-0.75, 0.46)	-1.18	(-1.82, -0.54)
Day 43							
08:00	17.95 N=122	17.64 N=111	17.46 N=141	0.49	(-0.13, 1.12)	0.17	(-0.51, 0.86)
10:00	16.95 N=120	16.28 N=106	16.63 N=141	0.32	(-0.31, 0.95)	-0.34	(-1.02, 0.33)
16:00	17.00 N=120	15.75 N=106	16.60 N=141	0.40	(-0.22, 1.02)	-0.85	(-1.53, -0.17)
Day 90							
08:00	18.24 N=116	17.58 N=91	17.47 N=140	0.77	(0.03, 1.50)	0.11	(-0.64, 0.86)
10:00	17.03 N=114	16.94 N=88	16.92 N=140	0.10	(-0.59, 0.80)	0.02	(-0.72, 0.77)
16:00	17.13 N=114	16.51 N=88	16.95 N=139	0.18	(-0.55, 0.91)	-0.44	(-1.16, 0.27)

Study AR-13324-CS302: Difference in Mean IOP (Netarsudil QD Compared to Timolol 0.5% BID) - PP Population With Observed Data (Baseline IOP<25)



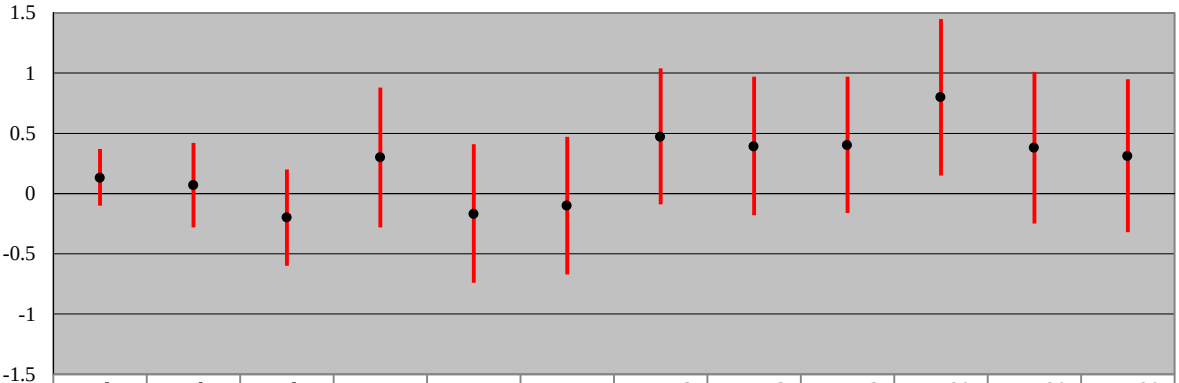
	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.25	-0.37	-0.71	-0.25	-0.82	-0.75	-0.13	-0.31	-0.22	0.03	-0.59	-0.55
Upper CI	0.25	0.41	0.14	0.99	0.41	0.46	1.12	0.95	1.02	1.5	0.8	0.91
Mean Difference	0	0.02	-0.28	0.37	-0.21	-0.15	0.49	0.32	0.4	0.77	0.1	0.18

In the population of patients with a maximum IOP <25 mmHg, there were no clinically significant differences in IOP reduction between netarsudil QD, netarsudil BID and timolol. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points. The upper 95% confidence limit for the differences in mean IOP between netarsudil BID and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at all of the 9 time points.

Study AR-13324-CS302: Study eye IOP (mmHg) by visit
(ITT with LOCF with Baseline IOP <25 MmHg)

Day and Time	Mean IOP netarsudil 0.02% QD	Mean IOP netarsudil 0.02% BID	Mean IOP Timolol 0.5% BID	Mean Difference From Timolol netarsudil 0.02% QD	95% CI	Mean Difference From Timolol netarsudil 0.02% BID	95% CI
Baseline							
08:00	22.54	22.56	22.41	0.13	(-0.10, 0.37)	0.15	(-0.10, 0.39)
10:00	21.23	21.28	21.16	0.07	(-0.28, 0.42)	0.11	(-0.24, 0.47)
16:00	20.40	20.59	20.60	-0.20	(-0.60, 0.20)	-0.01	(-0.41, 0.40)
Day 15							
08:00	17.91	17.69	17.61	0.30	(-0.28, 0.88)	0.07	(-0.58, 0.73)
10:00	16.75	16.81	16.92	-0.17	(-0.74, 0.41)	-0.11	(-0.74, 0.52)
16:00	16.73	16.34	16.83	-0.10	(-0.67, 0.47)	-0.49	(-1.12, 0.14)
Day 43							
08:00	17.85	17.97	17.38	0.47	(-0.09, 1.04)	0.60	(-0.03, 1.22)
10:00	16.93	17.06	16.54	0.39	(-0.18, 0.97)	0.52	(-0.10, 1.14)
16:00	16.96	16.38	16.56	0.40	(-0.16, 0.97)	-0.18	(-0.82, 0.46)
Day 90							
08:00	18.16	18.13	17.36	0.80	(0.15, 1.45)	0.77	(-0.09, 1.44)
10:00	17.15	17.35	16.77	0.38	(-0.25, 1.01)	0.58	(-0.06, 1.21)
16:00	17.11	16.80	16.79	0.31	(-0.32, 0.95)	0.00	(-0.63, 0.64)

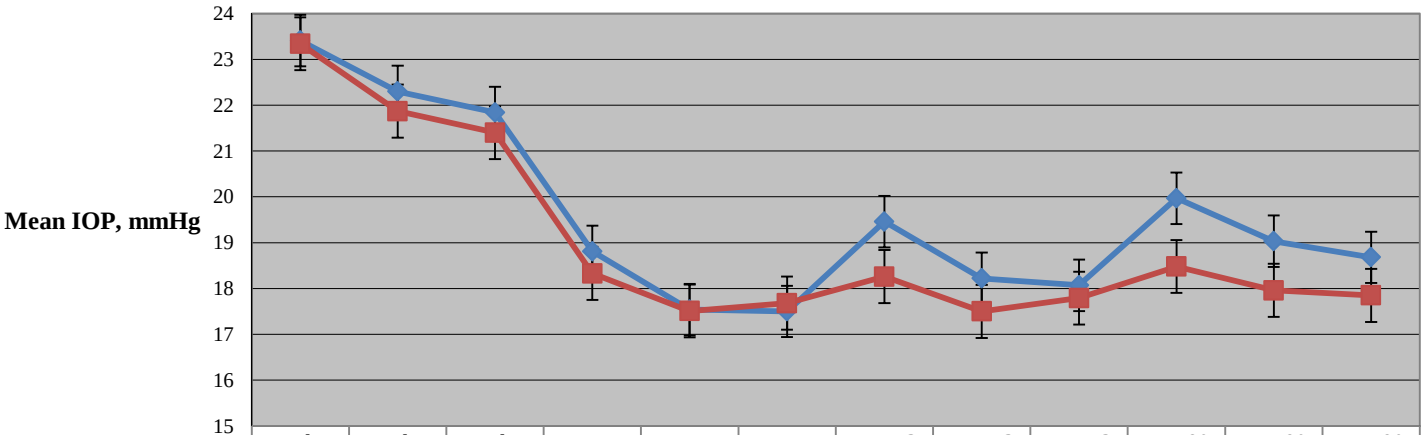
Study AR-13324-CS302: Difference in Mean IOP (Netarsudil QD Compared to Timolol 0.5% BID) - ITT with LOCF Population (Baseline IOP<25)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.1	-0.28	-0.6	-0.28	-0.74	-0.67	-0.09	-0.18	-0.16	0.15	-0.25	-0.32
Upper CI	0.37	0.42	0.2	0.88	0.41	0.47	1.04	0.97	0.97	1.45	1.01	0.95
Mean Difference	0.13	0.07	-0.2	0.3	-0.17	-0.1	0.47	0.39	0.4	0.8	0.38	0.31

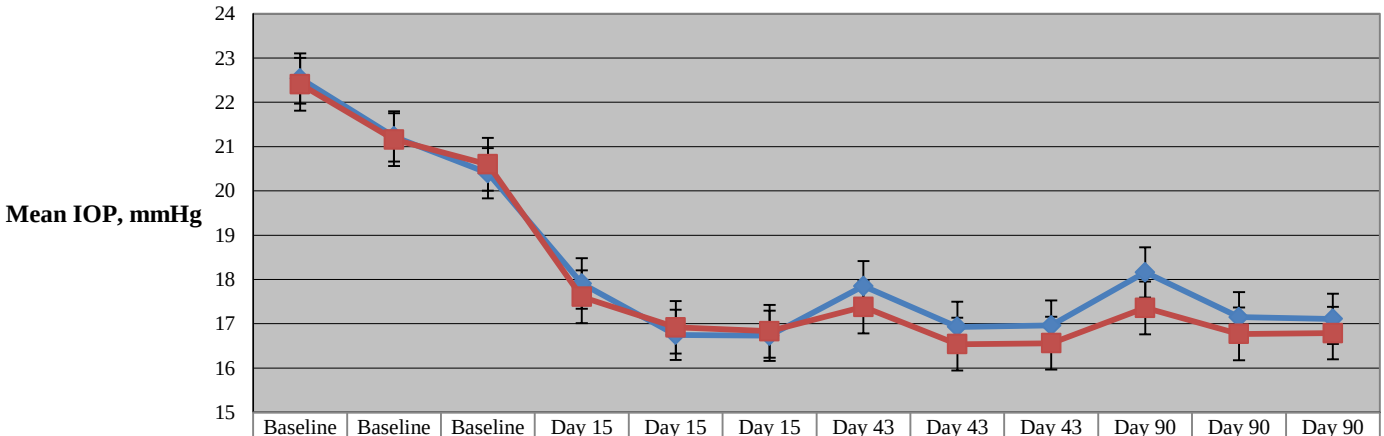
In the PP population of patients with an IOP <25 mmHg, there were no clinically significant differences in IOP reduction between netarsudil QD, netarsudil BID and timolol. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 7 of the 9 time points and the upper 95% confidence limit for the differences in mean IOP between netarsudil BID and timolol was within 1.0 mmHg at all of the 9 time points.

Study AR-13324-CS301: Mean IOP Comparison (ITT with LOCF Population)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
AR-13324	23.41	22.3	21.84	18.81	17.54	17.5	19.46	18.22	18.07	19.97	19.03	18.68
Timolol	23.34	21.87	21.4	18.33	17.51	17.68	18.26	17.5	17.79	18.48	17.96	17.85

Study AR-13324-CS302: Mean IOP Comparison (ITT with LOCF Population)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
AR-13324 QD	22.54	21.23	20.4	17.91	16.75	16.73	17.85	16.93	16.96	18.16	17.15	17.11
Timolol	22.41	21.16	20.6	17.61	16.92	16.83	17.38	16.54	16.56	17.36	16.77	16.79

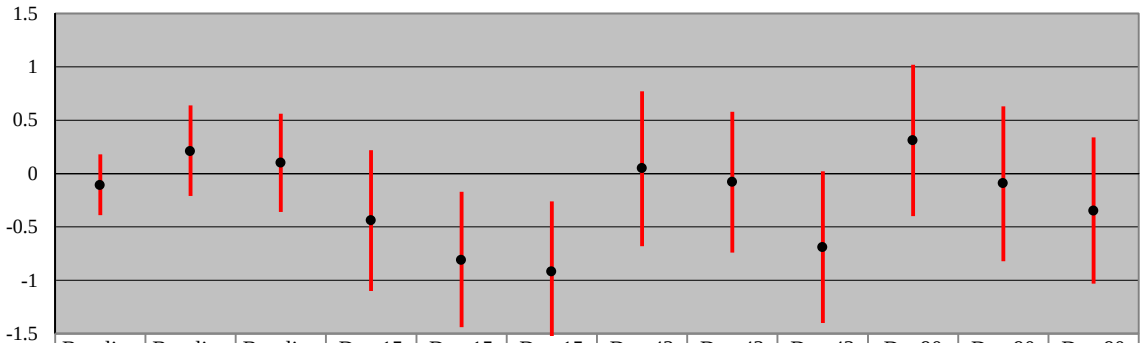
Post Hoc Efficacy Analysis for Study AR-13324-CS301

For Study AR-13324-CS301 there was a post hoc efficacy analysis of subgroups with maximum baseline IOP < 25 mmHg.

