Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

Briefing Document

Product:	Rhopressa™ (netarsudil ophthalmic solution) 0.02%
NDA Number:	208254
Indication:	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Sponsor:	Aerie Pharmaceuticals, Inc. 2030 Main Street, Suite 1500 Irvine, CA 92614 949-526-8700
Meeting Date:	October 13, 2017

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

EXECUTIVE SUMMARY

The data presented in this briefing document demonstrate that Rhopressa™ (netarsudil ophthalmic solution) 0.02% is safe and effective for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT). The proposed dosage is 1 drop in the affected eye(s) once daily (QD) in the evening (PM).

Background

Glaucoma is a leading cause of irreversible blindness that affects more than 60 million people worldwide (Alward 1998, Casson 2012). Glaucoma can arise through various etiologies but vision loss is ultimately due to the progressive death of retinal ganglion cells and related damage to the optic nerve (Vrabec 2007). OAG is the most common form of glaucoma. OAG is defined as the ocular condition where the anterior chamber angle is open upon gonioscopic observation, there is some evidence of optic nerve damage or dysfunction (eg, visual field loss), and patients frequently exhibit elevated IOP. A second disease condition, OHT, has been identified as one for which patients have an elevated IOP compared to population-based cut-off values in the absence of apparent optic nerve damage (Kass 2002). Currently, the only modifiable risk factor for glaucomatous visual field loss is IOP. The standard of care for treating patients with OAG and OHT is reduction of IOP (Schwartz 2004).

The two primary mechanisms to lower IOP include decreasing the amount of aqueous humor production in the eye and increasing the outflow of aqueous humor from the eye. Aqueous humor flows out of the eye by two independent pathways, one of which is sensitive to eye pressure (trabecular outflow pathway), while the other operates independently of eye pressure (uveoscleral outflow pathway).

In a healthy eye, IOP is maintained within a narrow range through pressure-sensitive regulation of aqueous outflow through the trabecular outflow pathway. In a glaucomatous eye, IOP becomes elevated as a result of an abnormally high resistance to outflow in the trabecular pathway. The causes of increased outflow resistance are not fully understood but it appears to involve an increase in the contractile tone and stiffness of the trabecular meshwork, changes in extracellular matrix deposition and composition, and changes in the permeability of the endothelial cell lining of Schlemm's canal.

Several available classes of ocular hypotensive medications are differentiated by their mechanism of action, including miotics, beta-adrenergic receptor antagonists (beta-blockers), carbonic anhydrase inhibitors (CAIs), alpha-adrenergic receptor agonists (alpha-agonists), and prostaglandin analogues (PGAs). The pharmacodynamic effects of these medications can differ substantially as some affect aqueous humor production (beta-blockers, alpha-agonists, and CAIs) while others affect aqueous humor outflow (miotics, PGAs, and alpha-agonists). No commonly used agent acts primarily to increase outflow via a direct effect on the trabecular outflow pathway, the site of the pathology that causes elevated IOP.

From a clinician's perspective, the currently available treatments for glaucoma have different limitations and risks that must be considered when tailoring the choice of treatment to an

individual patient's needs and preferences. Some therapeutic classes have known systemic adverse effects, for example, beta-adrenergic antagonists (with cardiovascular and respiratory effects such as bradycardia, dyspnea, and wheezing) and alpha-agonists (with CNS effects such as dry mouth, fatigue, sedation, and dizziness). Ocular side effects are common with topical agents and the acceptability of different side effects can vary by patient. With respect to efficacy, the Baltimore Eye Survey of 5308 subjects found that 78% of 10,444 eyes with primary OAG (POAG) had screening IOP of < 25 mmHg (Sommer 1991), indicating the importance of achieving efficacy at these lower IOP levels. A regimen that encourages compliance is also an important consideration. Clinicians and patients would benefit from having an additional therapeutic option for individualizing glaucoma treatment.

