CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208254Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW NDA 208-254

Application Type	NDA
Application Number(s)	208-254
Priority or Standard	Standard
Submit Date(s)	2/28/17
Received Date(s)	2/28/17
PDUFA Goal Date	2/28/18
Division/Office	DTOP
Reviewer Name(s)	Sonal D. Wadhwa, MD
Review Completion Date	11/8/17
Established Name	Netarsudil ophthalmic solution 0.02%
(Proposed) Trade Name	Rhopressa
Applicant	Aerie Therapeutics, Inc.
Formulation(s)	Ophthalmic solution
Dosing Regimen	Instill one drop into the affected eye once daily in the evening
Applicant Proposed Indication(s)/Population(s)	Patients with open-angle glaucoma or ocular hypertension
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

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GLOSSARY

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

1 EXECUTIVE SUMMARY

Reference ID: 4178696

1.1. Product Introduction

AR-13324 (hereafter referred to as netarsudil) is a Rho kinase inhibitor. Rho kinase (ROCK) inhibitors represent a new class of medications that lower IOP. This product is an NME (new molecular entity). The established name is netarsudil ophthalmic solution and the proposed proprietary name is Rhopressa, 0.02%. During development, the product was also referred to as AR-13324. The proposed dosing regimen is one drop in the affected eye(s) once a day in the evening. The proposed indication is for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 208-254 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Rhopressa for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

The data contained in this submission establishes the efficacy of netarsudil ophthalmic solution 0.02% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension.

Studies 301, 302, and 304 demonstrate that the IOP lowering ability of netarsudil ophthalmic solution 0.02% in the subgroup of patients with baseline intraocular pressures of <25 mmHg is equivalent to timolol maleate ophthalmic solution ,0.5%.

The most common ocular adverse events for netarsudil are: conjunctival hyperemia, corneal verticillata, conjunctival hemorrhage, and instillation site pain. To date, no long term consequences of netarsudil administration have been identified.

The benefit of netarsudil ophthalmic solution, 0.02% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factor is elevated IOP.	Intraocular pressure is currently the accepted standard for establishing the efficacy of ocular hypotensive medications.
Current Treatment Options	• There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues. It is not uncommon for a patient with glaucoma to require more than one class of IOP lowering products to control elevated IOP.	This product, if approved, would make a new class of intraocular pressure lowering products available to patients needing more than one class of IOP lowering products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• IOP is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies 301, 302, and 304. These studies demonstrated that in the subset of patients with IOP <25, netarsudil ophthalmic solution 0.02% was equivalent to timolol maleate 0.5% at all time points measured.	Studies 301, 302, and 304 demonstrated that in the subset of patients with IOP <25 mmHg, netarsudil ophthalmic solution 0.02% was equivalent to timolol maleate ophthalmic solution 0.5%, a product known to lower IOP.
Risk	• Rho kinase (ROCK) inhibitors represent a new class of medications that lower IOP The risks for using Rho kinase (ROCK) inhibitors are not well established and include a high frequency of conjunctival hyperemia and the formation of corneal verticillate.	The safety database contained in this application identified potential adverse events which may be expected to occur at rates of 1% or greater following the use of netarsudil ophthalmic solution 0.02% dosed once daily in the evening.
Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Post-marketing Requirements or Phase 4 Commitments.	Routine monitoring and reporting of all adverse events are adequate.

2 THERAPEUTIC CONTEXT

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2.1. Analysis of Condition

Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. The various types of glaucoma are distinguished by the causative physiological defect. It affects one person in 200 over the age of 40. It is the leading cause of irreversible blindness in the United States. One of the primary risk factors is elevated IOP. The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy. When maximal tolerated medical therapy does not adequately control IOP, surgical therapy is the next option.

2.2. Analysis of Current Treatment Options

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

When medical therapy fails or is not tolerated, then laser or surgical treatment is recommended.

Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	Trade Name	Established Name
Alpha-2 agonists		

Pharmacologic Class/ Applicant	Trade Name	Established Name
Allergan, Inc.	Alphagan/Alphagan P	brimonidine tartrate
Alcon	Iopidine	apraclonidine
Beta-adrenergic antagonists		
Alcon	Betoptic/Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Bausch & Lomb	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Carbonic Anhydrase Inhibitors		
Duramed Pharamaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	Brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan/ Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Bausch & Lomb	Vyzulta	latanoprostene bunod
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine hydrochloride
Alcon	Simbrinza	carbonic anhydrase inhibitor/alpha-agonist
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

3 REGULATORY BACKGROUND

3.1. U.S. Regulatory Actions and Marketing History

Netarsudil is a new molecular entity. It is not currently marketed in the United States or in any other country in the world.

3.2. Summary of Pre-submission/Submission Regulatory Activity

Pre-Investigational New Drug 113064 telephone conference	10/31/11
End of Phase 2 meeting	4/11/14
Type C guidance telephone conference	6/12/15
Chemistry/Manufacturing Controls telephone conference	12/17/15

3.3. Foreign Regulatory Actions and Marketing History

Netarsudil ophthalmic solution is not marketed.

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI. The final consult report is pending. See CDTL review for complete findings.

4.2. Product Quality

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
Manufacturer drug substance	(b) (4)
Description drug product	The drug product contains 0.02% netarsudil and is a simple aqueous solution of compendial excipients, including benzalkonium chloride
Sterilization	The container closure system (bottle, dropper tip, and cap) has been qualified per USP requirements. These components are (b) (4) (b) (4) Netarsudil ophthalmic solution 0.02% is manufactured using (b) (4)

Manufacturer drug product	(b) (4)
Manufacturer drug product container closure system	
Drug product container closure system description	4 cc, white, low-density polyethylene (b) (4) round bottles 15 mm, white, (b) (4) low-density polyethylene (b) (4) dropper tip 15 mm (b) (4) white cap, polypropylene, extended tip (b) (4) (b) (4)
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

Composition and Components of Netarsudil Ophthalmic Solution 0.02%

Component	**Function**	**Netarsudil Concentration: 0.2 mg/mL**	
		Quantity per mL (mg)	**Quantity (% w/v)**
Netarsudil mesylate	Active Ingredient	0.2 (b) (4))[1]	0.02
Mannitol	(b) (4)		
Boric acid			
Benzalkonium chloride	Preservative	(b) (4)	0.015
Sodium hydroxide[3]	pH Adjuster	as needed	as needed
Water for Injection	(b) (4)	q.s.	q.s.
Total		**1 mL**	**100%**

(b) (4)

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

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

4.5. Clinical Pharmacology

4.5.1. Mechanism of Action

Netarsudil is a Rho kinase inhibitor for both isoforms of human Rho kinase (ROCK1 and ROCK2). This could contribute to the mechanisms by which netarsudil lowers IOP: increased outflow through the trabecular meshwork. However, the precise mechanism of the drug is still not completely understood.

4.5.2. Pharmacodynamics

Not applicable.

4.5.3. Pharmacokinetics

The clinical pharmacokinetics study AR-13324-CS101 was an open-label, non-comparative, single-arm, single-center study with 18 healthy adult male or female subjects. Subjects instilled netarsudil ophthalmic solution 0.02% for 8 days. Treatment was administered in each eye once a day in the morning. Blood samples were collected at multiple times after dosing at Day 1, Day 8, and Day 9 for subsequent measurement of AR-13324 and its metabolites.

There were no observed plasma AR-13324 concentrations above the lower limit of quantitation (LLOQ, 0.100 ng/mL) at any time point in any subject. Only 1 plasma concentration above the LLOQ for the metabolite AR-13503 was observed for 1 subject on Day 8 at 8 hours post-dose (0.11 ng/mL).

4.6. Devices and Companion Diagnostic Issues

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

4.7. Consumer Study Reviews

Not applicable. No consumer studies were conducted.

5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1. Table of Clinical Studies

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

Table of Clinical Studies

Study Name	Study Design	Test product	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status
AR-13324-CS101	Open-label, single-arm, single-site	Netarsudil ophthalmic solution 0.02% 1 gtt OU QD AM	18	Healthy subjects	8 days	Complete
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	7 days	Complete
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	7 days	Complete
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	28 days	complete
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	7 days	Complete

Study Name	Study Design	Test product	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status
AR-13324-CS301 Rocket 1 NCT02207491	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	3 months	Complete
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% 1 gtt OU BID Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	756	Subjects with elevated IOP	12 months	Complete

Study Name	Study Design	Test product	Number of Subjects	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study Status
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	12 months	Ongoing
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	6 months	Complete
AR-13324-OBS01	Observational, prospective, targeted	None (Non-interventional)	45	Subjects from AR-13324-CS301 and AR-13324-CS302 who developed corneal deposits	No set duration	Complete

5.2. Review Strategy

The sources of clinical data utilized in this review include the studies listed in Section 5.1.

6 REVIEW OF RELEVANT INDIVIDUAL TRIALS USED TO SUPPORT EFFICACY

6.1. 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% compared to timolol maleate ophthalmic solution, 0.5% in patients with elevated intraocular pressure

6.1.1. Study Design

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 compared to timolol maleate ophthalmic solution, 0.5% OU BID (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 vehicle 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
- Un-medicated (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

- 0 to 2 years of age
- Diagnosis of glaucoma due to elevated IOP
- No contraindications to the conduct of the trial as determined by the Investigator
- Subjects 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 ≥ 27 mmHg (unmedicated) in both eyes (individuals who were excluded by 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 (i.e., 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 following exceptions: 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 (i.e., 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 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 vehicle 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 AR-13324 (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's salient information. The product for each individual treatment assignment was packaged into identical subject packets that contained subject kits to cover the intended duration of treatment; each subject kit contained 2 bottles: either vehicle (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 distinguish the bottles for AM and PM dosing, and included the word "AM" or "PM" in clearly identifiable font size on the labels. The products were to be refrigerated (36°-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).

List of Investigators

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
101	Eric A. Cohn, DO Avail Clinical Research, LLC 860 Peachwood Drive DeLand, FL 32720 USA Sakowitz Eye Center 2850 Wellness Ave. Orange City, FL 32763 USA	PI	0
102	Michael S. Berlin, MD Glaucoma Institute of Beverly Hills 8733 Beverly Blvd., Suite 301 Los Angeles, CA 90048 USA	PI	1
103	Eugene B. McLaurin, MD Total Eye Care, P.A. 6060 Primacy Parkway, Ste. 200 Memphis, TN 38119 USA	PI	25
104	Carl T. Hartman, MD Southern California Eye Physicians & Associates 3300 E. South St., Suite 105 Long Beach, CA 90805 USA 3801 Katella Ave., Suite 130 Los Alamitos, CA 90720 USA	PI	5
105	Peter Wollan, MD Eye Physicians of Austin 5011 Burnet Road Austin, TX 78756 USA	PI	8
106	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way Suite 15 Petaluma, CA 94954 USA	PI	15
107	Harvey B. DuBiner, MD Eye Care Centers Management, Inc. (Clayton Eye Center) 1000 Corporate Center Dr., Suite 100, 120 Morrow, GA 30260 USA	PI	22
108	Richard Evans, MD Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240 USA	PI	16

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
109	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. 901 East Third Street Washington, MO 63090 USA	PI	12
110	Bradley Kwapiszeski, MD Heart of America Eye Care, P.A. 8901 W. 74th St., Suite 285/281 Shawnee Mission, KS 66204 USA	PI	29
111	Constance Okeke, MD Virginia Eye Consultants 241 Corporate Blvd. Norfolk, VA 23502 USA	PI	4
112	James H. Peace, MD United Medical Research Institute 431-433 N. Prairie Ave. Inglewood, CA 90301 USA	PI	17
113	Eugene E. Protzko, MD Seidenberg Protzko Eye Associates 2023 Pulaski Hwy Havre de Grace, MD 21078 USA 520 Upper Chesapeake Drive, Suite 401 Bel Air, MD 21014 USA	PI	5
114	Robert M. Saltzmann, MD Charlotte Eye Ear Nose & Throat Associates, P.A. 6035 Fairview Rd. Charlotte, NC 28210 USA 724 Aubrey Bell Lane Matthews, NC 28105 USA 400 Park St. Belmont, NC 28012 USA	PI	9
115	Howard I. Schenker, MD Rochester Ophthalmological Group, PC 2100 S. Clinton Ave. Rochester, NY 14618 USA	PI	32
116	Richard T. Sturm, MD Ophthalmic Consultants of Long Island 360 Merrick Rd., 3rd Floor Lynbrook, NY 11563 USA	PI	5
117	Gregory M. Sulkowski, MD Taustine Eye Center 1169 Eastern Parkway, Suite 3427 Louisville, KY 40217 USA	PI	5
118	David L. Wirta, MD Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663 USA	PI	35