Study AR-13324-CS301: Study eye Mean IOP (mmHg) by visit for Subjects with Baseline IOP <25 at All Timepoints (PP Population With Observed Data)

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

Study AR-13324-CS301: Mean IOP by Visit for Subjects with Baseline IOP <25 - PP Population



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.39	-0.21	-0.36	-1.1	-1.44	-1.58	-0.68	-0.74	-1.4	-0.4	-0.82	-1.03
Upper CI	0.18	0.64	0.56	0.22	-0.17	-0.26	0.77	0.58	0.02	1.02	0.63	0.34
Mean Difference	-0.11	0.21	0.1	-0.44	-0.81	-0.92	0.05	-0.08	-0.69	0.31	-0.09	-0.35

In the population of patients with a maximum IOP <25 mmHg, netarsudil ophthalmic solution, 0.02% dosed QD was clinically similar to timolol maleate ophthalmic solution, 0.5% dosed BID in IOP lowering. The upper 95% confidence limit for differences in mean IOP was within 1.5 mmHg at all 9 time points and within 1.0 mmHg at 8 of the 9 time points.

AR-13324-CS304: A double-masked, randomized, multi-center, active controlled, parallel group, 6-month study with a 3-month interim analysis assessing the ocular hypotensive efficacy and safety of AR-13324 Ophthalmic Solution, 0.02% QD compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure. Rho Kinase Elevated Intraocular Pressure Treatment Trial (ROCKET 4)

AR-13324-CS304 was similarly designed to the previous Phase 3 studies but was in progress when the original NDA was submitted. The 3-month interim efficacy analysis is available. See Statistical Review of Efficacy in the following section.

Statistical Review and Evaluation of Efficacy

Based on the statistical review of the three Phase 3 studies (AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304) submitted in the NDA, we concur with the Applicant's overall efficacy conclusion that netarsudil 0.02% once-daily (QD) (also referred to as netarsudil QD) is efficacious for the reduction of elevated intraocular pressure (IOP). However, netarsudil QD is less efficacious compared to the comparator, timolol ophthalmic solution 0.5% twice daily (BID), for subjects with higher maximum baseline IOP (≥ 25 mmHg).

The following tables and figures provide additional insight into the effect of netarsudil QD for each Phase 3 study. The tables and figures are based on observed data for the per protocol population. For all studies, the ITT population was also evaluated, and the results were consistent. In addition, the results were robust to various methods of handling missing data under varying assumptions.

Study AR-13324-CS301

For subjects with maximum baseline IOP < 25 mmHg, the netarsudil and timolol groups had similar average IOP reductions from baseline, ranging from 3.7 to 5.1 mmHg and 3.2 to 4.7 mmHg, respectively (Table 1 and Figure 1).

However, for subjects with maximum baseline IOP ≥ 25 mmHg, the netarsudil group had a lower average IOP reduction at Day 43 and Day 90 compared to timolol. The average IOP reduction was lower in the netarsudil group by approximately 1 to 3 mmHg for these two days. Additionally, the difference in IOP reduction was most noticeable at the 8am time point for all three days (Days 15, 43, and 90).

Table 1: Study 301 Mean IOP Change from Baseline in Study Eye (mmHg) by Study Visit (PP Observed)

	Maximum Baseline IOP < 25 mm Hg					**Maximum Baseline IOP ≥ 25 mmHg**				
	Netarsudil QD		**Timolol**		**Difference (95% CI) [1]**	**Netarsudil QD**		**Timolol**		**Difference (95% CI) [1]**
	N	Mean	N	Mean		N	Mean	N	Mean	
Baseline										
08:00	113	22.39	124	22.50	-0.11 (-0.39, 0.18)	69	25.11	64	25.05	0.06 (-0.34, 0.47)
10:00	113	21.28	124	21.07	0.21 (-0.21, 0.64)	69	23.92	64	23.58	0.34 (-0.25, 0.94)
16:00	113	20.62	124	20.52	0.10 (-0.36, 0.56)	69	23.68	64	23.25	0.43 (-0.31, 1.17)
Day 15										
08:00	108	-5.06	123	-4.74	-0.32 (-0.93, 0.28)	69	-4.33	64	-5.64	1.31 (0.32, 2.30)
10:00	107	-5.11	122	-4.09	-1.02 (-1.69, -0.34)	69	-4.91	64	-4.96	0.06 (-0.96, 1.07)
16:00	107	-4.22	122	-3.41	-1.01 (-1.73, -0.28)	69	-4.86	64	-3.77	-0.36 (-1.50, 0.77)
Day 43										
08:00	105	-4.50	121	-4.71	0.21 (-0.49, 0.90)	65	-3.35	63	-5.96	2.61 (1.45, 3.78)
10:00	105	-4.40	121	-4.12	-0.28 (-0.98, 0.41)	65	-3.77	63	-5.21	1.44 (0.28, 2.60)
16:00	105	-4.08	120	-3.25	-0.83 (-1.59, -0.06)	65	-3.76	63	-4.71	0.95 (-0.26, 2.16)
Day 90										
08:00	99	-4.18	119	-4.61	0.44 (-0.22, 1.09)	58	-2.59	62	-5.54	2.95 (1.82, 4.09)
10:00	99	-3.94	119	-3.66	-0.28 (-1.02, 0.46)	59	-2.31	62	-4.62	2.32 (1.11, 3.52)
16:00	99	-3.65	119	-3.19	-0.46 (-1.21, 0.28)	59	-2.75	62	-4.77	2.02 (0.77, 3.27)

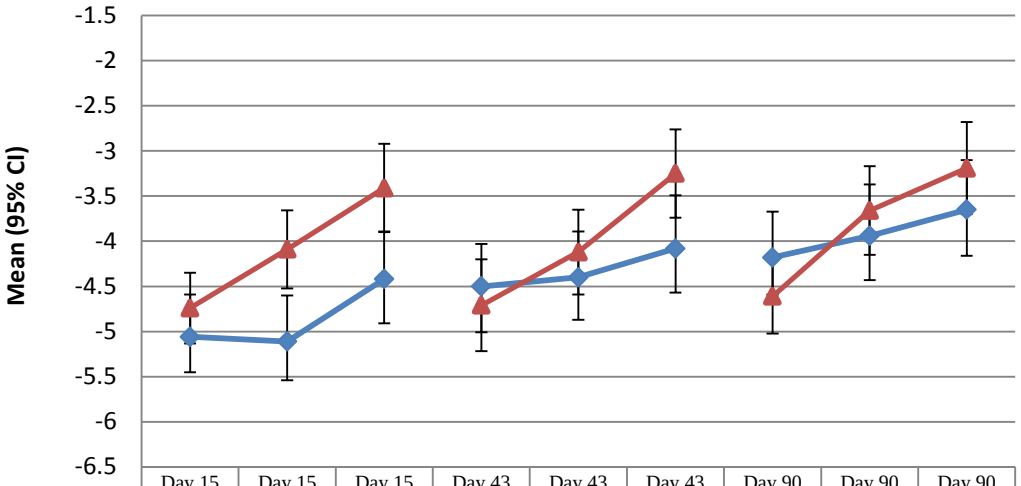
CI = Confidence Interval

[1] Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.

Source: Table 14.2.1.1.99.13 of Study 301 report and statistical reviewer's calculation for Baseline ≥ 25 mm Hg analysis.

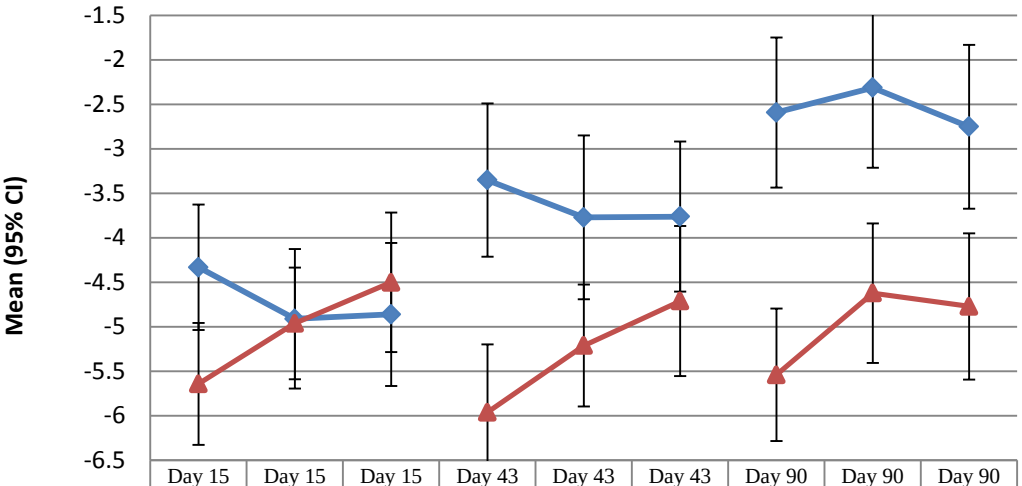
Figure 1: Study 301 Mean IOP Change from Baseline in Study Eye by Study Visit (PP Observed)

Maximum Baseline IOP < 25 mmHg



	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-5.06	-5.11	-4.42	-4.5	-4.4	-4.08	-4.18	-3.94	-3.65
Timolol	-4.74	-4.09	-3.41	-4.71	-4.12	-3.25	-4.61	-3.66	-3.19

Maximum Baseline IOP >= 25 mmHg

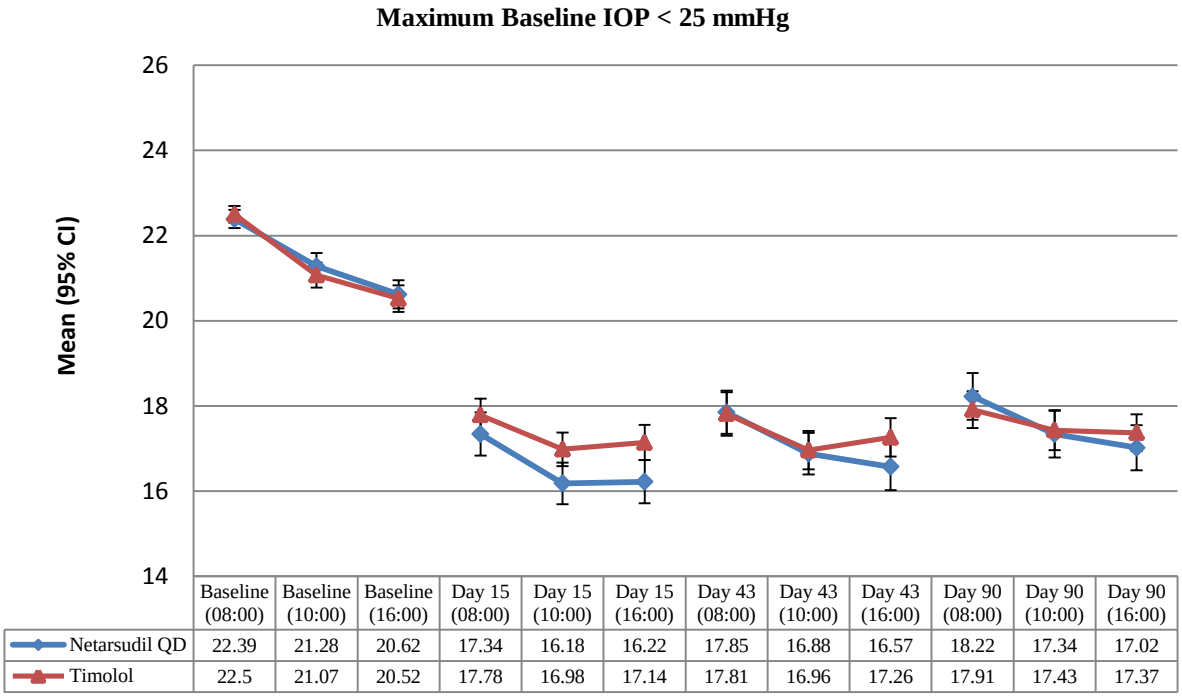


	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-4.33	-4.91	-4.86	-3.35	-3.77	-3.76	-2.59	-2.31	-2.75
Timolol	-5.64	-4.96	-4.5	-5.96	-5.21	-4.71	-5.54	-4.62	-4.77