Rho kinase (ROCK) inhibitors represent a new class of potential glaucoma medications that lower IOP by directly increasing trabecular outflow. The tissues of the trabecular outflow pathway are avascular and rely on aqueous humor to supply nutrients, growth factors, and antioxidants. The most commonly prescribed glaucoma medications lower IOP by shunting aqueous humor through the uveoscleral pathway or decreasing aqueous production. While these IOP-lowering mechanisms help protect the optic nerve from damage, they may decrease the perfusion of aqueous humor through the trabecular meshwork, which may promote further degradation of the trabecular outflow pathway.

Netarsudil (AR-13324) is a ROCK and norepinephrine transporter (NET) inhibitor discovered and developed by Aerie Pharmaceuticals. Netarsudil was shown to lower IOP in studies in rabbits and monkeys. Based on nonclinical and clinical studies, netarsudil appears to reduce IOP by increasing trabecular outflow facility, reducing episcleral venous pressure (EVP), and decreasing production of aqueous humor. There is no measurable systemic exposure to netarsudil or its primary metabolite following once-daily dosing in humans.

Aerie's clinical development program for netarsudil includes 10 completed clinical studies: 5 Phase 1 or Phase 2 studies, 4 Phase 3 studies, and 1 non-interventional observational study. The Phase 3 studies were active-controlled with timolol as the comparator and had treatment durations of 3 months (CS301), 6 months (CS304), and 12 months (CS302 and CS303). Studies CS301, CS302, and CS304 evaluated efficacy and safety, and CS303 evaluated safety. The observational follow-on study evaluated visual function in subjects who had cornea verticillata or corneal opacity as an ongoing adverse event (AE) when they exited from study CS302. Additional supportive data are available from studies evaluating PG324, a fixed dose combination of netarsudil and latanoprost, which include netarsudil 0.02% monotherapy as a separate treatment arm.

Results of Phase 1 and Phase 2 Studies

The mechanisms of action by which netarsudil lowers IOP were studied in humans. CS102, a double-masked, randomized, paired-comparison, vehicle-controlled study in 11 healthy subjects with baseline IOPs of 14 to 21 mmHg, evaluated aqueous humor dynamics after administration of netarsudil 0.02% QD PM for 7 days. At baseline and after completion of treatment subjects underwent non-invasive measurements of aqueous humor dynamics in each eye, including IOP, EVP, tonography, and aqueous flow as determined by fluorophotometry. Relative to baseline, netarsudil lowered IOP by 27%, increased outflow

facility by 19%, and lowered EVP by 9% (all $p < 0.05$). A 16% reduction in aqueous flow relative to baseline was also documented but did not reach statistical significance.

The lack of measurable systemic absorption of netarsudil and its IOP-lowering effect in normotensive subjects were shown in CS101, an open-label study in 18 healthy subjects in which netarsudil 0.02% was administered QD AM in both eyes for 8 days. No netarsudil plasma concentrations above the lower limit of quantitation (LLOQ, 0.100 ng/mL) were observed at any timepoint in any subject and only 1 plasma sample from 1 subject (out of 251 samples analyzed) had a concentration above the LLOQ for the primary metabolite AR-13503. Given these low plasma concentrations, and the fact that netarsudil and AR-13503 are highly protein-bound in plasma, it is unlikely that netarsudil would have any systemic pharmacological effects after topical ocular dosing in humans, nor the potential for systemic drug-drug interactions.

Also in this study of subjects with low baseline IOP (14 to 20 mmHg), netarsudil produced substantial IOP reductions that were statistically significant ($p < 0.001$) at all postdose timepoints, reaching a maximum reduction of 6 mmHg. The results were similar to the IOP reduction seen in normotensive primate studies, and supported the potential efficacy of netarsudil in glaucoma patients with lower baseline IOPs.

The selection of netarsudil 0.02% as the concentration to advance into Phase 3 studies was based on the results of 2 randomized, double-masked, vehicle- or active-controlled Phase 2 dose-response studies in subjects with OAG or OHT. CS201 evaluated netarsudil 0.01%, 0.02%, and 0.04% compared to vehicle after administration QD AM for 7 days. Based upon mean reduction in IOP from baseline, netarsudil 0.01% was less effective than netarsudil 0.02% and 0.04% concentrations, and netarsudil 0.02% had similar efficacy and superior tolerability compared to netarsudil 0.04%.