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
119	Gary W. Jerkins, MD Nashville Vision Associates 4306 Harding Road, Suite 202 Nashville, TN 37205 USA	PI	11
121	Sherif M. El-Harazi, MD, MPH Lugene Eye Institute 1510 S. Central Ave., Suite 300 Glendale, CA 91204 USA	PI	20
122	Robert Ritch, MD Glaucoma Associates of New York, PC 310 E. 14th Street, Suite 304, South Building New York, NY 10003 USA	PI	8
123	Mark S. Rubin, MD International Eye Associates, PA 1545 Hand Ave., Suite B3 Ormond Beach, FL 32174 USA Millennium Research 1545 Hand Ave., Suite B2 Ormond Beach, FL 32174 USA	PI	10
124	Leonard R. Cacioppo, MD Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL 34613 USA	PI	5
125	David L. Cooke, MD Great Lakes Eye Care 2848 Niles Road Saint Joseph, MI 49085 USA	PI	35
126	Jonathan S. Myers, MD Wills Eye Hospital 840 Walnut Street, Suite 1110 Philadelphia, PA 19107 USA	PI	3
128	Farrell C. Tyson, MD Argus Research at Cape Coral Eye Center 4120 Del Prado Blvd. Cape Coral, FL 33904 USA	PI	8
129	Todd E. Woodruff, MD The Glaucoma Center, Inc. One Park West Blvd., Suite 310 Akron, OH 44320 USA	PI	1
131	Philip Lee Shettle, DO Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773 USA	PI	6
132	Thasarat S. Vajaranant, MD University of Illinois at Chicago, Department of Ophthalmology & Visual Sciences 1855 West Taylor Street Chicago, IL 60612 USA	PI	0

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
133	David Belyea, MD George Washington University Medical Faculty Associates 2150 Pennsylvania Ave. Washington, DC 20037 USA	PI	1
134	Scott Smetana, MD Eye Associates of Colorado Springs 2770 N. Union Blvd., Suite 240 Colorado Springs, CO 80909 USA	PI	10
135	Carl Tubbs, MD Specialty Eye Care 11960 Lioness Way, Suite 190 Parker, CO 80134 USA	PI	4
136	Karen L. Klugo, MD ApexEye 5240 E. Galbraith Rd., Suite B Cincinnati, OH 45236 USA	PI	5
137	Sanjay Asrani, MD Duke Eye Center 2351 Erwin Rd. Durham, NC 27710 USA	PI	7
138	Ned M. Reinstein, MD Reinstein Eye Associates 7171 S. Yale Ave., Suite 101 Tulsa, OK 74136 USA	PI	5
139	Julie Tsai, MD 343 West Houston Street, Suite 109 San Antonio, TX 78205 USA TQMR, LLC (administrative only) 24165 IH-10 West, Suite 217 San Antonio, TX 78257 USA	PI	20
140	Jacob W. Brubaker, MD Grutzmacher, Lewis & Sierra 1515 River Park Drive, Suite 100 Sacramento, CA 95815-4605 USA Northern California Research 3840 Watt Ave., Building E Sacramento, CA 95821 USA	PI	7

Study Endpoints

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.

Statistical Analysis Plan

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 (AR-13324 – timolol) were within 1.5 mmHg at all time points and within 1.0 mmHg at the majority of time points (at least 5 of 9), then the null hypothesis was to be rejected in favor of the alternative hypothesis and AR-13324 was to be considered clinically non-inferior to timolol. The 2-sample t-test was to be used to test whether the difference equaled 0. Analyses were to be performed primarily on the PP population using observed data only (without imputation).

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.

6.1.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Reference ID: 4178696

Financial Disclosure

See Financial Disclosure template in Section 13.2.

Patient Disposition

Study AR-13324-CS301: Subject Disposition

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 (94%)
Discontinued	31 (15%)	13 (6%)
Reason for Subject Discontinuation		
Adverse Event	20 (65%)	4 (31%)
Withdrawal of Consent	3 (10%)	2 (15%)
Non-compliant	0	1 (8%)
Lost to Follow-up	0	1 (8%)
Lack of Efficacy	3 (10%)	0
Investigator Decision	2 (7%)	0
Protocol Violation	3 (10%)	5 (39%)

Protocol Violations/Deviations

There were 8 protocol violations. Major deviations were reported for 41 subjects, all of whom were excluded from the PP population. The most frequent categories of major deviations were visit out of window (12 subjects), incorrect study drug instillation or assignment at site (11 subjects), subject failure to follow instructions (10 subjects), and inclusion/exclusion criteria violations (5 subjects).

Table of Demographic Characteristics

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

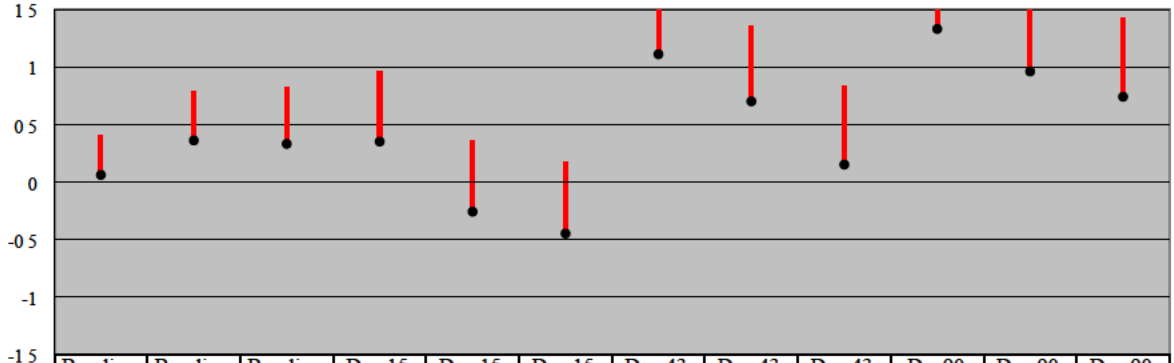
Characteristic	Netarsudil 0.02% QD N=202	Timolol 0.5% BID N=209
Study eye diagnosis		
POAG	134 (66%)	136 (65%)
OHT	68 (34%)	73 (35%)
Sex		
Male	88 (44%)	73 (35%)
Female	114 (56%)	136 (65%)
Age (years)		
Mean	65.8	64.2
Range	20, 96	26, 90
Race		
Asian	2 (1%)	4 (2%)
Black or African-American	43 (21%)	51 (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 (68%)
Hazel	24 (12%)	14 (7%)

Efficacy Results – Primary Endpoint

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: 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

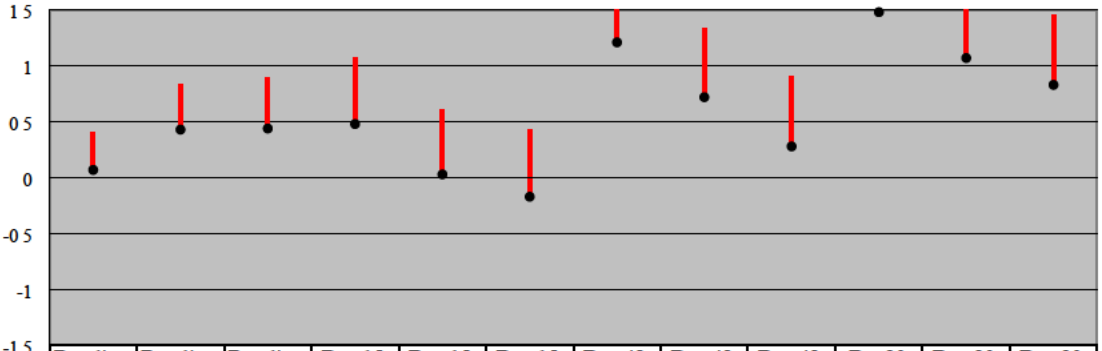
Reviewer's Comment:

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



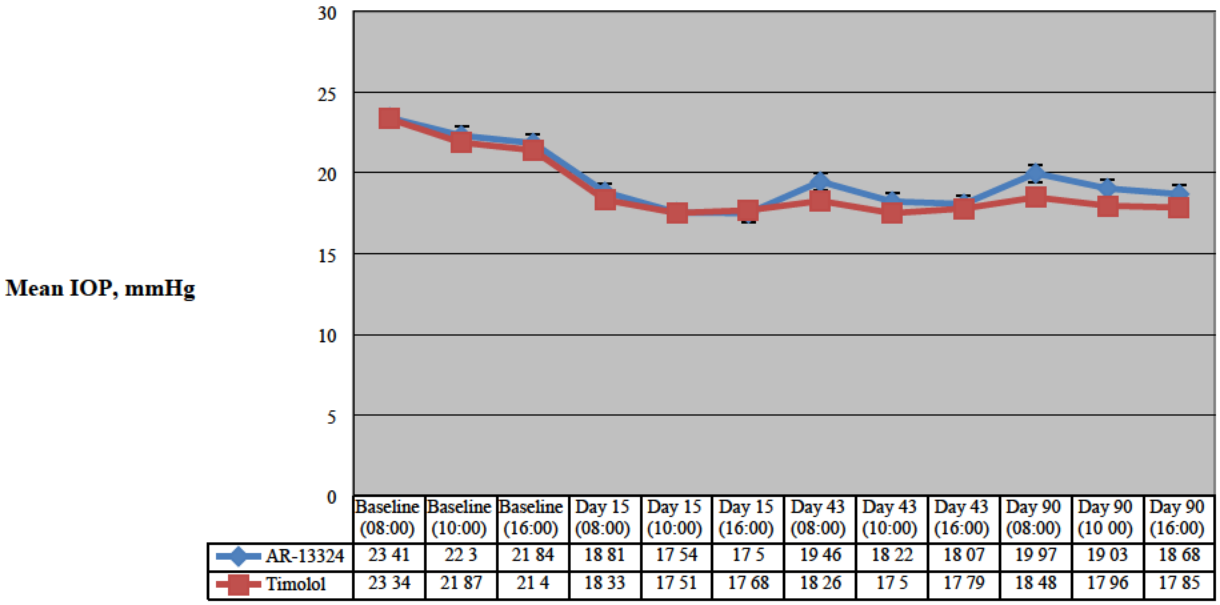
	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.27	0.02	-0.02	-0.11	-0.56	-0.77	0.56	0.1	-0.36	0.85	0.43	0.2
Upper CI	0.41	0.84	0.9	1.07	0.61	0.43	1.86	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

Reviewer's Comment:

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. It was also true, as for the PP population, that netarsudil did not demonstrate non-inferiority to timolol in the ITT population. This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

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

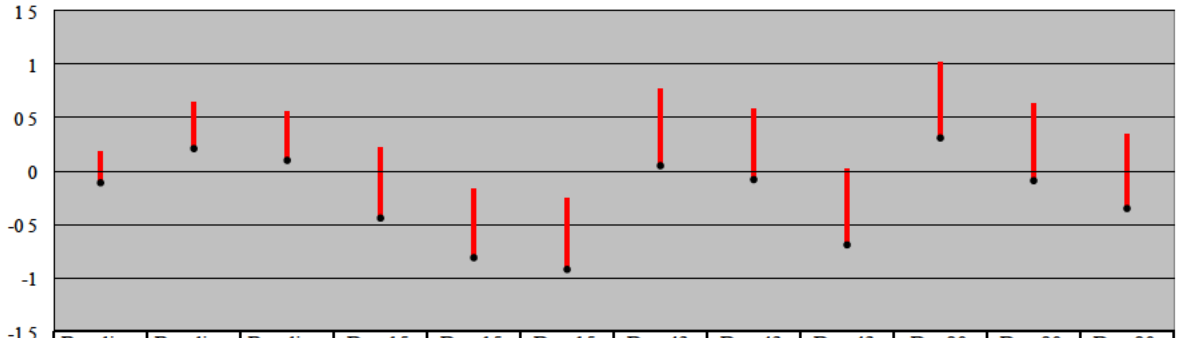
Additional Analyses Conducted on the Individual Trial

For Study AR-13324-CS301 there was a post hoc efficacy analysis of subgroups with maximum baseline IOP < 25 mmHg. There original pre-specified analysis was on patients with IOP < 27 mmHg.