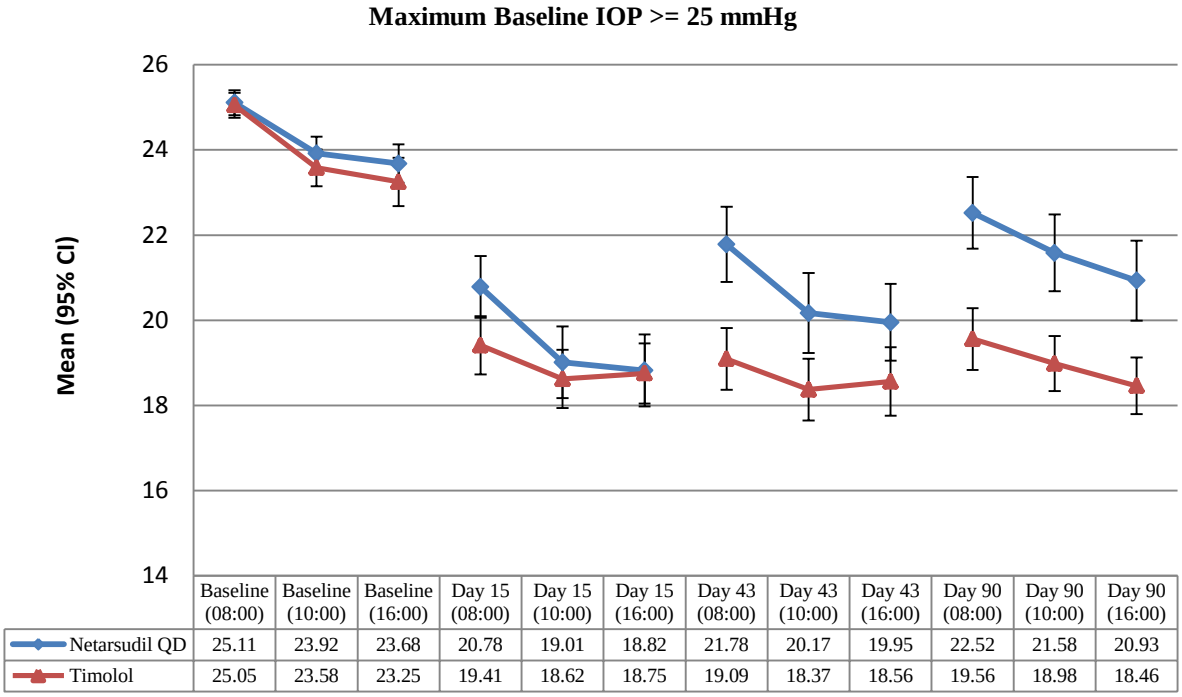
Source: Table 14.2.1.1.99.13 of Study 301 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

The summary results for the mean IOP over time are presented in the following figure and are consistent with those of the mean IOP change from baseline.

Figure 2: Study 301 Mean IOP in Study Eye by Study Visit (PP Observed)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	22.39	21.28	20.62	17.34	16.18	16.22	17.85	16.88	16.57	18.22	17.34	17.02
Timolol	22.5	21.07	20.52	17.78	16.98	17.14	17.81	16.96	17.26	17.91	17.43	17.37



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	25.11	23.92	23.68	20.78	19.01	18.82	21.78	20.17	19.95	22.52	21.58	20.93
Timolol	25.05	23.58	23.25	19.41	18.62	18.75	19.09	18.37	18.56	19.56	18.98	18.46

Source: Table 14.2.1.1.99.13 of Study 301 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

Study AR-13324-CS302

For subjects with maximum baseline IOP < 25 mmHg, the netarsudil and timolol groups had similar average IOP reductions from baseline, ranging from 3.3 to 4.6 mmHg and 3.7 to 5.1 mmHg, respectively (Table 2 and Figure 3).

However, for subjects with maximum baseline IOP ≥ 25 mmHg, the netarsudil group had a smaller average IOP reduction from baseline at 8am and 10am time points for all three days (Days 15, 43, and 90) compared to timolol. The average IOP reduction was lower in the netarsudil group by approximately 1.0 to 2.5 mmHg at these morning time points.

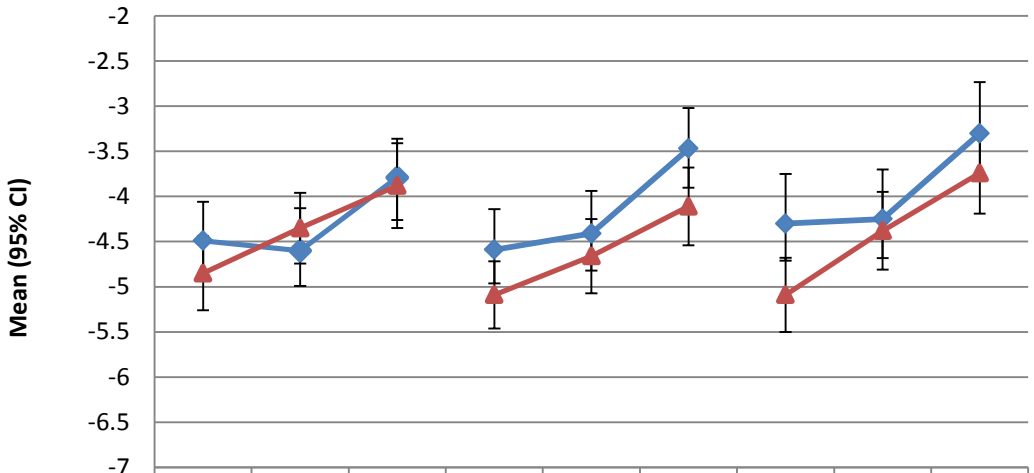
Table 2: Study 302 Mean IOP Change from Baseline (mmHg) in Study Eye by Study Visit (PP Observed)

	Maximum Baseline IOP < 25 mm Hg					**Maximum Baseline IOP ≥ 25 mmHg**				
	Netarsudil QD		**Timolol**		**Difference (95% CI) [1]**	**Netarsudil QD**		**Timolol**		**Difference (95% CI) [1]**
	N	Mean	N	Mean		N	Mean	N	Mean	
Baseline										
08:00	129	22.54	142	22.54	0.00 (-0.25, 0.25)	77	25.14	75	25.18	-0.04 (-0.37, 0.30)
10:00	129	21.29	142	21.27	0.02 (-0.37, 0.41)	77	24.02	75	23.89	0.13 (-0.44, 0.71)
16:00	129	20.43	142	20.71	-0.28 (-0.71, 0.14)	77	23.46	75	23.33	0.13 (-0.56, 0.83)
Day 15										
08:00	127	-4.50	142	-4.85	0.35 (-0.25, 0.95)	74	-4.51	75	-5.87	1.37 (0.46, 2.27)
10:00	126	-4.60	141	-4.35	-0.24 (-0.86, 0.37)	73	-4.52	74	-5.36	0.84 (-0.23, 1.91)
16:00	126	-3.79	141	-3.88	0.08 (-0.55, 0.72)	74	-4.93	74	-4.30	-0.63 (-1.57, 0.31)
Day 43										
08:00	122	-4.59	141	-5.09	0.50 (-0.09, 1.09)	71	-3.35	74	-5.93	2.57 (1.46, 3.69)
10:00	120	-4.41	141	-4.66	0.24 (-0.38, 0.86)	67	-3.81	74	-5.32	1.51 (0.45, 2.57)
16:00	120	-3.47	141	-4.11	0.64 (0.01, 1.26)	67	-3.94	74	-4.85	0.91 (-0.09, 1.91)
Day 90										
08:00	116	-4.30	140	-5.09	0.79 (0.10, 1.49)	61	-3.43	74	-5.56	2.13 (1.04, 3.21)
10:00	114	-4.25	140	-4.38	0.12 (-0.58, 0.82)	59	-3.50	73	-5.29	1.79 (0.53, 3.06)
16:00	114	-3.30	139	-3.74	0.45 (-0.27, 1.17)	56	-4.46	73	-4.32	-0.14 (-1.30, 1.02)

[1] Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.
Source: Table 14.2.1.1.1 of Study 302 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

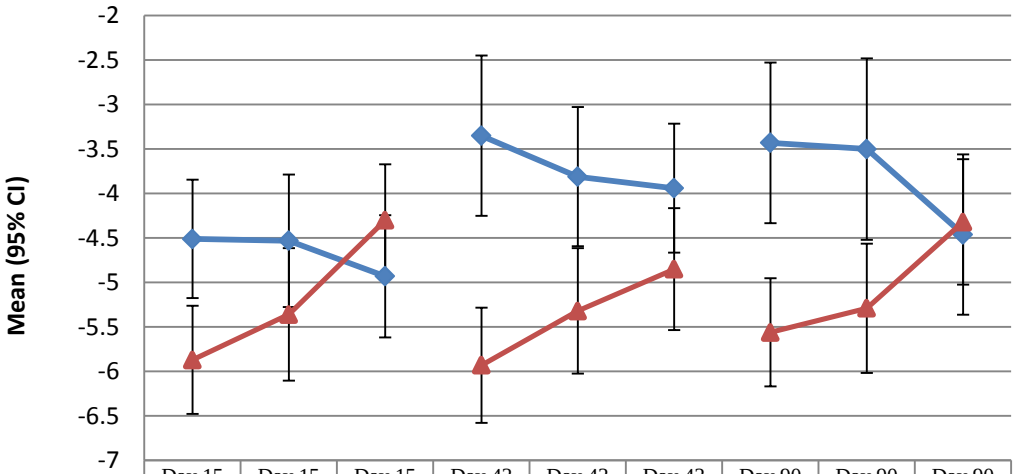
Figure 3: Study 302 Mean IOP Change from Baseline in Study Eye by Study Visit (PP Observed)

Maximum Baseline IOP < 25 mmHg



	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-4.49	-4.6	-3.79	-4.59	-4.41	-3.47	-4.3	-4.25	-3.3
Timolol	-4.85	-4.35	-3.88	-5.09	-4.66	-4.11	-5.09	-4.38	-3.74

Maximum Baseline IOP >= 25mmHg

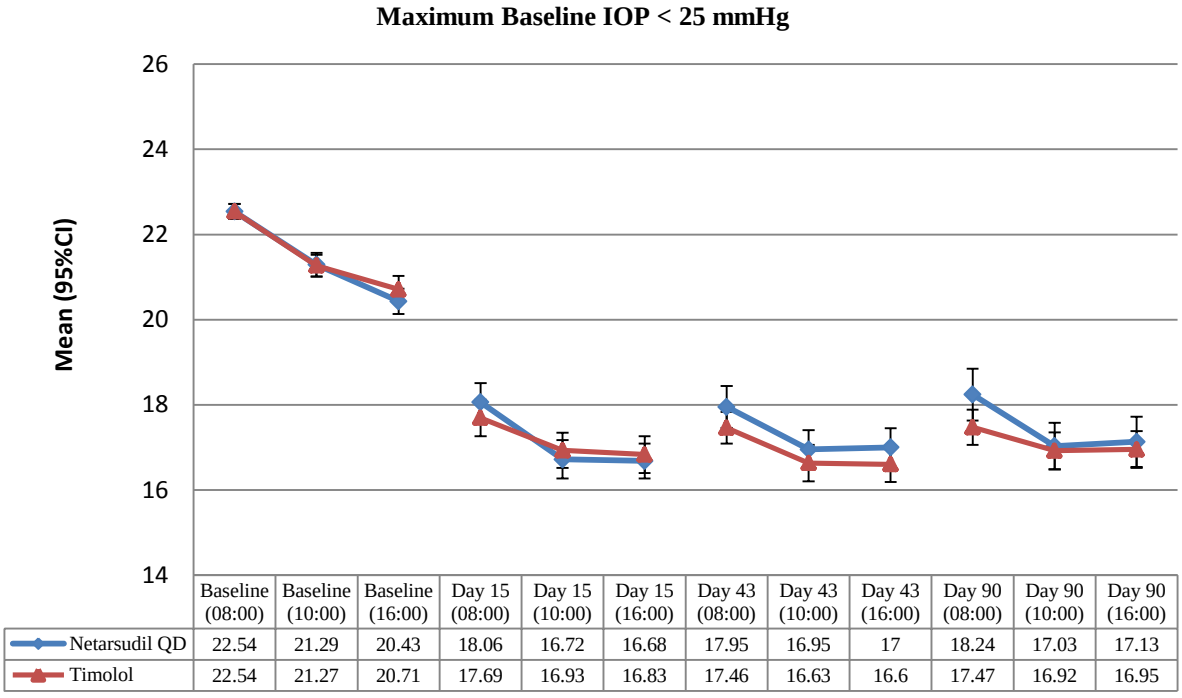


	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-4.51	-4.53	-4.93	-3.35	-3.81	-3.94	-3.43	-3.5	-4.46
Timolol	-5.87	-5.36	-4.3	-5.93	-5.32	-4.85	-5.56	-5.29	-4.32