CS202 evaluated netarsudil 0.01% and 0.02% and latanoprost ophthalmic solution 0.005% after QD PM dosing for 28 days. Netarsudil 0.01% and 0.02% produced clinically relevant and statistically significant changes from baseline in IOP ranging from -5.2 to -6.6 mmHg across the 9 post-treatment timepoints. The 0.02% concentration was numerically more effective than 0.01% at 8 of the 9 timepoints.

An important finding of the CS202 study was that while netarsudil 0.02% was approximately 1 mmHg less effective than latanoprost in mean diurnal IOP (mean change of -5.7 and -6.8 mmHg, respectively) in the total study population with baseline IOP of 22 to 36 mmHg, netarsudil and latanoprost were statistically equivalent in the pre-specified analysis of subjects with baseline IOP of 22 to 26 mmHg, with mean change of -5.7 and -6.0 mmHg, respectively. In contrast to latanoprost, which produced smaller IOP reductions at lower baseline IOP and larger reductions at higher baseline IOP, IOP reductions with netarsudil were similar in subgroups with lower and higher baseline IOP.

Equal diurnal and nocturnal IOP-lowering with netarsudil treatment was demonstrated in CS204, a pilot double-masked, vehicle-controlled study to evaluate IOP-lowering with netarsudil over the 24-hour period in subjects with OAG or OHT. Netarsudil 0.02% was dosed QD PM to 8 subjects with baseline IOP > 17 and < 30 mmHg and compared to vehicle

after dosing for 7 days. To minimize disturbance to the subjects during nocturnal hours, IOP was measured with a handheld Perkins tonometer rather than a Goldmann Applanation tonometer. Netarsudil demonstrated statistically significant mean change from nocturnal baseline IOP of -3.5 mmHg ($p < 0.0001$), equivalent to the mean change from baseline IOP produced by netarsudil during the diurnal period (-3.5 mmHg).

Phase 3 Efficacy Results

Three Phase 3 studies (CS301, CS302, and CS304) were double-masked, randomized, multicenter, active-controlled, parallel-group comparison trials designed to confirm the IOP-lowering efficacy of netarsudil 0.02% dosed QD PM over a 3-month period. Key aspects of the study design are shown in Table 1. These trials had equal randomization to the treatment arms (with stratification in CS304 by baseline IOP < 25 mmHg and ≥ 25 mmHg). All treatments were administered to both eyes and subjects in the QD PM groups received vehicle QD AM for masking. The Phase 3 dosing regimen was selected based on results of Phase 2 studies.

Subjects in these trials were required to have a diagnosis of OAG or OHT in both eyes. Subjects were not eligible if their glaucoma or OHT had a pseudoexfoliation or pigment dispersion component, if they had a history of angle closure or narrow angles, or if they had previous glaucoma intraocular surgery or glaucoma laser procedures in either eye. Subjects who had a known hypersensitivity or contraindication to beta-adrenoceptor antagonists were excluded. Required washout periods for ocular hypotensive medications were specified. IOP following washout from prior IOP-lowering medications, if applicable, was required to be > 20 mmHg at 08:00 hours and > 17 mmHg at 10:00 and 16:00 hours. Additionally, IOP had to be < 27 mmHg in both eyes at all qualification timepoints in CS301 and CS302 and < 30 mmHg in CS304.