Study AR-13324-CS301: Study Eye Mean IOP (mmHg) By Visit for Subjects with Baseline IOP <25 at All Timepoints, POST HOC ANALYSIS
(PP Population with Observed Data)

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

Reviewer's Comment:

Netarsudil ophthalmic solution, 0.02% dosed qd was non-inferior to timolol maleate ophthalmic solution 0.5% dosed bid in a post hoc analysis of subjects with maximum baseline iop < 25 mmHg. 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.

6.2. 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 Ophthalmic Solution, 0.02% QD and BID compared to Timolol Maleate Ophthalmic Solution, 0.5% BID in patients with elevated intraocular pressure

6.2.1. Study Design

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 and Netarsudil ophthalmic solution 0.02% dosed OU BID compared to Timolol maleate ophthalmic solution 0.5% dosed OU BID 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 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 was 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), vehicle (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).

List of Investigators

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
201	James D. Branch, MD 224 Town Run Lane Winston-Salem, NC 27101	PI	40
202	David C. Brown, MD Eye Centers of Florida 4101 Evans Ave. Ft. Myers, FL 33901	PI	2
203	Michael J. Depenbusch, MD Arizona Eye Center 604 W. Warner Rd. Suite B-6 Chandler, AZ 85225	PI	18
204	John Linn, MD Eye Specialty Group 825 Ridge Lake Blvd. Memphis, TN 38120	PI	32
205	John W. Boyle IV,MD Gulf South Eye Associates 4224 Houma Blvd. Suite 100 Metairie, LA 70006	PI	10
206	Louis M. Alpern, MD The Cataract & Glaucoma Center 4171 N. Mesa Bldg. D Ste. 100 El Paso, TX 79902	PI	22
208	Douglas G. Day, MD Coastal Research Associates 11205 Alpharetta Highway, Suite J3 Roswell, GA 30076	PI	22
209	Jeffery Raymond Lozier, MD Arch Health Partners 15611 Pomerado Road, 4th Floor Poway, CA 92064	PI	15
210	Kenneth Sall, MD Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701	PI	30
211	Stacy R. Smith, MD 1548 East 4500 South Salt Lake City, UT 84117	PI	9

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
212	Michael Emile Tepedino, MD Cornerstone Eye Care 1400 East Hartley Drive High Point, NC 27262	PI	15
213	Thomas Richard Walters, MD Texan Eye, PA/Keystone Research Ltd. 5717 Balcones Drive Austin, TX 78731-4203	PI	19
214	Mark J. Weiss, MD 1717 South Utica, Suite 107 Tulsa, OK 74104	PI	33
216	Eran Duzman, MD 4605 Barranca Pkwy Ste. 100 Irvine, CA 92604	PI	13
217	Robert J. Smyth-Medina, MD North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Missions Hills, CA 91345	PI	20
218	Donald Love McCormack, MD Boulder Medical Center PC 2750 Broadway Boulder, CO 80304	PI	20
219	Thomas Graul, MD Eye Surgical Associates 1710 So. 70th St. Lincoln, NE 68506	PI	3
220	Adam C. LePosa, OD 6115 Falls Road Baltimore, MD 21209	PI	3
221	Donald L. Budenz, MD, MPH 5151 Bioinformatics Bldg., CB 7040 130 Mason Famr Road Chapel Hill, NC 27599 UNC Kittner Eye Center 2226 Nelson Hwy, Ste. 200 Chapel Hill, NC 27517	PI	1
222	Howard Barnebey, MD 1920 116th Ave NE Bellevue, WA 98004 Specialty Eye Centre 901 Boren Ave. Suite 1020 Seattle, WA 98104	PI	9
223	Gregory A. Eippert, MD Ophthalmic Physicians, Inc. 9485 Mentor Ave. Suite 110 Mentor, OH 44060	PI	0

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
224	Rebecca Reid Breckenridge Murphy, MD Upstate Pharmaceutical Research 1655 East Greenville Street Anderson, SC 29621	PI	4
225	Darrell WuDunn, MD, PhD Indiana University-Eugene and Marilyn Glick Eye Institute 1160 W. Michigan Street Indianapolis, IN 46202	PI	4
226	Blake G. Simmons, OD, FAAO St. Luke's Eye Care & Laser Center 1715 N. Weber St., Suite 360 Colorado Springs, CO 80907	PI	8
227	Elizabeth D. Sharpe, MD Glaucoma Consultants and Center for Eye Research, PA 721 Long Point Rd. Suite 407 Mt. Pleasant, SC 29464	PI	21
228	Vicky C. Pai, MD 2619 E. Colorado Blvd. #100 Pasadena, CA 91107	PI	6
230	Gary S Hirshfield, MD Hirshfield Eye Associates 176-60 Union Turnpike Fresh Meadows, NY 11366	PI	11
231	Robert Benza, MD Apex Eye 7850 Camargo Rd. Cincinnati, OH 45243	PI	19
232	Edward J. Meier, MD Eye Care Associates of Greater Cincinnati dba, Apex Eye 6394 Thornberry Court Suite 810 Mason, OH 45040	PI	5
233	Stephen E. Smith, MD Eye Associates of Fort Myers 4225 Evans Ave Fort Myers, FL 33901	PI	8
234	Joshua Kim, MD Center For Sight 2601 S. Tamiami Trail Sarasota, FL 34239	PI	13
235	Raj K. Goyal, MD, FACS Chicago Eye Specialists 8541 South State Street Chicago, IL 60619	PI	1
236	Anthony Realini, MD, MPH WVU Eye Institute 1 Medical Center Drive Morgantown, WV 26506	PI	2

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
237	William C. Christie, MD Scott & Christie and Associates, PC 105 Brandt Drive Cranberry Township, PA 16066	PI	28
238	Christopher Lin, MD Shasta Eye Medical Group, Inc. 3190 Churn Creek Road Redding, CA 96002	PI	9
239	Norman Levy, MD Florida Ophthalmic Institute 7106 NW 11th Place Suite B Gainesville, FL 32605	PI	6
240	El-Roy D. Dixon, MD Dixon Eye Care 806 N. Jefferson Street Albany, GA 31701	PI	25
241	Robert L. Stamper, MD 10 Koret Way San Francisco, CA 94143 UCSF Dept. of Ophthalmology, Glaucoma Clinic 533 Parnassus Ave San Francisco, CA 94143	PI	1
242	Thomas K. Mundorf, MD Mundorf Eye Center 1718 E. Fourth Street Charlotte, NC 28204	PI	9
243	Victor H. Gonzalez, MD Valley Retina Institute, P.A. 1205 N. Ed. Carey Drive Harlingen, TX 78550	PI	2
244	Eydie Miller-Ellis, MD University of Pennsylvania Department of Ophthalmology Scheie Eye Institute Philadelphia, PA 19104	PI	2
245	Bradley S. Danies, MD 135 Gold Star Blvd. Worcester, MA 01606 Reliant Medical Group Inc. at Worcester Medical Center 123 Summer Street, Suite 390 North Worcester, MA 01608	PI	1
246	Kandon K Kamae, MD Spokane Eye Clinical Research 427 South Bernard Spokane, WA 99204	PI	6

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
247	Steven M. Silverstein, MD Silverstein Eye Centers 4240 Blue Ridge Blvd. Kansas City, MO 64133	PI	5
248	Matthew J. Swanic, MD AdvanceMed Clinical Research, Administrative Office 8565 S. Eastern Ave. Las Vegas, NV 89123	PI	14
249	Steven T. Simmons, MD Glaucoma Consultants of the Capital Region 1240 New Scotland Road Slingerlands, NY 14624	PI	3
250	Armin Vishteh, MD Havana Research Institute LLC. 2211 W. Magnolia #290 Burbank, CA 91506	PI	5
251	Andrew Gardner Logan, MD Andrew Gardner Logan dba Logan Ophthalmic Research, LLC 7401 N. University Drive Tamarac, FL 33321	PI	36
252	Hamed Bazargan Lari, MD Summit Medical Group 1 Diamond Hill Road Berkley Heights, NJ 07922	PI	0
254	William L. Haynes, MD Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803	PI	6
255	James Crandall, MD Asheville Eye Associates 2311 Asheville Highway Hendersonville, NC 28791	PI	2
256	Ramon A. Berenguer, MD Florida Medical Center & Research, Inc. 1501 NW 36 Street Miami, FL 33142	PI	2
257	Julie Tsai, MD 343 West Houston Street, Suite 109 San Antonino, TX 78205	PI	13
258	David L. Wirta Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	PI	32
259	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way Suite 12 Petaluma, CA 94954	PI	4

List of Investigators			
Site Number	Investigator	Role	No. Subjects Enrolled
260	Sherif M. El Harazi, MD, MPH Lugene Eye Institute 1510 South Central Avenue Glendale, CA 91204	PI	18
261	Harvey B. DuBiner, MD Eye Care Centers Management, Inc. (Clayton Eye Center) 1000 Corporate Center Dr., Ste 100, 120 Morrow, GA 30260	PI	10
262	Eugene B. McLaurin, MD Total Eye Care, P.A. 6060 Primacy Parkway Memphis, TN 38119	PI	43
263	Bradley Kwapiszeski, MD Heart of America Eye Care, PA 8901 W. 74th Street Shawnee Mission, KS 66204	PI	11
264	Richard Evans, MD Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240	PI	10
265	James H. Peace, MD United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	PI	14
266	Richard Strum, MD Ophthalmic Consultants of Long Island 360 Merrick Road, 3rd Floor Lynbrook, NY 11563	PI	1

Study Endpoints

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 IOP and change from baseline diurnal IOP at each post-treatment visit
- Sub-group analyses based upon pre-study characteristics such as demographics, un-medicated 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.

Statistical Analysis Plan

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), testing Netarsudil QD versus timolol first, then in a hierarchical fashion testing netarsudil BID versus

timolol 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.

Protocol Amendments

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

Protocol Amendment	Item Changed	From	To
			level of 0.05. Two-sided 95% confidence intervals will be reported unless otherwise specified
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

6.2.2. Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Financial Disclosure

See financial disclosure template in Section 13.2.

Patient Disposition

Study AR-13324-CS302

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 (61%)	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 (67%)	132 (79%)	15 (32%)
Withdrawal of Consent	9 (9%)	13 (8%)	9 (19%)
Non-compliant	3 (3%)	1 (1%)	3 (6%)
Lost to Follow-up	1 (1%)	3 (2%)	0
Lack of Efficacy	10 (10%)	4 (2%)	2 (4%)
Disallowed Concurrent Medication	2 (2%)	2 (1%)	5 (11%)
Investigator Decision	1 (1%)	2 (1%)	2 (4%)
Protocol Violation	4 (4%)	6 (4%)	10 (21%)
Death	2 (2%)	0	0
Other	2 (2%)	5 (3%)	1 (2%)

Protocol Violations/Deviations

There were 20 protocol violations. Major deviations were reported for 139 subjects.