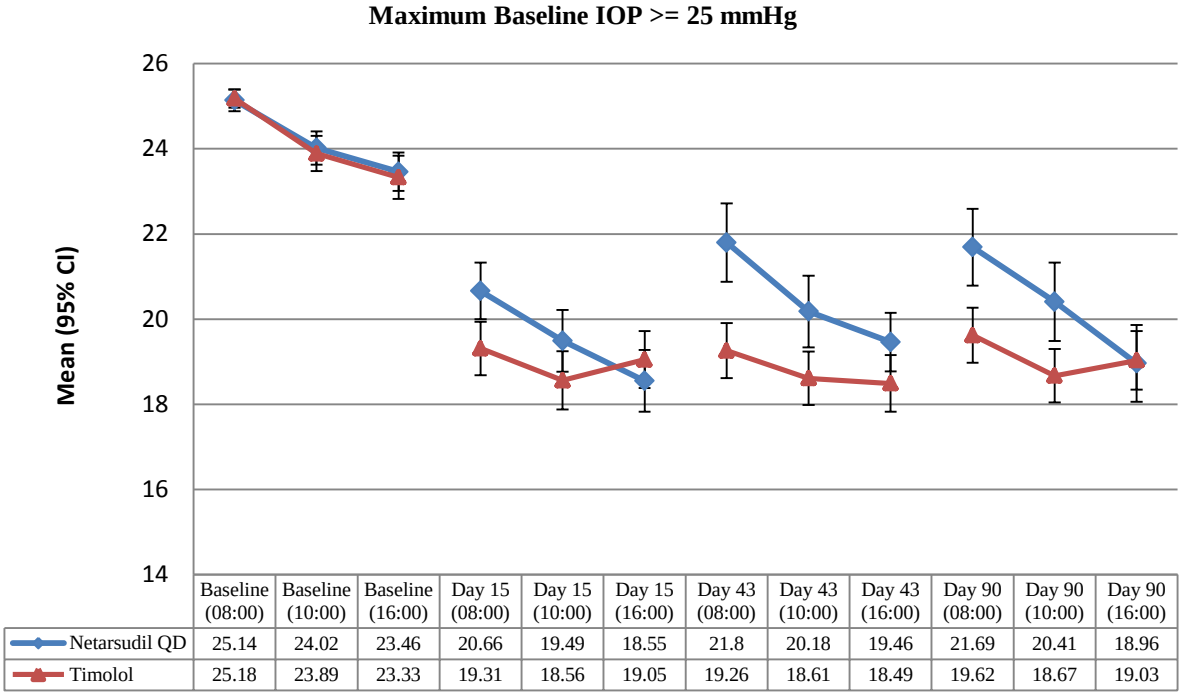
Source: Table 14.2.1.1.1 of Study 302 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

The summary results for the mean IOP over time are presented in the following figure and are consistent with those of the mean IOP change from baseline.

Figure 4: Study 302 Mean IOP in Study Eye by Study Visit (PP Observed)



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	22.54	21.29	20.43	18.06	16.72	16.68	17.95	16.95	17	18.24	17.03	17.13
Timolol	22.54	21.27	20.71	17.69	16.93	16.83	17.46	16.63	16.6	17.47	16.92	16.95



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	25.14	24.02	23.46	20.66	19.49	18.55	21.8	20.18	19.46	21.69	20.41	18.96
Timolol	25.18	23.89	23.33	19.31	18.56	19.05	19.26	18.61	18.49	19.62	18.67	19.03

Source: Table 14.2.1.1.1 of Study 302 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

Study AR-13324-CS304

The statistical review of Study 304 has been completed; therefore, the results of the study are included in this section. Study 304 was a 3-month efficacy and 6-month safety study evaluating the treatment effect of netarsudil QD relative to timolol 0.5% BID. This study had similar design, efficacy endpoints, and analysis methods as Studies 301 and 302 except for the following:

- Study 304 enrolled adult subjects with a broader range of IOP at baseline (> 20 mmHg and < 30 mmHg at 8am at the first and second qualification visits 2 to 7 days apart; and >17 mmHg and < 30 mmHg at 10am and 16pm at the second qualification visit), compared to Studies 301 and 302 (> 20 mmHg and < 27 mmHg at 8am at the first and second qualification visits 2 to 7 days apart; and >17 mmHg and < 27 mmHg at 10am and 16pm at the second qualification visit)
- In the primary efficacy analysis, Studies 304 and 302 focused on the per protocol subjects with maximum baseline IOP < 25 mmHg whereas Study 301 focused on the per protocol subjects with maximum baseline IOP < 27 mmHg.

For subjects with maximum baseline IOP < 25 mmHg, the netarsudil and timolol groups had similar average IOP reductions from baseline, ranging from 3.9 to 4.7 mmHg and 3.8 to 5.2 mmHg, respectively (Table 3 and Figure 5).

However, for subjects with maximum baseline IOP ≥ 25 mmHg, the netarsudil group had a smaller average IOP reduction from baseline at 8am and 10am time points for all three days (Days 15, 43, and 90) compared to timolol. The average IOP reduction was lower in the netarsudil group by approximately 1 to 2 mmHg at the morning time points at Day 43 and Day 90.

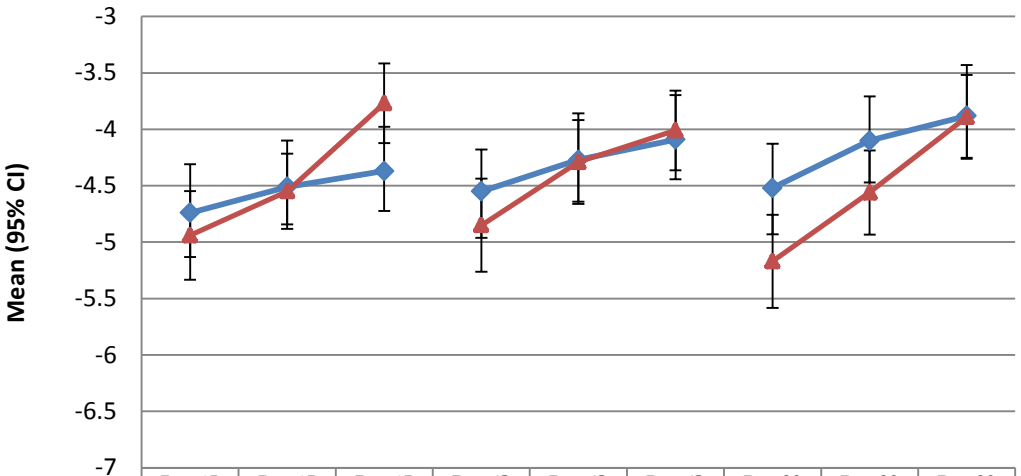
Table 3: Study 304 Mean IOP Change from Baseline (mmHg) in Study Eye by Study Visit (PP Observed)

	Maximum Baseline IOP < 25 mm Hg					**Maximum Baseline IOP ≥ 25 mmHg**				
Day Time	**Netarsudil QD**		**Timolol**		**Difference (95% CI) [1]**	**Netarsudil QD**		**Timolol**		**Difference (95% CI) [1]**
	N	Mean	N	Mean		N	Mean	N	Mean	
Baseline										
08:00	186	22.40	186	22.44	-0.05 (-0.27, 0.18)	120	26.30	130	25.96	0.34 (-0.16, 0.85)
10:00	186	21.06	186	21.27	-0.21 (-0.55, 0.14)	120	25.18	130	24.91	0.26 (-0.29, 0.81)
16:00	186	20.69	186	20.69	0.01 (-0.37, 0.38)	120	24.48	130	23.99	0.49 (-0.16, 1.13)
Day 15										
08:00	184	-4.74	183	-4.94	0.21 (-0.38, 0.79)	118	-4.74	129	-5.81	1.07 (0.21, 1.93)
10:00	181	-4.51	183	-4.55	0.04 (-0.49, 0.58)	116	-5.09	129	-5.56	0.46 (-0.45, 1.38)
16:00	181	-4.37	183	-3.77	-0.60 (-1.12, -0.08)	116	-4.42	129	-4.79	0.37 (-0.44, 1.18)
Day 43										
08:00	177	-4.55	183	-4.85	0.30 (-0.25, 0.86)	112	-4.30	127	-6.13	1.82 (0.91, 2.74)
10:00	177	-4.27	182	-4.29	0.02 (-0.54, 0.57)	109	-4.78	127	-5.69	0.91 (0.02, 1.81)
16:00	176	-4.09	182	-4.01	-0.09 (-0.61, 0.44)	109	-4.37	127	-4.33	-0.04 (-0.90, 0.82)
Day 90										
08:00	167	-4.52	179	-5.17	0.66 (0.08, 1.23)	94	-4.54	121	-6.04	1.50 (0.52, 2.49)
10:00	166	-4.10	179	-4.56	0.46 (-0.09, 1.02)	93	-4.19	120	-5.91	1.72 (0.74, 2.71)
16:00	165	-3.88	179	-3.89	0.01 (-0.57, 0.60)	93	-4.08	120	-4.85	0.77 (-0.11, 1.66)

[1] Difference from Timolol 0.5% and two-sided CIs are based on 2-sample t-tests comparing Rhopressa QD vs Timolol 0.5%.
Source: Table 14.2.1.1.1 of Study 304 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

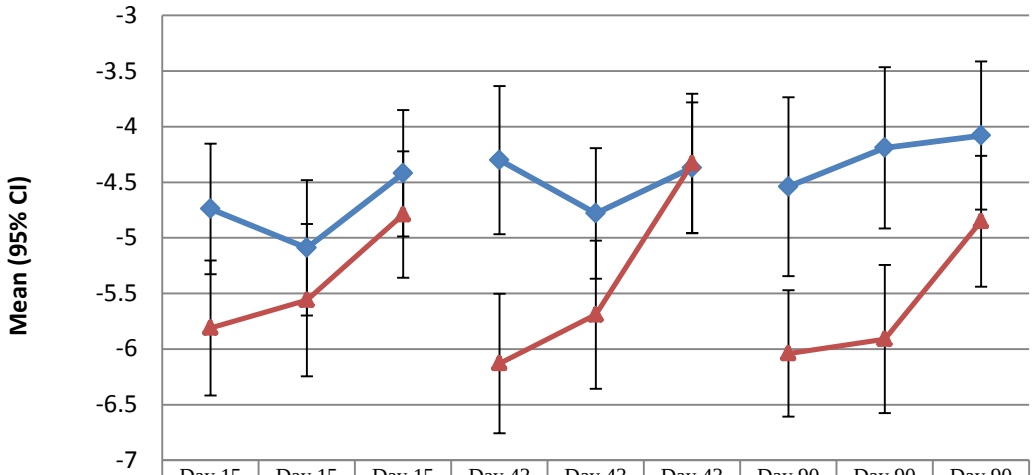
Figure 5: Study 304 Mean IOP Change from Baseline in Study Eye by Study Visit (PP Observed)

Maximum Baseline IOP < 25 mmHg



	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-4.74	-4.51	-4.37	-4.55	-4.27	-4.09	-4.52	-4.1	-3.88
Timolol	-4.94	-4.55	-3.77	-4.85	-4.29	-4.01	-5.17	-4.56	-3.89