Table 1 Overview of Phase 3 Efficacy Study Design

Study	Treatment	Baseline IOP
CS301 90-day safety and efficacy	Once-daily (PM) netarsudil 0.02% (n = 202) Twice-daily timolol (n = 209)	> 20 to < 27 mmHg
CS302 12-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 251) Twice-daily netarsudil 0.02% (n = 254) Twice-daily timolol (n = 251)	> 20 to < 27 mmHg
CS304 6-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 351) Twice-daily timolol (n = 357)	> 20 to < 30 mmHg

In the 3 efficacy studies, 411 subjects were enrolled at 37 US sites in CS301, 756 subjects were enrolled at 62 US sites in CS302, and 708 subjects were enrolled at 52 US sites in CS304. Across the 3 studies, the numbers of subjects with maximum baseline < 27 mmHg were 628, 206, and 654 in the netarsudil QD, netarsudil BID, and timolol groups, respectively, and the corresponding numbers with maximum baseline < 25 mmHg were 494, 159, and 510.

The primary efficacy endpoint was mean IOP at 08:00, 10:00, and 16:00 hours at Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90). Mean IOP assessed at 9 timepoints over a 3-month period (3 timepoints throughout the day at Week 2, Week 6, and Month 3) has previously served as the primary efficacy endpoint in Phase 3 trials for IOP-lowering products approved in the US.

The primary analysis of mean IOP used individual 2-sample 95% t-distribution confidence intervals (CIs) for each comparison of netarsudil QD to timolol at each of the 9 timepoints. If the upper 95% confidence limit for the difference (netarsudil – timolol) was within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority (at least 5 of 9), then netarsudil was to be considered clinically non-inferior to timolol. For CS302, which included a netarsudil BID treatment arm, the primary analysis was hierarchical to preserve alpha, first testing netarsudil QD to timolol then, if QD demonstrated clinical non-inferiority, secondarily testing netarsudil BID for non-inferiority to timolol.

The intent-to-treat (ITT) population comprised all randomized subjects who received at least 1 dose of study medication. The per-protocol (PP) population was a subset of the ITT population that included subjects (and their visits) who did not have a major protocol violation likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. In addition to inclusion/exclusion criteria violations, the types of protocol deviations that may have been considered major included out-of-window visit, incorrect study drug assignment or instillation, subject failure to follow instructions, and use of prohibited concomitant medication. The PP populations served as the primary analysis set for these trials designed to demonstrate non-inferiority to an active comparator.

The primary analysis population in CS301 was the overall PP population of subjects with maximum baseline IOP < 27 mmHg (with a post hoc analysis on the PP subset with maximum baseline IOP < 25 mmHg), and in CS302 and CS304 was the PP population with maximum baseline IOP < 25 mmHg. Secondary analyses were also conducted on the ITT

population and sensitivity analyses were conducted using various methods to impute missing data.

The efficacy results were clinically relevant, statistically significant, and similar across the 3 studies. Non-inferiority of netarsudil QD to timolol BID was demonstrated in each study in the PP and ITT populations of subjects with maximum baseline IOP < 25 mmHg (this was a post hoc analysis in CS301). In CS304, but not in CS301 or CS302, netarsudil QD also met the criteria for demonstrating non-inferiority to timolol in subjects with maximum baseline IOP < 27 mmHg. In addition, non-inferiority to timolol was demonstrated in subjects with maximum baseline IOP < 30 mmHg in CS304, the only study among the 3 efficacy studies that included subjects with maximum baseline IOP ≥ 27 and < 30 mmHg.

In the pooled efficacy analysis of PP subjects with maximum baseline IOP < 25 mmHg, netarsudil 0.02% QD and BID produced clinically relevant and statistically significant ($p < 0.0001$) reductions in mean IOP from baseline at all timepoints studied. Mean IOP changes from baseline with netarsudil across the 9 observation timepoints ranged from -3.6 to -4.8 mmHg and -4.1 to -5.4 mmHg for QD and BID, respectively, and those for timolol BID ranged from -3.7 to -5.0 mmHg.

Non-inferiority of netarsudil QD and BID to timolol was demonstrated in the pooled analysis, with the upper 95% confidence limit for the differences in mean IOP between netarsudil QD and timolol and netarsudil BID and timolol within 1.0 mmHg at all of the 9 timepoints. The differences in mean IOP for netarsudil QD vs timolol (expressed as [netarsudil – timolol]) ranged from -0.5 to +0.6 mmHg and for netarsudil BID ranged from -1.3 to 0.0. While the BID regimen was shown to be effective, due to the high discontinuation rate with that regimen, regulatory approval is being sought for the QD regimen.