Table of Demographic Characteristics

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

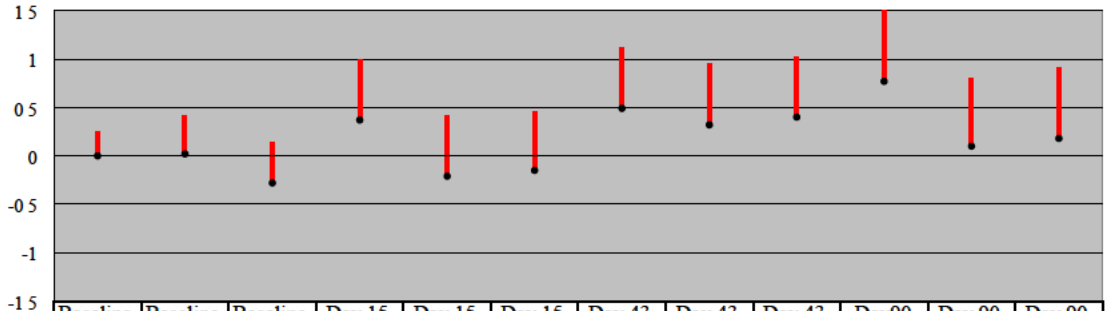
Characteristic	Netarsudil 0.02% QD N=251	Netarsudil 0.02% BID N=254	Timolol 0.5% BID N=251
Study eye diagnosis			
POAG	167 (67%)	158 (62%)	171 (68%)
OHT	84 (33%)	96 (38%)	80 (40%)
Sex			
Male	103 (41%)	89 (35%)	101 (40%)
Female	148 (59%)	165 (65%)	150 (60%)
Age (years)			
Mean	65.83	64.1	63.0
Range	14,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

Efficacy Results – Primary Endpoint

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 From Timolol Netarsudil 0.02% QD	95% CI	Mean Difference From Timolol Netarsudil 0.02% BID	95% CI
Baseline (Visit 3)							
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: Mean IOP (Netarsudil 0.02% QD Compared to Timolol 0.5% BID) from Baseline - PP 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	-0.25	-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

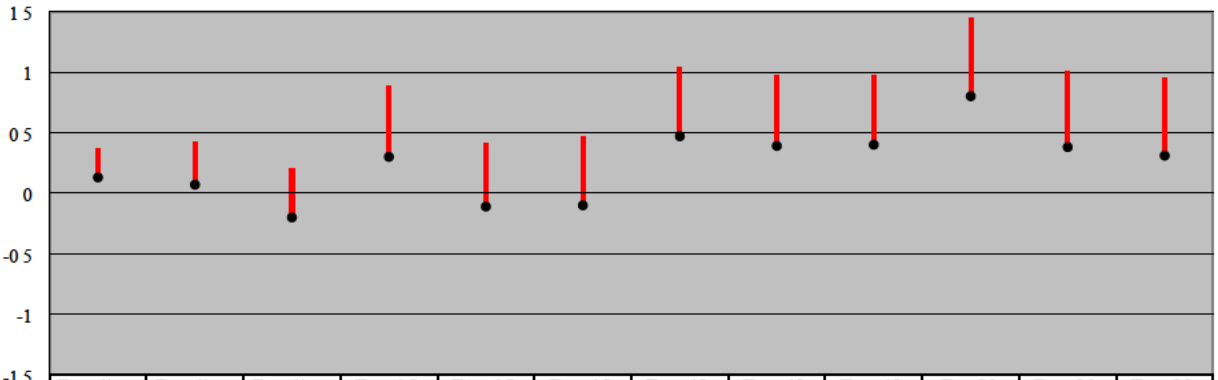
Reviewer's Comment:

Non-inferiority of netarsudil QD and BID to timolol was demonstrated in the PP population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 6 of the 9 time points, therefore meeting the pre-specified criteria for non-inferiority. 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, therefore meeting the pre-specified criteria for non-inferiority.

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: Mean IOP (Netarsudil 0.02% QD Comparred to Timolol 0.5% BID) - ITT with LOCF Population (Baseline IOP<25)



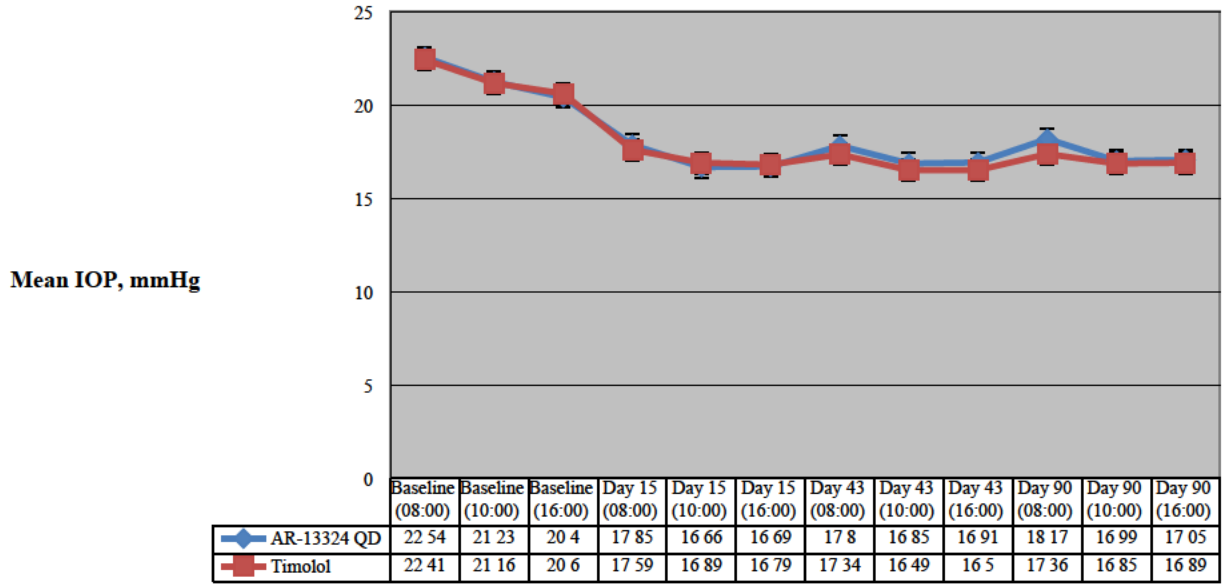
	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.1	-0.28	-0.6	-0.28	-0.74	-0.67	-0.09	-0.18	-0.16	0.15	-0.25	-0.32
Upper CI	0.37	0.42	0.2	0.88	0.41	0.47	1.04	0.97	0.97	1.45	1.01	0.95
Mean Difference	0.13	0.07	-0.2	0.3	-0.11	-0.1	0.47	0.39	0.4	0.8	0.38	0.31

Reviewer's Comment:

As for the PP population, both netarsudil QD and BID demonstrated non-inferiority to timolol in the ITT population with maximum baseline IOP < 25 mmHg. The upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol was within 1.5 mmHg at all of the 9 time points and within 1.0 mmHg at 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. This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

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 85	16 66	16 69	17 8	16 85	16 91	18 17	16 99	17 05
Timolol	22 41	21 16	20 6	17 59	16 89	16 79	17 34	16 49	16 5	17 36	16 85	16 89

Reviewer's Comment:

In Study 302, two doses of netarsudil were studied (QD and BID dosing). (b) (4)

Reference ID: 4178696

6.3. Study AR-13324-CS304 [Rho Kinase Elevated Intraocular Pressure Treatment Trial (ROCKET 4)]: 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

6.3.1. Study Design

This was a double-masked, randomized, multicenter, active-controlled, parallel-group, 6-month study to assess the ocular hypotensive efficacy and the safety of netarsudil ophthalmic solution 0.02% QPM, OU compared to timolol maleate ophthalmic solution 0.5% BID, OU in adult subjects with elevated IOP. Prior to enrollment, subjects had a Screening Visit and 2 qualification visits to allow for washout of ocular hypotensive medication if needed. Subjects who met the eligibility criteria were randomized in a 1:1 ratio to receive netarsudil or timolol. Subjects were instructed to self-administer their masked medication OU BID, in the morning and evening, for 180 days. For subjects in the netarsudil group, the masked morning dose was placebo and the masked evening dose was netarsudil to maintain masking of the assigned treatment. 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), Day 90 (Month 3), Month 4 (Day 120), Month 5 (Day 150), and Month 6 (Day 180). A visit variation of ± 3 days was allowed for the Day 15 through Month 5 visits and ± 7 days was allowed for the Month 6 visit according to the protocol. Planned enrollment was approximately 700 subjects (350 per treatment group) at approximately 60 sites in the US. Efficacy was evaluated at all study visits by IOP measurements at 08:00, 10:00, and 16:00 hours. IOP measurements collected after Month 3 were used as safety assessments. The primary safety measures were gonioscopy and pachymetry (at screening), visual acuity, pupil size, visual field testing, biomicroscopic and dilated ophthalmoscopic examination, ocular tolerability as judged by a comfort test, ocular symptoms, and adverse events (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 conducted according to the protocol.

Description and schedule of visits and procedures
Subjects were randomized to receive the investigational product (netarsudil 0.02% QPM and placebo QAM in order to maintain masking) or the comparator (timolol maleate ophthalmic solution 0.5% BID). All treatments were OU. Doses were self-administered by the study subjects.

Inclusion criteria
Inclusion criteria was similar to Study AR-13324:CS301 except for different IOP criteria and no pediatric patients. For Study CS304 IOP criteria was: un-medicated (post-washout) IOP > 20 mmHg and < 30 mmHg in one or both eyes at 2 qualification visits at 08:00 hour, 2-7 days apart. At the second qualification visit, have IOP > 17 mmHg and < 30 mmHg in one or both eyes at

10:00 and 16:00 hours. If only one eye qualified at the second qualification visit, that eye would have to be the same as the eye that qualified at the first qualification visit

For CS301 IOP Criteria was un-medicated (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).

Exclusion Criteria was similar to Study AR-13324-CS301.

Identity of Investigational Products

Netarsudil ophthalmic solution 0.02% used in this study is a sterile, isotonic, buffered aqueous solution containing netarsudil (0.02%), boric acid, mannitol, Water for Injection, and preserved with benzalkonium chloride (0.015%). The product formulation is adjusted to approximately pH 5. Lot Numbers 228501 and 242811 were used during the 6-month study. Netarsudil placebo was an identical formulation, but lacking the active ingredient, netarsudil (Lot Number 230271).

Timolol maleate ophthalmic solution 0.5% was supplied as a commercially-available generic product, presented as a sterile, isotonic, buffered, aqueous solution. Each mL contains 5 mg of timolol (6.8 mg of timolol maleate). Inactive ingredients are monobasic and dibasic sodium phosphate, sodium hydroxide to adjust pH, and Water for Injection. Benzalkonium chloride 0.01% is included as a preservative. Timolol Lot Numbers 229526F, 233643F, 246026F and 261895F were used throughout the study.

Study Schedule

Day (D)/Week (W)/Month (M)	Screening	Qual #1	Qual. #2 D1			Post D1 Treatment Period Assessments											
						W2 (Day 15±3)			W6 (Day 43±3)			M3 (Day 90±3), M4 (Day 120±3), M5 (Day 150±3)			M6 (Day 180±7)		
Visit	1	2	3.0	3.1	3.2	4.0	4.1	4.2	5.0	5.1	5.2	6.0-8.0	6.1- 8.1	6.2-8.2	9.0	9.1	9.2
Hour (XY = XY:00)		08	08	10	16	08	10	16	08	10	16	08	10	16	08	10	16
Informed Consent	X																
Inclusion/Exclusion	X	X	X	X	X												
Washout[1]	X																
Demography	X																
Medical/Ophthalmic History	X	X	X														
Concomitant Medications	X	X	X			X			X			X			X		
HR/BP	X	X	X			X			X			X			X		
Urine Pregnancy Test[2]	X														X		
Clinical Labs (Chem/Hem)	X[3]															X	
Symptoms/AEs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comfort Test[5]						X			X			X			X		
Visual Acuity (ETDRS)	X	X	X			X			X			X			X		
Pupil size			X									M3			X		
IOP	X	X[6]	X[6]	X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X
Biomicroscopy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy[7]/ Pachymetry[8]	G/P																
Visual Field[9]	X											M3			X		
Ophthalmoscopy (dilated)	X													M3			X
Eye-Drop Instillation Evaluation.	X																
Study Dose (Self-admin)						X			X			X			X		
Study Medications Dispensed					X			X			X			X			
Study Medications Collected						X[10]			X[10]			X[10]			X[10]		
Study Completed																	X

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

Reference ID: 4178696

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

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

Visit Requirements: IOP measurements at all visits are to be made within ±½ hour of the protocol-specified times of 08:00, 10:00 and 16:00 hours with the exception of the screening visit.

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

[1] Subjects currently using ocular hypotensive medications must undergo a minimum washout period (Table 1 for details).
[2] Urine pregnancy test for women of childbearing potential is required.
[3] For subjects who are unable or unwilling to have blood drawn for clinical labs at Visit 1 (screening), the blood sample may be drawn at Visit 2 (Qualification Visit #1) so long as the results of the clinical labs are available for that subject prior to Visit 3 (Qualification Visit #2).
[4] Ocular symptoms: Subjects will be queried at each visit "How are you feeling?" and treatment emergent AEs beginning at Visit 4 (Qualification Visit #2) will be documented on the AE form. Additional symptoms reported after screening and before randomization will be documented on the medical history form. AEs will be recorded for every study visit (ie, at 08:00, 10:00, and 16:00 hours) as needed.
[5] Comfort test: At 08:00 hour for study drug visits, subjects will be queried "Did you experience any discomfort when placing the drops in your eyes?"
[6] Individuals returning at an unscheduled visit within 1 week are required to only remeasure IOP in both eyes (Section 6.2.3 to Section 6.2.6).
[7] Gonioscopy evaluation up to 3 months prior to randomization is acceptable.
[8] Pachymetry within one week of Screening is acceptable.
[9] Entry visual field evaluation up to 3 months prior to randomization is acceptable. Visual field collection must meet the requirement for automated threshold visual field assessment (eg, 30-2 or 24-2 Humphrey) and reliability.
[10] Collect used kit(s) dispensed during the previous visit.