Maximum Baseline IOP >= 25 mmHg



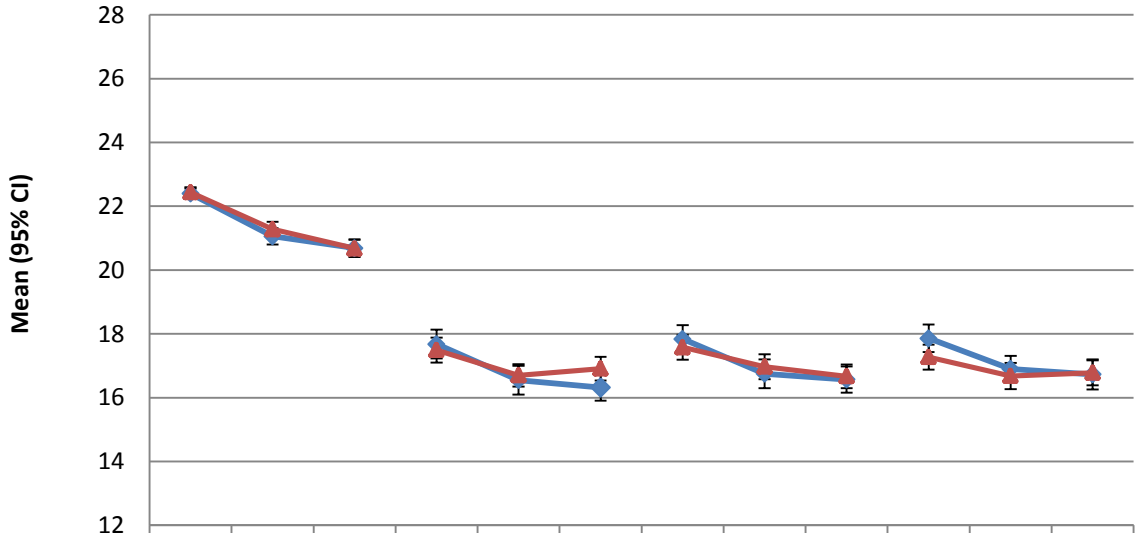
	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	-4.74	-5.09	-4.42	-4.3	-4.78	-4.37	-4.54	-4.19	-4.08
Timolol	-5.81	-5.56	-4.79	-6.13	-5.69	-4.33	-6.04	-5.91	-4.85

Source: Table 14.2.1.1.1 of Study 304 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

The summary results for the mean IOP over time are presented in the following figure and are consistent with those of the mean IOP change from baseline.

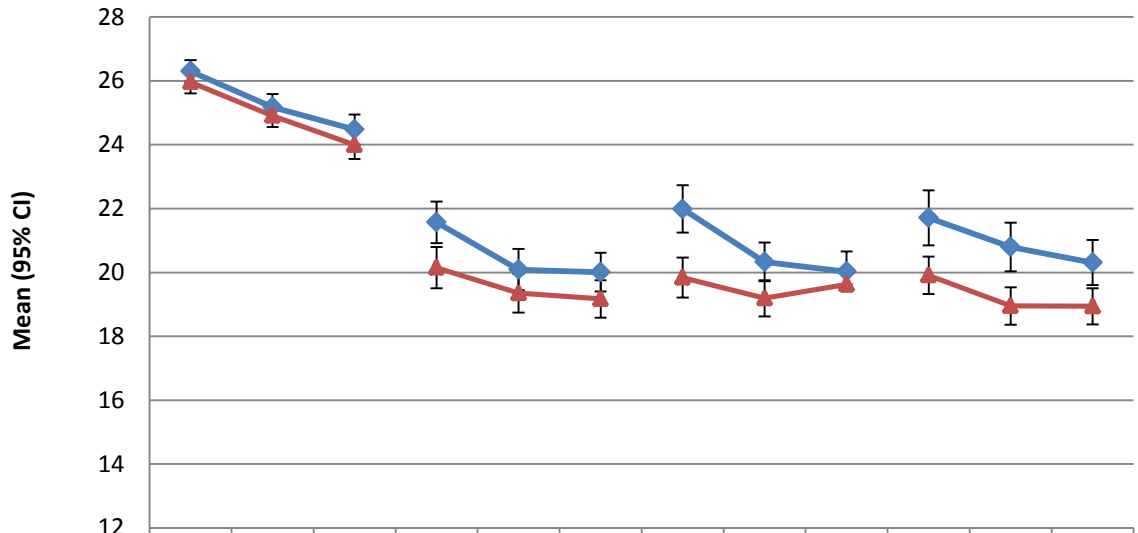
Figure 6: Study 304 Mean IOP in Study Eye by Study Visit (PP Observed)

Maximum Baseline IOP < 25 mmHg



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	22.4	21.06	20.69	17.68	16.55	16.32	17.84	16.75	16.57	17.86	16.9	16.73
Timolol	22.44	21.28	20.68	17.49	16.7	16.91	17.58	16.97	16.67	17.27	16.68	16.78

Maximum Baseline IOP >= 25 mmHg



	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day 90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Netarsudil QD	26.3	25.18	24.48	21.57	20.09	20.01	21.99	20.33	20.03	21.71	20.8	20.31
Timolol	25.96	24.91	23.99	20.15	19.35	19.17	19.84	19.19	19.63	19.91	18.95	18.94

Source: Table 14.2.1.1.1 of Study 304 report; and statistical reviewer's calculation for Baseline ≥ 25 mmHg analysis.

Clinical Review of Safety

The safety database for this application is based primary from 2 clinical studies (Studies AR-13324-CS301 and AR-13324-CS302). Between the 2 studies there were 707 patients in the safety database who received Rhopressa (454 in QD dosing and 253 BID dosing).

Study AR-13324-CS301: Exposure to Study Medication by Treatment Group (Safety Population)

	netarsudil 0.02% QD N=203	**Timolol 0.5% BID N=208**
Days of Exposure		
Mean (sd)	82.8	87.4
Minimum	3	4
Maximum	112	138

Study AR-13324-CS302: Exposure to Study Medication by Treatment Group (Safety Population)

	netarsudil 0.02% QD N=251	**netarsudil 0.02% BID N=253**	**Timolol 0.5% BID N=251**
Days of Exposure			
Mean (sd)	259.7	185.2	324.5
Minimum	1	2	1
Maximum	385	375	371

Deaths

Study AR-13324-CS301: No deaths occurred during the study.

Study AR-13324-CS302: Two subjects in the netarsudil QD treatment group died during the course of the study secondary to a myocardial infarction.

Study AR-13324-CS301: Serious Treatment Emergent AEs

Subject Number/Treatment Group	**SAE**
timolol 108-016	Worsening of adenomyosis
timolol 112-010	CHF Left upper extremity numbness
timolol 116-009	CVA
netarsudil 123-011	Prostate CA
netarsudil 128-002	Exacerbation of CAD
netarsudil 128-003	HTN
netarsudil 135-01	Pneumonia Acute respiratory failure

Study AR-13324-CS302: Serious Treatment Emergent AEs

Treatment Group	Subject	Serious Adverse Event
netarsudil BID	228-006	Bacterial peritonitis, UTI
netarsudil BID	231-006	Carotid artery stenosis
netarsudil BID	262-016	Cholecystitis
netarsudil BID	262-027	Hip fracture
netarsudil BID	244-001	Ligament rupture
netarsudil BID	209-002	MI
netarsudil BID	226-012	MI
netarsudil BID	218-021	Perforated gastric ulcer
netarsudil BID	212-006	Pneumonia, pulmonary embolism
netarsudil BID	216-001	Worsening of cataract
netarsudil BID	262-045	Worsening of PSA, Synovial cyst
netarsudil QD	250-010	Abdominal pain
netarsudil QD	230-014	Angioedema
netarsudil QD	211-004	Breast CA
netarsudil QD	212-016	Broken foot, acute renal failure
netarsudil QD	217-026	CAD
netarsudil QD	206-022	Cholelithiasis. Excerbation of CAD
netarsudil QD	251-010	Epistaxis
netarsudil QD	234-019	Internal bleeding secondary to motor vehicle accident
netarsudil QD	209-002	Myelodysplastic syndrome
timolol	263-011	Atrial fibrillation
timolol	228-005	Back pain
timolol	251-044	Cellulitis
timolol	227-015	CVA, trial fibrillation
timolol	246-005	Embolic stroke
timolol	217-021	Fatal MI
timolol	259-002	Fatal MI
timolol	262-020	HTN
timolol	238-001	Melanoma
timolol	202-003	Peripheral artery occlusion, Fall
timolol	254-008	Post-operative ileus
timolol	248-030	Prostate CA
timolol	239-003	Pulmonary artery stenosis, atrial flutter, bradycardia, fluid overload
timolol	204-041	Renal failure
timolol	222-010	Worsening of arthritis
timolol	213-003	Worsening of CAD

Study AR-13324-CS301: Subjects Discontinued Due to Treatment-Emergent AE

Treatment Group	Subject	AE
netarsudil	107-016	Allergic conjunctivitis
netarsudil	107-025	Allergic conjunctivitis
netarsudil	112-010	Congestive cardia failure
netarsudil	110-013	Conjunctival edema
netarsudil	128-003	Conjunctival vascular disorder
netarsudil	119-007	Conjunctivitis, and cornea stain present
netarsudil	123-007	Diarrhea
netarsudil	131-004	Eye irritation
netarsudil	118-021	Eye pain
netarsudil	118-004	Eye pruritus
netarsudil	128-009	Eyelid edema
netarsudil	109-003	Eyelid pruritus and contact dermatitis
netarsudil	110-020	Eyelids pruritus
netarsudil	122-005	Hypersensitivity
netarsudil	108-015	Iris adhesions, angle closure glaucoma, and iris bombe
netarsudil	106-010	Lacrimation increased
netarsudil	125-021	Lacrimation increased and conjunctival hyperemia
netarsudil	107-030	Nausea, feeling abnormal, and swollen tongue
netarsudil	123-011	Prostate CA
netarsudil	105-011	Upper limb fracture
netarsudil	115-025	Vision blurred
netarsudil	124-004	Visual acuity reduced
timolol	114-009	Dyspnea
timolol	115-015	Nausea and dizziness
timolol	135-001	Pneumonia, acute respiratory failure, dysphagia, and UTI

Study AR-13324-CS302: Subjects Discontinued Due to Treatment-Emergent AE

Treatment Group	Subject	AE
netarsudil BID	209-001	Conjunctival hyperemia
netarsudil BID	214-004	Conjunctival hyperemia
netarsudil BID	218-007	Conjunctival hyperemia
netarsudil BID	218-010	Conjunctival hyperemia
netarsudil BID	232-006	Conjunctival hyperemia
netarsudil BID	233-001	Conjunctival hyperemia
netarsudil BID	245-003	Conjunctival hyperemia
netarsudil BID	248-004	Conjunctival hyperemia
netarsudil BID	262-025	Conjunctival hyperemia
netarsudil BID	243-004	Corneal verticillata
netarsudil BID	219-007	Eye discharge, Visual acuity reduced
netarsudil BID	226-009	Eye infection
netarsudil BID	209-013	Eye irritation, Eye pruritis, conjunctival hyperemia
netarsudil BID	209-012	Instillation site erythema
netarsudil BID	237-003	Photophobia
netarsudil BID	214-009	Vision blurred, conjunctival hyperemia
netarsudil BID	214-012	Vision blurred, conjunctival hyperemia
netarsudil QD	203-008	Allergic conjunctivitis
netarsudil QD	218-002	Conjunctival hyperemia
netarsudil QD	214-001	Eye irritation
netarsudil QD	219-008	Eyelid edema, Erythema of eyelid, Eye pain, Eye irritation, Eye pruritis, Photophobia
netarsudil QD	260-025	Instillation site erythema
netarsudil QD	214-006	Instillation site pain, conjunctival hyperemia
netarsudil QD	202-004	Lacrimation increased
netarsudil QD	208-001	Punctate keratitis
timolol	214-032	Vision blurred

Study AR-13324-CS301: Treatment Emergent Adverse Events for >=1% Subjects in Either Treatment Group (Safety Population)

	netarsudil 0.02% N=203	**Timolol 0.5% N=208**
Eye Disorders		
Conjunctival hyperemia	108	17
Conjunctival hemorrhage	27	1
Erythema of eyelid	12	0
Vision blurred	11	1
Corneal deposits	11	0
Visual acuity reduced	8	3
Conjunctival vascular disorder	8	1
Eye irritation	8	1
Lacrimation increase	8	0
Conjunctivitis allergic	6	0
Blepharitis	4	2
Eyelid edema	4	2
Dry eye	2	3
Punctate keratitis	4	1
Conjunctival edema	4	0
Eye pruritus	4	0
Photophobia	4	0
Eyelid pruritus	3	0
Foreign Body Sensation	3	1
Vitreous detachment	3	1
Chalazion	2	0
Eye pain	2	0
General disorders		
Instillation site pain	30	42
Instillation site erythema	24	4
Instillation site discomfort	10	9
Instillation site pruritus	3	2
Investigations		
Vital dye staining cornea present	17	19
Blood glucose increased	2	4
ALT increased	2	0
AST increased	2	0
Infections		
Nasopharyngitis	3	2
Sinusitis	2	3
Urinary Tract Infection	2	2
Influenza	2	1
Conjunctivitis	2	0
Tooth infection	2	0
Bronchitis	0	2
Upper respiratory tract infection	0	2
Nervous system disorders		
Sinus headache	2	1
Dizziness	1	2

	netarsudil 0.02% N=203	**Timolol 0.5% N=208**
Respiratory disorders		
Cough	2	0
Sinus congestion	2	0
Ear disorders		
Vertigo	1	3
Vascular disorder		
HTN	2	1

Study AR-13324-CS302: Treatment Emergent Adverse Events for >=1% Subjects in Any Treatment Group (Safety Population)

	netarsudil 0.02% QD N=251	**netarsudil 0.02% BID N=253**	**Timolol 0.5% N=251**
Eye Disorders			
Conjunctival hyperemia	152	168	35
Corneal verticillata	64	64	2
Conjunctival hemorrhage	49	49	2
Vision blurred	27	44	7
Lacrimation increased	19	25	0
Visual acuity reduced	22	22	6
Eye pruritus	14	20	3
Conjunctival edema	8	19	0
Erythema of eyelid	14	12	2
Eye irritation	11	13	8
Punctate keratitis	12	12	5
Eyelid edema	11	12	3
Eye pain	10	11	8
Dry eye	3	1	5
FBS	7	14	1
Allergic conjunctivitis	6	11	1
Photophobia	5	8	1
Blepharitis	4	8	1
Corneal opacity	1	11	0
Eye discharge	4	8	3
Dry eye	6	4	6
Vitreous detachment	4	3	2
Eyelid pruritus	2	4	1
Meibomian gland dysfunction	4	2	2
Cataract	3	2	5
Ocular discomfort	1	4	2
Chalazion	3	1	1
Conjunctival follicles	1	3	0
Corneal disorder	1	3	0
Corneal edema	0	4	0
Eyelid margin crusting	2	2	0
Iritis	1	2	0
Posterior capsule opacification	1	2	0

	netarsudil 0.02% QD N=251	**netarsudil 0.02% BID N=253**	**Timolol 0.5% N=251**
Diplopia	2	0	0
Ectropion	2	0	0
Halo vision	0	2	0
Night blindness	0	2	0
Trichiasis	2	0	0
Vitreous floaters	1	1	2
Pinguecula	0	1	2
Blepharospasm	0	0	3
General disorders			
Instillation site pain	45	45	41
Instillation site erythema	14	32	5
Instillation site discomfort	9	7	5
Instillation site pruritus	3	2	3
Fatigue	2	0	0
Instillation site foreign body sensation	0	2	0
Instillation site irritation	2	0	1
Investigations			
Vital dye staining cornea present	14	17	14
Blood pressure increased	4	3	2
IOP increased	4	1	2
Blood triglycerides increased	4	0	1
Blood glucose increased	2	1	1
Conjunctivitis staining	1	2	0
Optic nerve cup/disc ratio increased	1	2	0
Eosinophil count increased	2	0	0
Heart rate irregular	2	0	0
Infections			
Conjunctivitis	6	8	3
Upper Respiratory Infection	5	9	7
Nasopharyngitis	5	2	3
Sinusitis	3	4	3
Urinary Tract Infection	2	5	4
Bronchitis	2	2	0
Conjunctivitis viral	1	3	2
Influenza	2	1	2
Kidney infection	2	1	1
Pneumonia	0	3	1
Conjunctivitis bacterial	0	2	0
Cellulitis	1	0	3
Hordeolum	1	0	2
Nervous system disorders			
Headache	6	10	9
Dizziness	4	1	1
Visual field defect	5	0	1
Disturbance in attention	0	3	0

	netarsudil 0.02% QD N=251	**netarsudil 0.02% BID N=253**	**Timolol 0.5% N=251**
Skin disorders			
Dermatitis allergic	2	6	0
Dermatitis contact	4	3	0
Telangiectasia	0	2	0
Rash	1	0	2
Injury			
Ligament sprain	2	1	2
Muscle strain	3	0	0
Fall	2	0	3
Procedural pain	2	0	0
Metabolism			
Type 2 Diabetes	2	3	2
Diabetes	2	1	0
Vitamin D deficiency	1	1	2
Hyperkalemia	0	0	2
Respiratory disorders			
Cough	3	1	5
Epistaxis	1	2	1
Musculoskeletal disorders			
Back pain	4	1	5
Osteoarthritis	2	0	0
Arthralgia	0	0	5
Neck pain	0	0	2
Synovial cyst	0	0	2
GI disorders			
Nausea	1	3	2
Diarrhea	0	2	1
GERD	0	2	0
Cardiac disorders			
CoronaryArtery Disease	3	2	0
Atrial fibrillation	3	1	0
Myocardial Infarction	2	1	1
Bradycardia	2	0	2
Renal Disorders			
Nephrolithiasis	0	2	0
Vascular disorders			
Hypertension	1	4	3
Hypotension	0	0	2
Blood disorders			
Anemia	2	3	2
Immune system disorders			
Seasonal allergy	3	1	1

	netarsudil 0.02% QD N=251	**netarsudil 0.02% BID N=253**	**Timolol 0.5% N=251**
Hypersensitivity	1	2	0
Neoplasms			
Basal cell CA	1	0	3
Ear disorders			
Vertigo	1	1	2
Congenital disorders			
Corneal dystrophy	1	2	0
Reproductive disorders			
Prostatomegaly	2	0	0

Laboratory Findings

Clinical laboratory (Chem 7) and hematology (CBC) were checked at the beginning and end of the trial.

Study AR-13324-CS301: There were no notable differences between the treatment groups in the change from baseline to Day 90 clinical chemistry values and hematology values.

Study AR-13324-CS302: There were no notable differences between the treatment groups in the change from baseline to Day 90 or to Month 12 for clinical chemistry values or hematology values.

Vital Signs

Heart rate and blood pressure was checked at the beginning and end of the trial.

Study AR-13324-CS301: There were no statistically significant changes from baseline in vital signs in the netarsudil group. However, statistically significant reductions from baseline in mean heart rate were observed in the timolol group. Mean heart rate at baseline was 71.3 ± 9.9 bpm and declined to 68.1 ± 9.3 bpm, 67.9 ± 8.6 bpm, and 69.7 ± 9.8 bpm (mean decreases of 3.1, 3.2, and 1.6 bpm) at Day 15, Day 43, and Day 90, respectively. A statistically significant increase in diastolic blood pressure of 1.4 mmHg at Day 90 was also observed in the timolol group.

Study AR-13324-CS302: Mean systolic BP did not differ significantly from baseline for any treatment group at any on-treatment visit. Mean change in diastolic BP differed significantly from baseline at the Month 12 / Exit Visit for the netarsudil QD group (difference = -1.5 mmHg), and at the Month 9 Visit for the netarsudil BID group (difference = -2.7 mmHg). Mean change from baseline for heart rate ranged from -1.3 to -0.2 bpm for netarsudil QD, from 0.0 to 0.6 bpm for netarsudil BID, and from to -2.7 to -1.6 bpm for timolol. Changes from baseline were significant for netarsudil QD at the Month 12 / Exit Visit, and for timolol at each of the on-treatment visits.

Corneal Endothelial Cell Counts

Corneal endothelial cell counts were collected in Study AR-13324-CS302 at baseline and Day 90. Mean endothelial cell density in the study eye of subjects in the netarsudil QD, BID and timolol groups was 2480, 2447 and 2455 cells/mm2, respectively, at baseline and 2489, 2450, and 2451 cells/mm2, respectively, at Day 90.

AR-13324-CS302: Endothelial Cell Counts (ECC) at Baseline and Day 90

	netarsudil QD	**netarsudil BID**	**Timolol**
Baseline ECC (cells/mm2)	2480	2447	2455
Day 90 ECC (cells/mm2)	2489	2450	2451

Special Safety Studies

Study AR-13324-OBS01: A prospective, targeted, non-interventional (observational) study of subjects who developed corneal deposits in clinical trials AR-13324-CS301 and AR-13324-CS302

Study Objectives:

- To evaluate visual function using the VF-14 questionnaire and Pelli-Robson Contrast Sensitivity (CS) test in subjects in clinical trials AR-13324-CS301 and AR-13324-CS302 with corneal deposits (corneal verticillata) at the initial study visit
- To assess changes in corneal deposits (corneal verticillata) over time using a published grading scale for amiodarone-induced cornea verticillata (Orlando 1984)

Description of Study

This was a targeted, prospective, multicenter, non-interventional (observational), cohort study designed to follow up and collect additional safety data in subjects who developed corneal verticillata in clinical trials AR-13324-CS301 and AR-13324-CS302. Subjects in clinical trials AR-13324-CS301 or AR-13324-CS302 identified by verbatim adverse event (AE) terms of corneal whorls, corneal haze, subepithelial corneal deposits/, vortex epitheliopathy, or cornea verticillata/corneal verticillata in one or both eyes were eligible to participate in this study.

The safety databases for the 2 studies were searched to identify eligible subjects on 11/20/15. The 11/20/15 date marks the day following the receipt of formal FDA guidance on the topic obtained at the Agency's pre-NDA meeting with the Sponsor. As of this date, all subjects continuing in the ongoing study AR-13324-CS302 had completed at least 6 months of dosing with study drug.

Eligible subjects were to be categorized into 1 of 2 different subgroups:

- Group A: Subjects who developed corneal verticillata who had completed clinical study AR-13324-CS301 or AR-13324-CS302
- Group B: Subjects who developed corneal verticillata who were early terminated or discontinued in either clinical study AR-13324-CS301 or AR-13324-CS302

Note: For logistical reasons, all study sites selected for participation in this study must have had more than 1 subject with this corneal finding as of 11/20/15.

Subjects in Groups A and B came in for an initial visit where they provided updated ocular and general medical history, underwent further ETDRS visual acuity testing, and corneal verticillata grading. If a subject was noted to have no evidence of corneal verticillata at the initial visit, this visit also served as the final study visit and the subject was exited from the observational study. Subjects who were noted to have persistence of the corneal finding returned within a 2-week interval when they self-administered the Visual Function-14 (VF-14) questionnaire and underwent CS testing. All subjects with persistent corneal verticillata returned for monthly surveillance visits where they underwent ETDRS visual acuity testing and corneal grading for 3 months or until resolution or stabilization. If the corneal verticillata persisted at the 3-month time point, subjects returned every 2 months for ETDRS visual acuity testing and corneal grading until resolution or stabilization which is defined as no worsening of the corneal verticillata grading. Once resolution was recorded with corneal grading of 0 or stabilization was confirmed in both eyes, the subject returned within a 2-week interval to undergo CS testing, ETDRS visual acuity testing, and repeat the VF-14 questionnaire to complete the study.

Subjects participating in this observational study were not treated with any investigational products during this study. They did, however, recommence or continue treatment with IOP-lowering agents or other topical ocular medications (Rx or OTC) as recommended by their eye care provider/practitioner. The previous treatment assignments in clinical trials AR-13324-CS301 and AR-13324-CS302 were to be used for the analysis. As no subjects from AR-13324-CS301 were enrolled, only the Groups 2 and 3 from AR-13324-CS302 subjects were used for the analysis.