Reference ID: 4178696

List of Investigators

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
401	David L. Wirta, MD Eye Research Foundation 520 Superior Avenue, Suite 235 Newport Beach, CA 92663	PI	31
402	Jason Bacharach, MD North Bay Eye Associates, Inc. 104 Lynch Creek Way, Suite 15 Petaluma, CA 94954	PI	20
403	Robert Benza, MD Apex Eye 7850 Camargo Rd. Cincinnati, OH 45243	PI	18
404	Sherif M. El-Harazi, MD Lugene Eye Institute 1510 South Central Avenue, Suite 300 Glendale, CA 91204	PI	44
405	Bradley Kwapiszeski, MD Heart of America Eye Care 8901 W. 74th Street, Suite 285/281 Shawnee Mission, KS 66204	PI	21
406	Jeffrey Raymond Lozier, MD Arch Health Partners 15611 Pomerado Road, 4th Floor Poway, CA 92064	PI	11
407	James H. Peace, MD United Medical Research Institute 431-433 North Prairie Avenue Inglewood, CA 90301	PI	20
408	Kenneth Sall, MD Sall Research Medical Center 11423 187th Street, Suite 200 Artesia, CA 90701	PI	49
409	Elizabeth Sharpe, MD Glaucoma Consultants and Center for Eye Research PA 721 Long Point Rd., Suite 407 Mt. Pleasant, SC 29464	PI	12

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
410	Robert John Smyth-Medina, MD North Valley Eye Medical Group, Inc. 11550 Indian Hills Road, Suite 341 Mission Hills, CA 91345	PI	23
411	Thomas Richard Walters, MD Texan Eye, PA/Keystone Research, Ltd. 5717 Balcones Drive Austin, TX 78731-4203	PI	32
412	Leonard Robert Cacioppo, MD Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL 34613	PI	12
414	Gregory M. Sulkowski, MD Taustine Eye Center 1169 Eastern Parkway, Suite 3427 Louisville, KY 40217	PI	6
415	Julie Tsai, MD 343 West Houston Street, Suite 109 San Antonio, TX 78205	PI	14
416	Christopher Lin, MD Shasta Eye Medical Group, Inc. 3190 Churn Creek Road Redding, CA 96002	PI	14
417	Henry McQuirter, OD Eye Specialty Group 825 Ridge Lake Blvd. Memphis, TN 38120	PI	37
418	Michael Tepedino, MD Cornerstone Eye Care 1400 E. Hartley Drive High Point, NC 27262	PI	36
419	Douglas G. Day, MD Coastal Research Associates, LLC 11205 Alpharetta Highway, Suite J3 Roswell, GA 30076	PI	31
420	Andrew Gardner Logan, MD Andrew Gardner Logan dba Logan Ophthalmic Research, LLC 7401 N. University Drive, Suite #201 Tamarac, FL 33321	PI	19
421	Richard Sturm, MD Ophthalmic Consultants of Long Island 360 Merrick Road, 3rd Floor Lynbrook, NY 11563	PI	5

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
422	Michael S. Korenfeld, MD Comprehensive Eye Care, Ltd. 901 East Third Street Washington, MO 63090	PI	11
425	Thomas K. Mundorf, MD Mundorf Eye Center 1718 E. Fourth Street, Suite 703 Charlotte, NC 28204	PI	8
426	Philip Lee Shettle, DO Shettle Eye Research, Inc. 13113 66th Street N. Largo, FL 33773	PI	20
428	Eugene E. Protzko, MD Seidenberg Protzko Eye Associates 2023 Pulaski Hwy. Havre de Grace, MD 21078	PI	17
429	Robert Ritch, MD New York Eye and Ear Infirmary 310 E. 14th St., Suite 304 New York, NY 10003	PI	4
430	Stacy R. Smith, MD Stacy R. Smith, MD, PC 1548 East 4500 South, Suite 105 Salt Lake City, UT 84117	PI	6
432	Carl B. Tubbs, MD Glaucoma Consultants of Colorado DBA Insight Vision Group 11960 Lioness Way, Suite 190 Parker, CO 80134	PI	10
433	James D. Sutton, MD Mississippi Eye Associates 3631 Bienville Blvd. Ocean Springs, MS 39564	PI	9
434	Robert C. Sorenson, MD, PhD Inland Eye Specialists 3953 West Stetson Avenue Hemet, CA 92545	PI	3
435	Robert F. Haverly, MD Laser Eye Surgery of Erie 311 West 24th Street, Suite 401 Erie, PA 16502	PI	11
436	John W. Boyle IV, MD Gulf South Eye Associates 4224 Houma Blvd., Suite 100 Metairie, LA 70006	PI	3

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
438	David B. Tukel, MD Tukel-Kozlow Eye Center 1922 Monroe Street Dearborn, MI 48124	PI	6
439	Max Kim, MD Arizona Glaucoma Specialists 20940 North Tatum Blvd, Suite 250 Phoenix, AZ 85050	PI	2
440	Pankajkumar G. Shah, MD DCT-Shah Research, LLC dba Discovery Clinical Trials 1506 E. Griffin Parkway Mission, TX 78572	PI	21
441	Samuel Eric Seltzer, MD Carolinas Centers for Sight, PC 400 North Cashua Drive Florence, SC 29501	PI	4
443	Valerie A. Colborn, OD Colborn Eye Care 315 Pine State Street Lillington, NC 27546	PI	5
444	Lydia Lane, MD Little Rock Eye Clinic, LLP 201 Executive Court, Suite A Little Rock, AR 72205	PI	4
445	David T. Douglass, OD Eye Center Northeast 955 Broadway Bangor, ME 04401	PI	19
446	Richard J. Ou, MD Houston Eye Associates 915 Gessner #250 Professional Bldg. 3 Houston, TX 77024	PI	8
447	Barry A. Schechter, MD Florida Eye Microsurgical Institute, Inc. 1717 Woolbright Rd. Boynton Beach, FL 33426	PI	5
448	David G. Shulman, MD David G. Shulman, MD, PA 999 East Basse Road, Suite 127, 103 San Antonio, TX 78209	PI	6
449	Gregory J. Panzo, MD Mid Florida Eye Center, PA 17560 US Highway 441 Mount Dora, FL 32757	PI	4

List of Investigators			
Site Number	**Investigator**	**Role**	**No. Subjects Enrolled**
451	Deepta Ghate, MD UNMC-Truhlsen Eye Institute 985540 Nebraska Medical Center (Mailing) 3902 Leavenworth Street (Physical) Omaha, NE 68198-5540	PI	3
452	Albert S. Khouri, MD Rutgers, New Jersey Medical School, IOVS 90 Bergen Street, Suite 6100 Newark, NJ 07103	PI	3
454	Inder Paul Singh, MD The Eye Center of Racine and Kenosha Ltd. 9916 75th Street, Suite 101 Kenosha, WI 53142	PI	4
456	Edward Y. Koo, MD Peninsula Ophthalmology Group 1720 El Camino Real, #225 Burlingame, CA 94010	PI	5
457	Barry Katzman, MD West Coast Eye Care Associates 6945 El Cajon Blvd. San Diego, CA 92115	PI	14
458	Kenneth Olander, MD, PhD University Eye Specialists 622 Smithview Drive Maryville, TN 37803	PI	8
459	Jose F. Cardona, MD Indago Research and Health Center, Inc. 3700 W 12th Ave, Suite 300 Hialeah, FL 33012	PI	15
460	Stephen E. Smith, MD Eye Associates of Fort Myers 4225 Evans Avenue Fort Myers, FL 33901	PI	5
462	Carl Hartman, MD Southern California Eye Physicians and Associates 3300 E. South St. Suites 100, 105 Long Beach, CA 90805	PI	7
463	Michelle Butler, MD Glaucoma Associates of Texas 10740 N. Central Expy Ste. 300 Dallas, TX 75231	PI	3

Study Endpoints

Primary Efficacy Endpoint:

- The primary efficacy endpoint is the mean IOP at the following time points: 08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits (The primary efficacy population, as defined in the SAP, was the PP population with maximum baseline IOP of <25 mmHg).

Secondary Efficacy Endpoints:

- Mean IOP at the following time points: 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) Visits in subjects entering the trial with maximum baseline IOP < 26 mmHg and < 27 mmHg (08:00, 10:00, and 16:00 hours) in the study eye, and in all subjects regardless of study eye IOP
- Additionally, the following endpoints were summarized for both populations of subjects (i.e., including 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 IOP and change from baseline diurnal IOP at each post-treatment visit
    - Sub-group analyses based upon pre-study characteristics such as demographics, un-medicated baseline IOP, and pre-study ocular hypotensive medications

Statistical Analysis Plan

Primary Efficacy Endpoint Analysis Methods

The primary analysis of the primary outcome will be completed using individual two-sample 95% t-distribution confidence intervals for each comparison at each time point (08:00, 10:00, and 16:00 at the Week 2, Week 6, and Month 3 Visits) using the per protocol population. If the upper limits of the 95% confidence intervals are < 1.5 mmHg at all time points and <1.0 mmHg at a majority of time points (at least 5 of 9), then the null hypothesis will be rejected in favor of the alternative hypothesis and netarsudil ophthalmic solution 0.02% will be considered to be clinically non-inferior to timolol maleate ophthalmic solution 0.5%. Results will be presented in both tabular and graphical form. Analyses will be performed primarily on the PP population using on observed data only (without imputation) and secondarily using: LOCF where LOCF will be performed using time-relevant measures; baseline observation carried forward (BOCF) using time-relevant measures; and using multiple imputation methods to determine the robustness of results. Additionally, the above analyses will be repeated on the ITT population to determine robustness of results.

Secondary analyses of the primary endpoint will employ a linear model with IOP at the given visit and time point as the response, baseline IOP as a covariate, and treatment as a main effect factor, using the per protocol population. Baseline IOP is defined as the last non-missing measure at the corresponding time point prior to treatment. The least squares mean differences between netarsudil and timolol will be presented as well as the 95% confidence interval. Two-sample t-tests, between netarsudil and timolol, on the change from baseline IOP at each time

point and visit, including 95% t-distribution confidence intervals on the difference (netarsudil – timolol) also will be conducted. Similar analyses will be completed on the secondary endpoints: change from baseline IOP measures at each time point and visit, mean diurnal IOP and change from baseline diurnal IOP measures. Note that the linear model analysis including baseline IOP as a covariate will only be completed for the IOP values at the given visit and time point and will not be presented for change from baseline.

Interim analyses
When all patients have completed three months of treatment, the Sponsor will unmask the study to analyze the 3-month efficacy and safety data. This is the time for primary analysis of the study. Efforts will be made to keep the investigators masked as to individual patient assignments as the patients continue to be evaluated for safety for the following 6 months. The Sponsor may conduct additional analyses, primarily for safety, as patients complete the 6-month visit.

Analysis Populations

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

Protocol Amendments

No protocol amendments.

6.3.2. **Study Results**

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Financial Disclosure

See Financial Disclosure template in Section 13.2.

Patient Disposition

Study AR-13324-CS304

Population	Netarsudil 0.02%	Timolol 0.5%
Safety	351	357
Intent to Treat (ITT)	351	357
Per Protocol (PP)	306	316

Study AR-13324-CS304: Subject Disposition (ITT Population)

Number of Randomized Subjects	Netarsudil 0.02% N=351	Timolol 0.5% N=357
Study Completion		
Completed	243 (69%)	314 (88%)
Discontinued	108 (31%)	43 (12%)
Reason for Subject Discontinuation		
Adverse Event	68 (19%)	4 (31%)
Withdrawal of Consent	12 (3%)	2 (15%)
Non-compliant	1	1 (8%)
Lost to Follow-up	1	1 (8%)
Lack of Efficacy	12 (3%)	0
Disallowed concurrent Medication	1 (0.3%)	3 (1%)
Investigator Decision	2 (1%)	4(1%)
Protocol Violation	5 (1%)	4 (1%)
Death	1 (0.3%)	0
Other	5 (1%)	2 (1%)

Protocol Violations/Deviations

There were 18 protocol violations. Major deviations were reported for 178 subjects.