Inclusion Criteria

- Current or past participant in AR-13324-CS302 who developed corneal deposits (corneal verticillata) during study participation with AE listing of corneal whorls, corneal haze, subepithelial corneal deposits, vortex epitheliopathy, or cornea verticillata/corneal verticillata as of cut-off date11/20/15
- Participants in AR-13324-CS302 who developed corneal deposits (corneal verticillata) during study participation after the above cutoff date and were enrolled at sites where the observational study was being conducted could also be enrolled in the study
- Been able and willing to give signed informed consent and participate in scheduled visits

Exclusion Criteria

- Participants in AR-13324-CS302 who did not develop corneal deposits (corneal verticillata) during study were excluded from entry into this targeted observational study.
- Past participants in AR-13324-CS302 who developed corneal deposits (corneal verticillata) during study participation were excluded if they:
    - were currently enrolled in another clinical trial
    - were enrolled after exiting above studies in another clinical trial
    - were planning to enroll in another clinical trial

Corneal Verticillata Grading (Orlando 1984)

- Grade I keratopathy : The earliest changes are golden brown microdeposits in the epithelium just anterior to Bowman's membrane. These appear as a "dusting" of the cornea at the inferior pupillary margin in the midperiphery. There is no fluorescein epithelial punctate staining, foreign body sensation, or other ocular symptoms.

- Grade II keratopathy: The deposits become aligned in a more linear pattern and extend from the inferior pupillary margin towards the limbus. This gives the appearance much like that of a "cat's whisker." All patients had a clear zone between the margin of the deposits and the limbus.

- Grade III keratopathy: The linear "filament-like" deposits seen in grade II increase in number and extend as branches from the inferior pupillary area into the visual axis. A whorled pattern is seen in the pupillary axis of the cornea.

- Grade IV keratopathy: Grade III with irregularly round "clumps" of golden-brown deposits.

Safety Measurements

The following assessments were performed in both eyes of all enrolled subjects:

- Pelli-Robson Contrast Sensitivity (CS) testing
- Best corrected visual acuity by ETDRS
- VF-14 questionnaire
- Corneal verticillata grading
- Time to corneal verticillata resolution/stabilization

Table 1 Schedule of Visits and Procedures - Groups 2 and 3 (All Subjects)

Surveillance Plan – Groups 2 and 3[1] Study Procedures	Observational study Visit 1 (after exiting studies CS302)	Observational study Visit 2 (within 2 weeks of Visit 1)	Monthly Visit X 3 (if corneal verticillata persist)	Bi-monthly visits after 3rd Monthly visit (if corneal verticillata persist)	Final Visit after Resolution/ Stabilization[2]
Informed Consent	X				
Ocular and General Medical History Review/Update	X	X	X	X	
Conmed Review	X	X	X	X	X
Symptoms/Assessment of Ocular and General History	X	X	X	X	X
VF-14 Questionnaire		X			X
BCVA (ETDRS)	X	X	X	X	X
Contrast Sensitivity		X			X
Corneal Verticillata Grading	X		X	X	

Source: Protocol Amendment 1, Appendix 16.1.1.

Abbreviations: CS302 = AR-13324-CS302

1. If no corneal verticillata were present at Visit 1, subjects were to complete the outlined procedures and exit the study. If corneal verticillata were present at Visit 1, then subjects were to return within a 2-week window for visual acuity with ETDRS testing, the VF-14 questionnaire, and CS testing. Following Visit 2, subjects were to come back for 3 monthly visits or until resolution or stabilization. If no resolution or stabilization was noted at the 3rd visit, subjects were to continue in the study with visits every 2 months until resolution or stabilization.
2. Should have had a rating score of 0 in both eyes or stabilization confirmed to exit the study.

Primary Safety Analyses

In subjects who had corneal verticillata at study entry, CS and visual acuity were summarized at the eye level (i.e., if a subject had a corneal verticillata in both eyes, then both eyes were included) for the initial assessments and for follow-up visits as well as change from the initial assessment (for visual acuity, change from baseline scores in AR-13324-CS302 were also completed), by treatment group, observational study group, and by whether or not the corneal verticillata event was ongoing at a given visit. The VF-14 scores were summarized similarly at the subject level.

Contrast Sensitivity Tests

The CS was tested using the Pelli-Robson charts at Visit 2 and Final Visit. The test was performed with trial frames on the participant containing the distance refraction determined

during Visual Acuity Testing, with + 0.75 diopters added for 1-meter testing. The number of letters read correctly was added to get the score for that eye. Scores from both eyes were recorded in the eCRF. The scores and the score changes from the initial visit (Visit 2) were summarized at eye level by treatment group and observational study group.

Best Corrected Visual Acuity

BCVA was taken at all visits as a measure of visual function. The number of letters missed was multiplied by 0.02 and added to the base value to determine the logMAR visual acuity. Base value was defined as the last line for which the subject reads at least 1 letter. The logMAR units BCVA = Base value + (n x 0.02), were recorded in the eCRF. The scores and the score changes from the baseline visit (as defined in AR-13324-CS302) and Visit 2 were summarized at eye level by treatment group, observational study group, and by whether or not the corneal verticillata event was ongoing at a given visit.

Visual Function Index Questionnaire

The VF-14 questionnaire is a brief questionnaire originally designed to measure functional impairment in a patient undergoing cataract surgery comprising of 18 questions covering 14 aspects of visual function affected by the patient's cataract. Responses to the questions are scored and a total score is calculated. In the study, the questions pertaining to visual function are prefaced by the following query and instructions: "Because of your vision, how much difficulty do you have with the following activities? Check the box that best describes how much difficulty you have, even with glasses. If you do not perform the activity for reasons unrelated to your vision, circle 'n/a.'" The responses are scored as 4 = None, 3 = A little, 2 = Moderate, 1 = Great deal, and 0 = Unable to do. An item is not included in the scoring if the person does not do the activity for some reason other than their vision. Scores on all activities that the person performed or did not perform because of vision were then averaged, yielding a value from 0 to 4. This value is multiplied by 25, giving a final score from 0 to 100:

- A score of 100 indicates the person was able to do all applicable activities
- A score of 0 indicates the person was unable to do all applicable activities because of vision

The VF-14 scores were collected at Visit 2 and Final Visit. The scores and the score changes from the initial visit (Visit 2) were summarized at subject level by treatment group and observational study group.

Corneal Verticillata

In subjects who had corneal verticillata at study entry, the corneal verticillata was graded under biomicroscopy at Visit 1 and the subsequent monthly and bi-monthly visits. The grading was from Grade 0 (None) to Grade 4 (Greatest). The scores and the score changes from the initial visit (Visit 1) were summarized at eye level by treatment group and observational study group, and subgroup by the eyes with ongoing corneal verticillata only. In addition, the following additional details were recorded in the listing: Corneal Haze (Present/Absent). The examiner also documented if the verticillata were present in the visual axis: Visual axis involvement (Yes/No).

Time to Corneal Verticillata Resolution/Stabilization

Resolution of corneal verticillata was defined as a corneal verticillata grading 0 and stabilization was defined as no worsening of the corneal verticillata grading. The time to corneal verticillata resolution or stabilization was evaluated in days relative to the start date of corneal verticillata at the eye level. Only those eyes with non-0 corneal verticillata grading at Visit 1 were included in this analysis. Kaplan-Meier methods were used to estimate median time to corneal verticillata resolution or stabilization, as well as the 25th and 75th percentiles by treatment group, observational study group, and overall netarsudil ophthalmic solution 0.02% treated subjects. Associated 95% confidence intervals were also estimated. Kaplan-Meier curves were also presented by treatment group, observational study group, and overall netarsudil ophthalmic solution 0.02% treated subjects.

A total of 47 subjects at 10 investigative sites were enrolled in this study; however, 2 subjects, 258-018 and 258-021, were identified to have an ocular history of corneal epithelial haze at Visit 1. Corneal epithelial haze is a confounding factor for corneal verticillata and the two subjects exited the study immediately. Therefore, 45 subjects were included in the analysis reports.

Study AR-13324-OBS01: Subject Disposition (Safety Population)

	netarsudil 0.02% QD N=25	**netarsudil 0.02% BID N=20**
Number of Subjects Without Corneal Verticillata at Entry	10	16
Safety Population	25	20
Study Completion		
Completed	22	20
Discontinued	3	0
Missing	0	0
Reason for Subject Discontinuation		
Withdrawal of Consent	0	0
Lost to Follow-up	1	0
Investigator Decision	0	0
Protocol Violation	0	0
Death	0	0
Other	2	0

Study AR-13324-OBS01: Demographics

Characteristic	netarsudil 0.02% QD N=25	netarsudil 0.02% BID N=20
Sex		
Male	16	6
Female	9	14
Age (years)		
Mean	71.2	67.2
Range	50, 83	50, 83
Race		
Asian	0	1
Black or African-American	0	1
White	25	18
Other	0	0
Ethnicity		
Hispanic or Latino	11	7
Not Hispanic or Latino	14	13
Iris color of study eye		
Blue/Grey/Green	9	3
Brown	13	15
Hazel	3	2
Have Corneal Verticillata at Study Entry		
Single eye only	0	0
Both eyes	15	4
None	10	16
Duration of Investigation Product Prior to Start of Verticillata (Days) -OD		
Mean	166.0	110.0
Range	40, 368	41, 268
Duration of Investigation Product Prior to Start of Verticillata (Days) -OS		
Mean	165.2	108.6
Range	40, 368	41, 268
Number of Doses Prior to start of Corneal Verticillata-OD		
Mean	166.0	220.0
Range	40, 368	82, 536
Number of Doses Prior to start of Corneal Verticillata-OS		
Mean	165.2	217.1
Range	40, 368	82, 536

Study AR-13324-OBS01: Corneal Verticillata Including Concomitant Medications Taken During Study

	netarsudil 0.02% QD N=25	**netarsudil 0.02% BID N=20**
Non-ocular Concomitant Medications		
Advil	2	1
Naproxen	0	3
Ibuprofen	1	1
Aleve	1	0
Aleve arthritis	1	0
Amiodarone	2	0
Ocular Concomitant Medications		
Azopt	1	0
Dorzolamide	1	0

Study AR-13324-OBS01: Mean and Mean Change From Baseline (Visit 1) in Corneal Deposit Grading

	netarsudil 0.02% QD N=25		**netarsudil 0.02% BID N=20**	
	Value	**Change From Visit 1**	**Value**	**Change From Visit 1**
V1: Initial Visit				
N	50		40	
Mean (sd)	1.12 (1.04)		0.28 (0.56)	
Min, Max	0, 3		0, 2	
Eyes With Ongoing Corneal Deposit				
N	30		8	
Mean (sd)	1.87 (0.63)		1.38 (0.52)	
Min, Max	1, 3		1, 2	
Visit 3				
N	26	26	8	8
Mean (sd)	1.31 (0.088)	-0.46 (0.65)	0.88 (0.99)	-0.50 (0.54)
Min, Max	0, 3	-2, 0	0, 2	-1, 0
Eyes With Ongoing Corneal Deposit				
N	21	21	4	4
Mean (sd)	1.62 (0.70)	-0.24 (0.44)	1.75 (0.50)	0
Min, Max	1, 3	-1, 0	1, 2	0, 0
Visit 4				
N	22	22	4	4
Mean (sd)	1.41 (0.67)	-0.41 (0.59)	1.75 (0.50)	0
Min, Max	0, 3	-2, 0	1, 2	0, 0
Eyes With Ongoing Corneal Deposit				
N	21	21	4	4
Mean (sd)	1.48 (0.60)	-0.33 (0.48)	1.75 (0.50)	0
Min, Max	1, 3	-1, 0	1, 2	0, 0
Visit 5				
N	22	22	4	4
Mean (sd)	1.00 (0.82)	-0.82 (1.01)	1.50 (0.58)	-0.25 (0.50)

Min, Max	0, 2	-3, 0	1, 2	-1, 0
Eyes With Ongoing Corneal Deposit				
N	15	15	4	4
Mean (sd)	1.47 (0.52)	-0.27 (0.46)	1.50 (0.58)	-0.25 (0.50)
Min, Max	1, 2	-1, 0	1, 2	-1, 0
Visit 6				
N	16	16	4	4
Mean (sd)	0.31 (0.70)	-1.44 (0.81)	0.50 (0.58)	-1.25 (0.96)
Min, Max	0, 2	-2, 0	0, 1	-2, 0
Eyes With Ongoing Corneal Deposit				
N	3	3	2	2
Mean (sd)	1.67 (0.58)	0	1 (0)	-0.50 (0.71)
Min, Max	1, 2	0, 0	1, 1	-1, 0
Visit 7				
N	4	4	2	2
Mean (sd)	0.50 (0.58)	-1.00 (0)	1 (0)	-0.50 (0.71)
Min, Max	0, 1	-1, -1	1, 1	-1, 0
Eyes With Ongoing Corneal Deposit				
N	2	2	2	2
Mean (sd)	1 (0)	-1 (0)	1 (0)	-0.50 (0.71)
Min, Max	1, 1	-1, -1	1, 1	-1, 0
Visit 8				
N	4	4	0	0
Mean (sd)	0.50 (0.58)	-1 (0)		
Min, Max	0, 1	-1, -1		
Eyes With Ongoing Corneal Deposit				
N	2	2	0	0
Mean (sd)	1 (0)	-1 (0)		
Min, Max	1, 1-1, -1	-1, -1.0		

Corneal verticillata were graded at Visit 1 and at all monthly/bi-monthly follow-up visits. Note that subjects were followed until corneal verticillata resolved in both eyes; therefore, an eye considered resolved at a prior visit was re-evaluated if corneal verticillata remained in the fellow eye.