Table of Demographic Characteristics

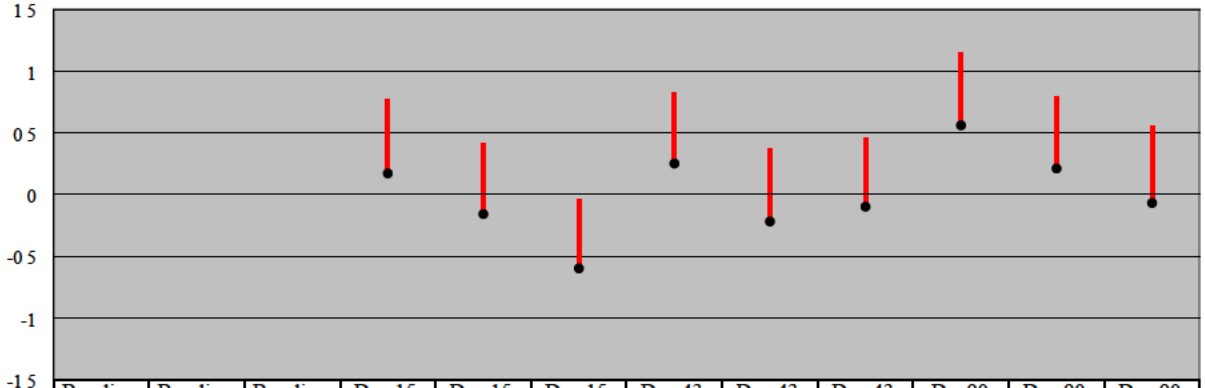
Characteristic	**Netarsudil 0.02% QD N=351**	**Timolol 0.5% BID N=357**
Study eye diagnosis		
POAG	223 (64%)	244 (68%)
OHT	128 (36%)	113 (32%)
Sex		
Male	143 (41%)	120 (34%)
Female	208 (59%)	237 (66%)
Age (years)		
Mean	64.1	64.5
Range	8, 89	29, 91
Race		
Native Hawaiian or Other Pacific Islander	0	1 (0.3%)
Asian	7 (2%)	6 (2%)
Black or African- American	84 (24%)	75 (21%)
Native American	0	0
White	259 (74%)	274 (77%)
Other	1 (0.3%)	0
Ethnicity		
Hispanic or Latino	89 (25%)	87 (24%)
Not Hispanic or Latino	262 (75%)	270 (76%)
Iris color of study eye		
Blue/Grey/Green	74 (21%)	90 (25%)
Brown	241 (69%)	227 (64%)
Hazel	36 (10%)	40 (11%)
Other	1 (0.4%)	0

Efficacy Results – Primary Endpoint

Study AR-13324-CS304: Study Eye Mean IOP (mmHg) By Visit (PP Population With Observed Data-Baseline IOP<25)

Day and Time	Mean IOP Netarsudil 0.02% QD	Mean IOP Timolol 0.5% BID	Mean Difference	95% CI
Baseline				
08:00	22.40 N=186	22.44 N=186		
10:00	21.06 N=186	21.27 N=186		
16:00	20.69 N=186	20.69 N=186		
Day 15				
08:00	17.68 N=184	17.51 N=183	0.17	(-0.43, 0.77)
10:00	16.55 N=181	16.71 N=183	-0.16	(-0.73, 0.41)
16:00	16.32 N=181	16.92 N=183	-0.60	(-1.16, -0.04)
Day 43				
08:00	17.84 N=177	17.60 N=183	0.25	(-0.34, 0.83)
10:00	16.75 N=177	16.98 N=182	-0.22	(-0.82, 0.37)
16:00	16.57 N=176	16.67 N=182	-0.10	(-0.66, 0.46)
Day 90				
08:00	17.86 N=167	17.29 N=179	0.56	(-0.02, 1.15)
10:00	16.90 N=16	16.69 N=179	0.21	(-0.37, 0.79)
16:00	16.73 N=165	16.80 N=179	-0.07	(-0.68, 0.55)

Study AR-13324-CS304: Mean IOP - PP Population (Baseline IOP<25)

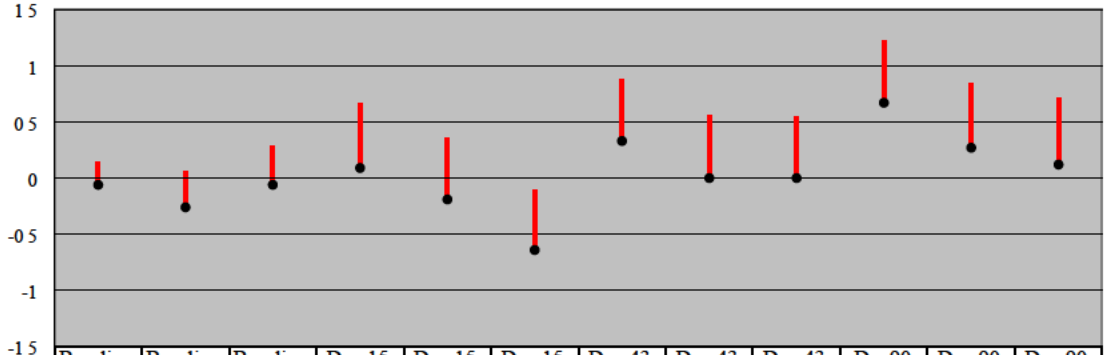


	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI				-0.43	-0.73	-1.16	-0.34	-0.82	-0.66	-0.02	-0.37	-0.68
Upper CI				0.77	0.41	-0.04	0.83	0.37	0.46	1.15	0.79	0.55
Mean Difference				0.17	-0.16	-0.6	0.25	-0.22	-0.1	0.56	0.21	-0.07

Study AR-13324-CS304: Study Eye Mean IOP (mmHg) by Visit (ITT with LOCF Population)

Day and Time	Mean IOP Netarsudil 0.02% QD N=214	Mean IOP Timolol 0.5% BID N=209	Mean Difference Between netarsudil and Timolol	95% CI
Baseline (Visit 3)				
08:00	22.37	22.44	-0.06	(-0.27, 0.14)
10:00	21.02	21.28	-0.26	(-0.59, 0.06)
16:00	20.61	20.67	-0.06	(-0.42, 0.29)
Day 15				
08:00	17.58	17.49	0.09	(-0.47, 0.66)
10:00	16.49	16.68	-0.19	(-0.74, 0.36)
16:00	16.22	16.86	-0.64	(-1.17, -0.11)
Day 43				
08:00	17.82	17.49	0.33	(-0.21, 0.88)
10:00	16.84	16.84	0	(-0.57, 0.56)
16:00	16.62	16.62	0	(-0.55, 0.55)
Day 90				
08:00	17.94	17.28	0.67	(0.11, 1.22)
10:00	16.93	16.66	0.27	(-0.29, 0.84)
16:00	16.86	16.73	0.12	(-0.46, 0.71)

Study AR-13324-CS304: Mean IOP - ITT with LOCF Population (Baseline IOP<25)



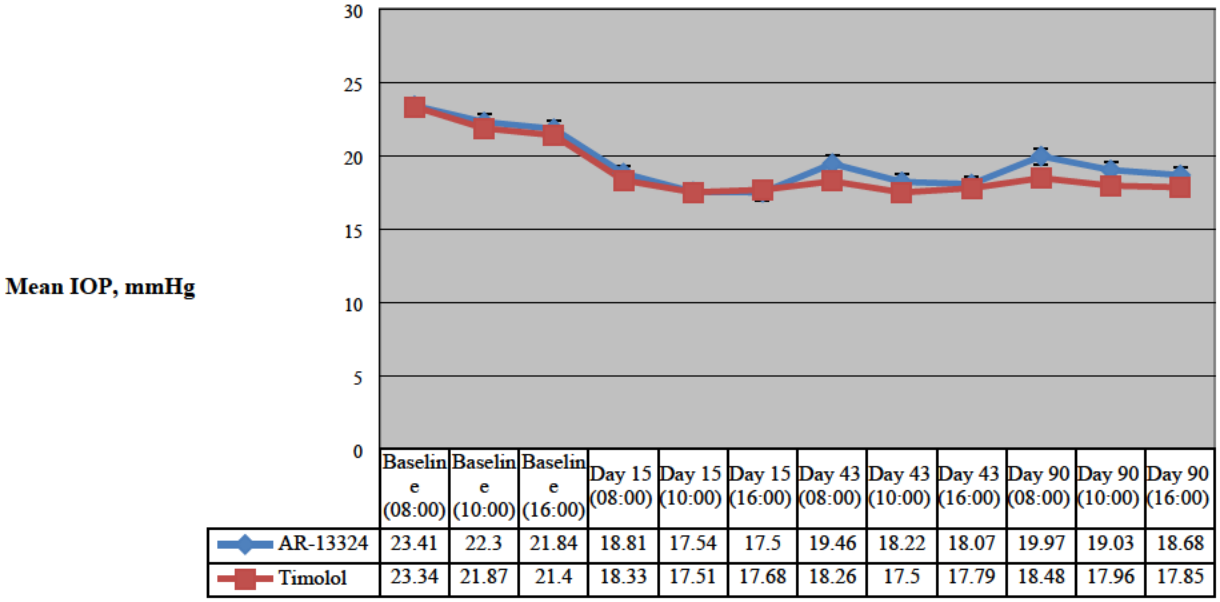
	Baseline (08:00)	Baseline (10:00)	Baseline (16:00)	Day 15 (08:00)	Day 15 (10:00)	Day 15 (16:00)	Day 43 (08:00)	Day 43 (10:00)	Day 43 (16:00)	Day90 (08:00)	Day 90 (10:00)	Day 90 (16:00)
Lower CI	-0.27	-0.59	-0.42	-0.47	-0.74	-1.17	-0.21	-0.57	-0.55	0.11	-0.29	-0.46
Upper CI	0.14	0.06	0.29	0.66	0.36	-0.11	0.88	0.56	0.55	1.22	0.84	0.71
Mean Difference	-0.06	-0.26	-0.06	0.09	-0.19	-0.64	0.33	0	0	0.67	0.27	0.12

Reviewer's Comment:

Netarsudil demonstrated non-inferiority to timolol in both the PP and ITT population with maximum baseline IOP < 25 mmHg. This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

Study AR-13324-CS304: 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-CS304: Brief Summary of Results of Non-inferiority Analysis of Netarsudil to Timolol Including All Baseline IOP

Analysis Population	Imputation	Was Netarsudil QD Non-Inferior to Timolol BID?
PP	None	Yes
	LOCF	No
	MCMC	No
ITT	None	Yes
	LOCF	No
	MCMC	No

Reviewer's Comment:

Netarsudil ophthalmic solution 0.02% met the pre-specified criteria for non-inferiority to timolol maleate ophthalmic solution 0.5% in the pre-specified secondary efficacy population of subjects with maximum baseline IOP <30 mmHg in the PP with observed data only but this was not reproduced in the ITT with LOCF Population.

7 INTEGRATED REVIEW OF EFFECTIVENESS

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

IOP is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint for Studies 301, 302, and 304 were similar except for the baseline IOP of the patients. The primary endpoint was mean IOP measured at multiple time points.

Study 301 failed in its primary endpoint and netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. It did, however, demonstrate that netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post hoc analysis. Netarsudil did have an IOP lowering effect at baseline IOPs ≥ 25, but was not statistically non-inferior to timolol when including these patients.

Study 302 achieved success in its primary endpoint and demonstrated that netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg. Netarsudil did have an IOP lowering effect at baseline IOPs ≥ 25, but was not statistically non-inferior to timolol when including these patients.

Study 304 achieved success in its primary endpoint and demonstrated that netarsudil was non-inferior to timolol in patients with a baseline IOP < 30 mmHg in the PP population, but this result was not replicated in the ITT population. In a secondary endpoint analysis, noninferiority of netarsudil to timolol was demonstrated in baseline IOP < 25 mmHg in both PP and ITT populations.

Summary of Efficacy Results (From Statistical Review)

Table 7.1.1-1 below taken from the statistical review shows in which studies the non-inferiority of netarsudil to timolol in mean IOP at the required time points was demonstrated.

Table 7.1.1 Summary Efficacy Results

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

7.1.2. Secondary and Other Endpoints

None.