Of the 90 eyes evaluated for corneal verticillata at Visit 1, 38 eyes had ongoing corneal verticillata at a mean grading of 1.76. At follow-up visits Visits 3-8, mean change from Visit 1 improved for all returning eyes and all eyes with ongoing corneal verticillata as follows:

- At Visit 3 (First Monthly Visit), 34 eyes showed a mean improvement of -0.47 from Visit 1. Of those, 25 eyes had ongoing corneal verticillata with a mean improvement of -0.20.
- At Visit 4 (Second Monthly Visit), 26 eyes showed a mean improvement of -0.35 from Visit 1. Of those, 25 eyes had ongoing corneal verticillata with a mean improvement of -0.28.
- At Visit 5 (Third Monthly Visit), 26 eyes showed a mean improvement of -0.73 from Visit 1. Of those, 19 eyes had ongoing corneal verticillata with a mean improvement of -0.26.

- At Visit 6 (First Bi-Monthly Visit), 20 eyes showed a mean improvement of -1.40 from Visit 1. Of those, 5 eyes had ongoing corneal verticillata with a mean improvement of -0.20.
- At Visit 7 (Second Bi-Monthly Visit), 6 eyes showed a mean improvement of -0.83 from Visit 1. Of those, 4 eyes had ongoing corneal verticillata with a mean improvement of -0.75.
- At Visit 8 (Third Bi-Monthly Visit), 4 eyes showed a mean improvement of -1.00 from Visit 1. Of those, 2 eyes had ongoing corneal verticillata with a mean improvement of -1.00.

Study AR-13324-OBS01: Time From Corneal Verticillata Start to Resolution/Stabilization by Treatment Group

	netarsudil 0.02% QD N=25	**netarsudil 0.02% BID N=20**
Time in Days to Corneal Verticillata Resolved/Stabilized		
N (eyes)	26	8
Mean (sd)	496.7 (117.47)	517.0 (145.17)
Range (Min, Max)	302, 774	329, 712

Study AR-13324-OBS01: Time From Last Dose to Resolution/Stabilization by Treatment Group

	netarsudil 0.02% QD N=25	**netarsudil 0.02% BID N=20**
Time in Days to Corneal Verticillata Resolved/Stabilized		
N (eyes)	26	8
Mean (sd)	317.2 (92.96)	419.0 (152.54)
Range (Min, Max)	189, 537	255, 631

In the two completed Phase 3 studies (AR-13324-CS301 and AR-13324-CS302), cornea verticillata was reported in 16.7% (76/454) of netarsudil QD subjects and 25.3% (64/253) of netarsudil BID subjects.

At the completion of Study AR-13324-OBS01, corneal verticillata resolved in all subjects except for 3 subjects (4 out of the 6 eyes) where cornea verticillata remained stabilized but unresolved.

Post-marketing Experience

Not applicable.

Points for Advisory Committee Consideration

1. Do the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?

2. Does the efficacy of netarsudil ophthalmic solution, demonstrated in the clinical trials, outweigh the safety risks identified for the drug product?

3. Do you have any suggestions concerning the proposed draft labeling of the product?

Draft Labeling for Discussion

Following is the applicant's draft labeling submitted on 8/30/2017. Agency suggested edits are noted in track changes. This is not a final label; Agency edits are ongoing.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RHOPRESSA™ safely and effectively. See full prescribing information for RHOPRESSA™.

RHOPRESSA™ (netarsudil ophthalmic solution) 0.02%, for topical ophthalmic use
Initial U.S. Approval: 20xx

----------INDICATIONS AND USAGE----------
RHOPRESSA™ (netarsudil ophthalmic solution) 0.02% is a Rho kinase ~~and norepinephrine transporter~~ inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

----------DOSAGE AND ADMINISTRATION----------
One drop into the affected eye(s) once daily in the evening. (2)

----------DOSAGE FORMS AND STRENGTHS----------
Ophthalmic solution containing 0.2 mg/mL netarsudil. (3)

----------CONTRAINDICATIONS----------
Known hypersensitivity to any ingredient in this product. (4)

----------ADVERSE REACTIONS----------
The most common adverse reaction is conjunctival hyperemia (54%)~~, the majority of which was mild in nature~~. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aerie Pharmaceuticals, Inc. at 1-800-xxx-xxxx, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: Month/Year

Full Prescribing Information: Contents*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

RHOPRESSA™ (netarsudil ophthalmic solution) 0.02% is a Rho kinase ~~and norepinephrine transporter~~ inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2. DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose ~~as normal~~in the evening.

IOP lowering effect ~~increases gradually after initial dosing and~~generally reaches a maximum following the seventh daily dose [see *Pharmacodynamics (12.2)*].

RHOPRESSA may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

3. DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 0.2 mg/mL netarsudil.

4. CONTRAINDICATIONS

Known hypersensitivity to any ingredient in this product.

5. WARNINGS AND PRECAUTIONS

5.1 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface [see *Patient Counseling Information (17)*].

5.2 Use with Contact Lenses

Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The most common ~~treatment-related~~ ocular adverse reaction observed in controlled clinical studies with RHOPRESSA (netarsudil ophthalmic solution) 0.02% dosed once daily was conjunctival hyperemia which was reported in ~~54~~57% of patients ~~and considered mild in the majority of patients (80%)~~. Other ~~treatment-related~~ ocular adverse reactions reported at an incidence greater than 10% in these clinical studies included cornea verticillata,

conjunctival hemorrhage, and instillation site pain. Ocular ~~treatment-related~~ adverse reactions reported at an incidence of 5 to 10% included ~~conjunctival hemorrhage, instillation site erythema,~~ vision blurred, lacrimation increased, visual acuity reduced, erythema of eyelid, instillation site erythema, and vital dye staining cornea present~~, erythema of eyelid and lacrimation increased~~.~~.~~

~~Ocular treatment-related adverse reactions reported at an incidence of 1 to 4% in clinical studies with RHOPRESSA 0.02% dosed once daily included visual acuity reduced, instillation site discomfort, eye irritation, eye pruritus, punctate keratitis, eyelid edema, conjunctivitis allergic, conjunctival edema, eye pain, foreign body sensation in eyes, photophobia, conjunctivitis, dry eye, installation site pruritus, eyelids pruritus, blepharitis, and eye discharge.~~

The cornea verticillata seen in RHOPRESSA-treated patients were first noted at 6 weeks of once daily dosing. ~~This event was reported as mild in 95% and moderate in 5% of patients.~~ This event did not result in any apparent functional changes in patients.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Netarsudil is not absorbed systemically following topical ophthalmic administration, and maternal use is not expected to result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

Netarsudil is not absorbed systemically by the mother following topical ophthalmic administration, and breastfeeding is not expected to result in exposure of the child to netarsudil.

8.4 Pediatric Use

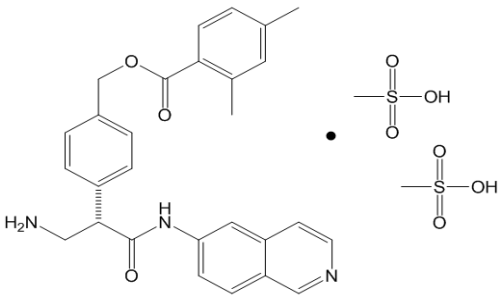
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

11. DESCRIPTION

Netarsudil is a Rho kinase and norepinephrine transporter inhibitor. Its chemical name is (S)-4-(3-amino-1-(isoquinolin-6-yl-amino)-1-oxopropan-2-yl)benzyl 2,4-dimethylbenzoate dimesylate. Its molecular formula is $C_{30}H_{35}N_3O_9S_2$ and its chemical structure is:



Netarsudil mesylate is a light yellow to white powder that is freely soluble in water, soluble in methanol, sparingly soluble in dimethyl formamide, and practically insoluble in dichloromethane and heptane.

RHOPRESSA (netarsudil ophthalmic solution) 0.02% is supplied as a sterile, isotonic, buffered aqueous solution of netarsudil mesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. Each mL of RHOPRESSA contains 0.2 mg of netarsudil. Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are: mannitol, boric acid, sodium hydroxide to adjust pH, and water for injection.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Netarsudil, a Rho kinase ~~and norepinephrine transporter~~ inhibitor, has been shown in animal and human studies to reduce IOP ~~by multiple mechanisms of action: increasing trabecular outflow facility, decreasing the production of aqueous humor and reducing episcleral venous pressure~~. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and glaucomatous visual field loss.

12.2 Pharmacodynamics

In a clinical study of RHOPRESSA dosed once daily in the morning, ~~IOP lowering effect increased gradually after the first daily dose, with~~ the largest reduction in mean IOP ~~of 7 mmHg~~was observed approximately 8 hours following the seventh daily dose.

12.3 Pharmacokinetics

Absorption

After administration of RHOPRESSA in each eye of healthy subjects once daily in the morning for 8 days, there were no observed netarsudil plasma concentrations above the lower limit of quantitation (LLOQ, 0.100 ng/mL) at any time point in any subject. Only 1 plasma sample from 1 subject had a concentration above the LLOQ for the primary metabolite of netarsudil (0.11 ng/mL).

Metabolism

No metabolism of netarsudil was observed during *in vitro* exposure to human plasma. Netarsudil is metabolized *in vitro* by human corneas to produce an active metabolite**.**

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil.

Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* rat micronucleus test.

Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

14. CLINICAL STUDIES

In two clinical trials, patients with open-angle glaucoma or ocular hypertension who were treated with RHOPRESSA 0.02% once daily in the evening had mean baseline IOP of 21 - 22 mmHg ~~and < 25 mmHg~~ and demonstrated up to 5 mmHg reductions in IOP. The IOP reduction with RHOPRESSA 0.02% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily in patients with baseline IOP of <25 mmHg.

16. HOW SUPPLIED/STORAGE AND HANDLING

RHOPRESSA™ (netarsudil ophthalmic solution) 0.02% is supplied sterile in opaque white low density polyethylene bottles and tips with white polypropylene caps.

2.5 mL fill in a 4 mL container
NDC # 70727-497-25

Storage: Store at 2° - 8°C (36° - 46°F) until opened. After opening, the product may be kept at 2° - 25°C (36° - 77°F) for up to 6 weeks.

17. PATIENT COUNSELING INFORMATION

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions [see *Warnings and Precautions (5.1)*].

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of RHOPRESSA.

Use with Contact Lenses

Advise patients that RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043
RHOPRESSA is a registered trademark of Aerie Pharmaceuticals, Inc.
Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.