7.1.3. Subpopulations

The following subgroups were analyzed: iris color, age (<65 years and >65 years), gender, and race. There were no notable differences in either study in any of the subgroups analyzed.

7.1.4. Dose and Dose-Response

In Study 302, two doses of netarsudil were studied (QD and BID dosing). (b) (4)

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Intraocular pressure was measured at three time points (8AM, 12PM, and 4PM) at Baseline, Week 3, Week 6, and Month 3 in Studies 301, 302, and 304. The mean IOP reduction for each of the time points 8AM, 12PM, and 4PM over the three month evaluation period were similar for patients with baseline IOP < 25 mmHg.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No potential efficacy issues in the post-market setting have been identified.

7.2.2. Other Relevant Benefits

There are no other relevant benefits for this drug product.

7.3. Integrated Assessment of Effectiveness

The data contained in this submission establishes the efficacy of netarsudil ophthalmic solution 0.02% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

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8 REVIEW OF SAFETY

8.1. Safety Review Approach

The support for safety is from 3 clinical studies (Studies AR-13324-CS301, AR-13324-CS302, and AR-13324-CS304).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

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

Study AR-13324-CS304: Exposure to Study Medication by Treatment Group (Safety Population)

	Netarsudil 0.02% QD N=351	**Timolol 0.5% BID N=357**
Days of Exposure		
Mean (sd)	147.4	167.7
Minimum	1	2
Maximum	1197	197

8.2.2. Relevant characteristics of the safety population:

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

8.2.3. Adequacy of the safety database:

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

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

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

8.3.2. Categorization of Adverse Events

Adverse events were categorized as ophthalmic and systemic.

8.3.3. Routine Clinical Tests

Routine ophthalmic examination assessments were conducted on all subjects including visual acuity assessments, manifest refractions, specular microscopy (a subset of subjects), slit lamp examination, and dilated fundus examinations. Routine physical examinations were not conducted. Clinical laboratory tests (Chem 7 and hematology) were performed at the beginning and end of the trials. Heart rate and blood pressure were checked at the beginning and end of the trials.

8.4. Safety Results

8.4.1. 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-CS304: One subject in the netarsudil QD group died during the study secondary to cardiac arrest.

8.4.2. Serious Adverse Events

Study AR-13324-CS301: Serious Treatment Emergent AEs

Subject Number/Treatment Group	Outcome	SAE
108-016 Timolol	Recovered/Resolved	Worsening of adenomyosis
112-010 Timolol	Both events resolved/resolved	CHF Left upper extremity numbness
116-009 Timolol	Not recovered/resolved	CVA
123-011 Rhopressa	Not recovered/resolved	Prostate CA
128-002 Rhopressa	Recovered/Resolved	Exacerbation of CAD
128-003 Rhopressa	Recovered/Resolved	HTN
135-001 Rhopressa	Both events recovered/Resolved	Pneumonia Acute respiratory failure

Study AR-13324-CS302: Serious Treatment Emergent AEs

Subject Number/Treatment Group	Outcome	SAE
202-003 Timolol	Both events recovered/resolved with sequelae	Peripheral artery occlusion Fall
204-041 Timolol	Recovered/Resolved	Renal failure
206-022 Rhopressa QD	Both events recovered/ resolved with sequelae	Cholelithiasis Exacerbation of CAD
209-002 Rhopressa QD	Recovered/Resolved	Myelodysplastic syndrome
209-002 Rhopressa BID	Recovered/Resolved	MI
211-004 Rhopressa QD	Recovered/Resolved with sequelae	Breast CA
212-006 Rhopressa BID	Both events recovered/resolved	Pneumonia Pulmonary embolism
212-016 Rhopressa QD	Recovered/Resolved	Broken foot Acute renal failure
213-003 Timolol	Recovered/Resolved	Worsening of CAD
216-001 Rhopressa BID	Recovered/Resolved	Worsening of cataract
217-021 Timolol	Fatal	MI
217-026 Rhopressa QD	Recovered/Resolved with sequelae	CAD
218-021	Recovered/Resolved	Perforated gastric ulcer

Rhopressa BID		
222-010 Timolol	Recovered/Resolved	Worsening of arthritis
226-012 Rhopressa BID	Recovered/Resolved	MI
227-015 Timolol	Recovered/Resolved	CVA Atrial fibrillation
228-005 Timolol	Recovered/Resolved with sequelae	Back pain
228-006 Rhopressa BID	Recovered/Resolved	Bacterial peritonitis UTI
230-014 Rhopressa QD	Recovered/Resolved	Angioedema
231-006 Rhopressa BID	Recovered/Resolved	Carotid artery stenosis
234-019 Rhopressa QD	Recovered/Resolved	Internal bleeding secondary to motor vehicle accident
238-001 Timolol	Recovered/Resolved	Melanoma
239-003 Timolol	All events recovered/resolved	Pulmonary artery stenosis Atrial flutter Bradycardia Fluid overload
244-001 Rhopressa BID	Recovered/Resolved	Ligament rupture
246-005 Timolol	Recovered/Resolved with sequelae	Embolic stroke
248-030 Timolol	Recovered/Resolved	Prostate CA
250-005 Rhopressa QD	Recovered/Resolved	Abdominal pain
251-010 Rhopressa QD	Recovered/Resolved	Epistaxis
251-044 Timolol	Recovered/Resolved	Cellulitis
254-008 Timolol	Recovered/Resolved	Post-operative ileus
258-002 Timolol	Fatal	MI
262-016 Rhopressa BID	Recovered/Resolved	Cholecystitis
262-020 Timolol	Recovered/Resolved	HTN
262-027 Rhopressa BID	Recovered/Resolved	Hip fracture
262-045 Rhopressa BID	Both events recovered/resolved	Worsening of PSA Synovial cyst
263-011 Timolol	Recovered/Resolved	Atrial fibrillation

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

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 (94%)
Discontinued	31 (15%)	13 (6%)
Reason for Subject Discontinuation		
Adverse Event	20 (65%)	4 (31%)
Withdrawal of Consent	3 (10%)	2 (15%)
Non-compliant	0	1 (8%)
Lost to Follow-up	0	1 (8%)
Lack of Efficacy	3 (10%)	0
Investigator Decision	2 (7%)	0
Protocol Violation	3 (10%)	5 (39%)

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 (61%)	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 (67%)	132 (79%)	15 (32%)
Withdrawal of Consent	9 (9%)	13 (8%)	9 (19%)
Non-compliant	3 (3%)	1 (1%)	3 (6%)
Lost to Follow-up	1 (1%)	3 (2%)	0
Lack of Efficacy	10 (10%)	4 (2%)	2 (4%)
Disallowed Concurrent Medication	2 (2%)	2 (1%)	5 (11%)
Investigator Decision	1 (1%)	2 (1%)	2 (4%)
Protocol Violation	4 (4%)	6 (4%)	10 (21%)
Death	2 (2%)	0	0
Other	2 (2%)	5 (3%)	1 (2%)

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Study AR-13324-CS304: Subject Disposition (ITT Population)

Number of Randomized Subjects	**Netarsudil 0.02% N=351**	**Timolol 0.5% N=357**
Study Completion		
Completed	243 (69%)	314 (88%)
Discontinued	108 (31%)	43 (12%)
Reason for Subject Discontinuation		
Adverse Event	68 (19%)	4 (31%)
Withdrawal of Consent	12 (3%)	2 (15%)
Non-compliant	1	1 (8%)
Lost to Follow-up	1	1 (8%)
Lack of Efficacy	12 (3%)	0
Disallowed concurrent Medication	1 (0.3%)	3 (1%)
Investigator Decision	2 (1%)	4(1%)
Protocol Violation	5 (1%)	4 (1%)
Death	1 (0.3%)	0
Other	5 (1%)	2 (1%)

8.4.4. Significant Adverse Events

See Section 8.4.2.

8.4.5.**Treatment Emergent Adverse Events and Adverse Reactions**

	AR-13324 CS301		AR-13324 CS302		
	AR-13324 0.02% QD PM	**Timolol 0.5% BID**	**AR-13324 0.02% QD PM**	**AR-13324 0.02% BID**	**Timolol 0.5% BID**
SOC PT	**(N=203) n (%)**	**(N=208) n (%)**	**(N=251) n (%)**	**(N=253) n (%)**	**(N=251)**
Eye Disorders	136 (67.0)	34 (16.3)	198 (78.9)	215 (85.0)	86 (34.3)
Conjunctival hyperemia	108 (53.2)	17 (8.2)	152 (60.6)	168 (66.4)	35 (13.9)
Cornea verticillata	12 (5.9)	0	64 (25.5)	64 (25.3)	2 (0.8)
Conjunctival hemorrhage	32 (15.8)	2 (1.0)	49 (19.5)	49 (19.4)	2 (0.8)
Erythema of eyelid	12 (5.9)	0	14 (5.6)	12 (4.7)	2 (0.8)
Vision blurred	11 (5.4)	1 (0.5)	27 (10.8)	44 (17.4)	7 (2.8)
Lacrimation increased	8 (3.9)	0	19 (7.6)	25 (9.9)	0
Visual acuity reduced	8 (3.9)	3 (1.4)	22 (8.8)	22 (8.7)	6 (2.4)
Eye pruritus	4 (2.0)	0	14 (5.6)	20 (7.9)	3 (1.2)
Conjunctival edema	4 (2.0)	0	8 (3.2)	19 (7.5)	0
Eye irritation	8 (3.9)	1 (0.5)	11 (4.4)	13 (5.1)	8 (3.2)
Foreign body sensation in eyes	2 (1.0)	1 (0.5)	7 (2.8)	14 (5.5)	1 (0.4)

8.4.6.**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.

Study AR-13324-CS304: There were no notable differences between the treatment groups in the change from baseline to Month 6 for clinical chemistry values or hematology values.

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8.4.7. **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.

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.

Study AR-13324-CS304: At baseline, mean systolic blood pressure was 133.4 and 132.0 mmHg, and mean diastolic blood pressure was 79.5 and 78.3 mmHg for netarsudil and timolol, respectively. Mean changes in both parameters throughout the duration of the study were less than 4 mmHg. At baseline, mean heart rate was 71.4 and 70.4 bpm for subjects in the netarsudil and timolol groups, respectively. Mean changes throughout the duration of the study were less than 1 bpm in the netarsudil group.

Reviewer's Comment:
The changes in vital signs are clinically significant for the timolol control as it is a beta blocker; this amount of drop in heart rate is expected.

8.4.8. **Electrocardiograms (ECGs)**

Not performed.

8.4.9. **QT**

Not applicable.

8.4.10. **Immunogenicity**

Not applicable.

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8.5. Analysis of Submission-Specific Safety Issues

Corneal Verticillata
Corneal verticillata were a common AE in all three studies.

Incidence of Corneal Verticillata

Study	Number of Subjects With Corneal Verticillata in Netarsudil Group	Number of Subjects With Corneal Verticillata in Timolol Group
301	11/203 (5%)	0/208
302	64/251 (26%) in QD group	2/251 (1%)
304	86/351 (25%)	0/357

Because of the corneal findings observed in Studies AR-13324-CS301 and AR-13324-CS302 there was an additional study AR-13324-OBS01 conducted to further study the corneal changes.

8.6. Safety Analyses by Demographic Subgroups

None.

8.7. Specific Safety Studies/Clinical Trials

On 6/23/17, the 4-month safety update was submitted. This submission included the CSR for Study AR-13324-OBS01.

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 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

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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 3 different subgroups:

- Group 1: Subjects who developed corneal verticillata who were currently enrolled and continuing in clinical study AR-13324-CS302
- Group 2: Subjects who developed corneal verticillata who had completed clinical study AR-13324-CS301 or AR-13324-CS302
- Group 3: 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.

The Last Patient/Last Visit for AR-13324-CS302 study occurred on 3/17/16, which was prior to the finalization and IRB approval of the protocol for AR-13324-OBS01. Therefore, there were no subjects enrolled in Group 1. In addition, all corneal verticillata cases reported in AR-13324-CS301 were resolved by the time AR-13324-OBS01 was initiated. Hence, no subjects from AR-13324-CS301 were enrolled. This CSR only includes the analysis and discussion of Group 2 and Group 3 with AR-13324-CS302 subjects. Subjects in Groups 2 and 3 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.

This observational study had no set duration. The Sponsor's expectation was that subjects consented would participate until resolution or stabilization of corneal verticillata. 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-CS301 or 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-CS301 or 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-CS301 or 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.

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Treatment

This was a non-interventional observational study. Subjects were not treated with any investigational products during this observational study. They were allowed, however, to 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 subjects from AR-13324-CS302 were used for the analysis.

Efficacy Measurements

There were no efficacy measurements in this observational study.

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

All subjects who entered the study underwent ETDRS visual acuity assessment and corneal verticillata grading. Subjects who were noted to have corneal verticillata at study entry had additional visual function assessments namely, VF-14 Questionnaire and Pelli-Robson CS Testing.

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.

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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

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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 to Grade 4(see above - Corneal Verticillata Grading (Orlando 1984)). 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.

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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

Study AR-13324-OBS01: Baseline Characteristics of Corneal Verticillata

	Netarsudil 0.02% QD N=25	**Netarsudil 0.02% BID N=20**
Have Corneal Verticillata at Study Entry		
OD only	0	0
OS only	0	0
OU	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

Of the 3 subjects (4 eyes) that completed the study with unresolved but stabilized corneal verticillata, 2 of the 3 were using a concomitant medication known to induce corneal epithelial changes. Subject 226-006 was using Advil and had unresolved corneal verticillata OS. Subject 263-002 was using naproxen and had unresolved corneal verticillata OU.

Study AR-13324-OBS01: Mean and Mean Change from Visit 2 in Visual Acuity Scores (logMAR), by Treatment Group and Corneal Verticillata Status

	Netarsudil 0.02% QD N=25		**Netarsudil 0.02% BID N=20**	
	Value	**Change From Baseline***	**Value**	**Change From Baseline***
Visit 2				
N (Eyes)	28	28	8	8
Mean	0.084	0.018	-0.38	-0.033
Range	-0.20, 0.32	-0.20, 0.20	-0.20, 0.10	-0.14, 0.08
Final Visit: After Resolution/Stabilization of Corneal Verticillata				
N (Eyes)	24	24	8	8
Mean	0.020	-0.038	0.003	0.008
Range	-0.26, 0.32	-0.26, 0.22	-0.18, 0.16	-0.10, 0.10
Change From V2 to Final Visit				
N (Eyes)	24		8	
Mean	-0.063		0.040	
Range	-0.30, 0.14		-0.04, 0.12	

* Baseline is defined as the last non-missing measurement taken prior to the first dose of study medication in study AR-13324-CS302.

Reviewer's Comment:

At the Final Visit, mean and median change from baseline BCVA was -0.026 and -0.020, respectively, for all subjects evaluated. Similarly, in this follow-up observational study, mean and median change from Visit 2 BCVA was -0.037 and -0.030, respectively, for 32 eyes at their Final Visit. Therefore, resolution of corneal verticillata was not associated with a clinically meaningful impact in visual acuity.

The mean change and median change in BCVA at Visit 2 (verticillata present) relative to the AR-13324-CS302 baseline (verticillata absent) was 0.007 and 0.000, respectively, similarly indicating that the presence of corneal verticillata was not associated with a clinically meaningful change in visual acuity in this observational study.

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

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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 was 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 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.

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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

Study AR-13324-OBS01: Narratives of Three Patients Whose Corneal Verticillata Did Not Resolve

Subject	Narrative
226-006	53-year old WM was enrolled in Group 2 as he completed the previous study (AR-13324-CS302). The OS eye was the study eye in the previous study. The treatment duration in the previous study was 357 days, and the subject participated in this study for 306 days. The duration of therapy prior to the start of corneal verticillata was 185 days (185 doses) in the previous study. The subject was enrolled in this study with grade 1 corneal verticillata OD and grade 2 corneal verticillata OS. The OD corneal verticillata resolved at Visit 7 and remained at grade 0 upon study completion at Visit 8. The OS corneal verticillata remained unresolved at grade 1 upon study completion Visit 8. Change from baseline VA after resolution/stabilization was -0.12 OD and -0.02 OS. The subject's ocular medical history included corneal whorls OU. Concomitant medications included Advil, Tylenol, aspirin, multivitamins, and Ocuvite. This subject used concomitant medication (Advil).
263-001	80-year old WF was enrolled in Group 2 when she completed the previous study (AR-13324-CS302). The OS was the study eye in the previous study. The treatment duration in the previous study was 364 days, and the subject participated in this study for 303 days. The duration of therapy prior to the start of corneal verticillata was 43 days (43 doses) in the previous study. The subject was enrolled in this study with grade 2 corneal verticillata OD and grade 1 corneal verticillata OS. The OS corneal verticillata resolved at Visit 6 and remained at grade 0 upon study completion at Visit 8. The OD corneal verticillata remained unresolved at grade 1 upon study completion at Visit 8. Change from baseline (AR-13324-CS302) VA after resolution/stabilization was 0.00 OD and 0.22 OS; there was no change in VA from this

Subject	Narrative
	study's Initial Visit to Final Visit. This subject's maximum visual acuity decrease OS was 0.42 (Visit 7) in the AR-13324-CS302 clinical study with mild verticillata (corneal whorls); in this observational study, change from baseline (AR-13324-CS302) VA was 0.22 with the same verticillata level. Therefore, the visual acuity decrease was probably caused by other factors, not the corneal verticillata. The subject's ocular medical history included corneal whorls OU. Non-ocular medical history included basal cell carcinoma. Concomitant medications included Imiquimod 5%, aspirin, MacularProtect Complete AREDS2, Vitamin D3, Refresh Optive Advance, Glucosamine, and Valsartan.
263-002	69-year old WM was enrolled in Group 3 as he was withdrawn from the previous study (AR-13324-CS302). The OS eye was the study eye in the previous study. The treatment duration in the previous study was 124 days, and the subject participated in this study for 285 days. The duration of therapy prior to the start of corneal verticillata was 43 days (86 doses) in the previous study. The subject was enrolled in this study with grade 1 corneal verticillata OD and grade 2 corneal verticillata OS. The subject completed the study with unresolved grade 1 corneal verticillata OU at Visit 7. Change from baseline VA after resolution/stabilization was 0.08 OD and 0.1 OS The subject's ocular medical history included corneal whorls OU. Concomitant medications included fiber, fish oil, lisinopril, naproxen, omeprazole, multivitamins, simvastatin, furosemide, tamulosin, and Cialis. This subject used concomitant medication (naproxen).

Reviewer's Comment:

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. From the completed studies, a total of 47 subjects were enrolled in the 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 complicating factor for corneal verticillata and the two subjects exited the study immediately. Therefore, 45 subjects were included in the analysis reports.

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. Two of the three subjects used concomitant medications (naproxen and Advil). There was no clinically meaningful change in the visual acuity from baseline with presence of corneal verticillata to resolution/stabilization of the corneal verticillata.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

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

8.8.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

8.8.3. **Pediatrics and Assessment of Effects on Growth**

On 8/11/14, a final agreed upon PSP was submitted to the IND 113,064. The proposal was to enroll pediatric subjects into both studies. At the completion of the studies, only two pediatric subjects, 11 and 14 years of age, were enrolled in one Phase 3 trial (AR-13324-CS302). Therefore, the product information will indicate that safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.8.4. **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

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

8.9. Safety in the Postmarket Setting

Not applicable

8.10. Additional Safety Issues From Other Disciplines

None.

8.11. Integrated Assessment of Safety

The safety database contained in this submission establishes the safety of netarsudil ophthalmic solution 0.02% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

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9 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

An Advisory Committee Meeting was held on 10/13/17.

VOTE #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?

YES-10
NO-0
ABSTAIN-0

If no, what additional trials would you recommend? Not applicable.

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

YES-9
NO-1
ABSTAIN-0

If no, what additional trials would you recommend?

DISCUSSION: Please discuss any suggestions you have concerning the proposed draft labeling of the product.

Summary of discussion:

- Recommend adding corneal verticillata to Highlights section
- Using more than once per day will increase side effects
- Put actual percentages for side effects in Section 6.1
- Add peak concentration in Section 12.3
- Add in vivo description for metabolism in Section 12.3

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10 LABELING RECOMMENDATIONS

10.1. Prescribing Information

See labeling recommendations under Section 13.3.

10.2. Patient Labeling

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

10.3. Nonprescription Labeling

Not applicable. This is a prescription NDA.

11 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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

11.1. Safety Issue(s) that Warrant Consideration of a REMS

Not applicable.

11.2. Conditions of Use to Address Safety Issue(s)

Not applicable.

11.3. Recommendations on REMS

Not applicable.

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12 POSTMARKETING REQUIREMENTS AND COMMITMENTS

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

13 APPENDICES

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 37		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 62		
Number of investigators who are Sponsor employees (including both full-time and part-time		

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

Covered Clinical Study (Name and/or Number): 304

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 52		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

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influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. **Prescribing Information**

Following is the applicant's submitted draft labeling with recommended revisions. An initial team labeling meeting was held on Tuesday, November 7, 2017. An additional team labeling meeting will be held on Thursday, November 16, 2017.

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
11/08/2017

WILLIAM M BOYD
11/08/2017

CLINICAL FILING CHECKLIST FOR NDA 208-254

NDA/BLA Number: 208-254 **Applicant: Aerie Pharmaceuticals, Inc.** **Stamp Date: 2/28/17**

Drug Name: Rhopressa **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			See Section 2.7.4
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			See Section 2.7.3
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			This is a 505(b)(1).
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? See Study Number:AR-13321-CS202 Arms: AR-13324 0.01% QD PM (75 patients) AR-13324 0.02% QD PM (72 patients) Latanoprost 0.005% QD PM (77 patients)	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 (AR-13324-CS301): a 3-month efficacy	X			

Reference ID: 4082364

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
	and safety study with 2 treatment arms (netarsudil 0.02% QD [202 randomized]; timolol 0.5% BID [209 randomized]) Pivotal Study #2: (AR-13324-CS302): a 3-month efficacy and 12-month safety study with 3 treatment arms (netarsudil 0.02% QD [251 randomized] and BID [251 randomized]; timolol 0.5% BID [253 randomized])				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			ECC (endothelial cell count) study results have been submitted. There is an ongoing study to evaluation the AE of corneal verticilatta. The interim results will be submitted with the 120 safety update. The acceptability of these results will be a review issue.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The original pediatric study plan (PSP) was submitted to the FDA on 5/30/14, and the revised PSP was accepted by the FDA on 12/2/14. Aerie intended to enroll patient between the ages of 0-2 in their phase 3 trials. No pediatric patients were enrolled in Study CS301 and only 2 were enrolled in study CS302. They are therefore now requesting a full waiver because it is "highly impractical" to enroll pediatric subjects. See 8/30/16 original submission.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

None

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 4082364

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SONAL D WADHWA
04/10/2017

WILLIAM M BOYD
04/10/2017

CLINICAL FILING CHECKLIST FOR NDA 208-254

NDA/BLA Number: 208-254 **Applicant: Aerie Pharmaceuticals, Inc.** **Stamp Date: 8/30/16**

Drug Name: Rhopressa **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505 (b) (1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: AR-13324-CS202 Arms: AR-13324 0.01% QD PM (75 patients) AR-13324 0.02% QD PM (72 patients) Latanoprost 0.005% QD PM (77 patients)	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			

File name: Clinical Filing Checklist for NDA 208-254

Reference ID: 3997203

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 (AR-13324-CS301): a 3-month efficacy and safety study with 2 treatment arms (netarsudil 0.02% QD [202 randomized]; timolol 0.5% BID [209 randomized]) Pivotal Study #2: (AR-13324-CS302): a 3-month efficacy and 12-month safety study with 3 treatment arms (netarsudil 0.02% QD [251 randomized] and BID [251 randomized]; timolol 0.5% BID [253 randomized])				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
	new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			ECC study results have been submitted.
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The original pediatric study plan (PSP) was submitted to the FDA on 5/30/14, and the revised PSP was accepted by the FDA on 12/2/14. Aerie intended to enroll patient between the ages of 0-2 in their phase 3 trials. No pediatric patients were enrolled in Study CS301 and only 2 were enrolled in study CS302. They are therefore now requesting a full waiver because it is "highly impractical" to enroll pediatric subjects.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

Reference ID: 3997203

CLINICAL FILING CHECKLIST FOR NDA 208-254

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

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

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3997203

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/s/

SONAL D WADHWA
10/11/2016

WILLIAM M BOYD
10/11/2016