Non-inferiority of both netarsudil treatment arms was confirmed in the ITT population and the robustness of the analysis was confirmed by multiple forms of data imputation including last observation carried forward (LOCF) and Monte-Carlo Markov Chain (MCMC).

Analyses of mean IOP and mean change from baseline IOP were performed for the following additional maximum baseline IOP categories within the pooled PP population: < 22, < 23, ≤ 23, < 24, < 26 mmHg, < 27 mmHg, and < 30 mmHg. Netarsudil QD demonstrated non-inferiority to timolol in all maximum baseline IOP populations.

IOP was measured at 08:00 hours throughout the 12-month duration of CS302 (as a safety variable after Month 3). For subjects with maximum baseline IOP < 25 mmHg, IOP change from baseline ranged from -3.7 to -4.6 mmHg for netarsudil QD throughout the 12-month duration, demonstrating persistence of ocular hypotensive efficacy.

Key efficacy results are summarized by study in Table 2.

Table 2 Efficacy of Netarsudil 0.02% QD PM Demonstrated at 3 Months in Studies CS301, CS302, CS304, and Pooled Analysis

Efficacy Endpoint	CS301	CS302	CS304	Pooled Analysis
Non-inferiority vs timolol in patients with baseline IOP < 25 mmHg	Met Post hoc	Met Primary analysis	Met Primary analysis	Met
Non-inferiority vs timolol in patients with baseline IOP ≤ 23 mmHg	Met Pre-specified	Not assessed	Not assessed	Met
Non-inferiority vs timolol in patients with baseline IOP < 27 mmHg	Not met Primary analysis	Not met Pre-specified	Met Pre-specified	Met
Non-inferiority vs timolol in patients with baseline IOP < 30 mmHg	Not assessed	Not assessed	Met Pre-specified	Met

Safety Results

Across the Phase 1 and Phase 2 studies, 130 subjects received netarsudil 0.02%, 97 received netarsudil 0.01%, and 19 received netarsudil 0.04%, all administered QD. Across the 4 Phase 3 studies (pooled safety analysis, including safety study CS303), 839 subjects received netarsudil 0.02% QD, the concentration and dosing frequency for which this application seeks approval. In addition, 289 subjects received netarsudil BID and 839 subjects received timolol.

Netarsudil ophthalmic solution 0.02% dosed QD was generally well tolerated. BID dosing had a less favorable safety profile as reflected in a high discontinuation rate during the 12-month Phase 3 study. For this reason, regulatory approval is being sought solely for the QD dosing regimen.

In the pooled Phase 3 safety analysis, the most prevalent treatment-emergent adverse event (TEAE) with netarsudil treatment was conjunctival hyperemia (QD 54.4%, BID: 69.9%). Conjunctival hyperemia is an expected pharmacological effect for the ROCK inhibitor drug class since ROCK inhibition is known to cause vasodilation. As expected, the incidence and severity of conjunctival hyperemia increased with increased dosing frequency (QD vs BID). Overall, the results indicate that the majority of the netarsudil QD subjects did not report noticing a change in eye redness (hyperemia) associated with netarsudil treatment during the studies. The majority of hyperemia findings were reported by investigators based on ocular examinations using a slit lamp biomicroscope.

The next most frequent TEAE was cornea verticillata (QD 20.9%, BID: 27.0% in the pooled Phase 3 studies). Cornea verticillata occurred at a much higher incidence in 12-month CS302 (QD: 25.5%; BID: 25.3%), 12-month CS303 (QD: 38.2%; BID: 38.9%), and 6-month CS304 (QD: 24.5%) than in 3-month CS301 (QD: 5.9%). In the timolol group, this event was reported in CS302 at an incidence of 0.8% and 0% in the other 3 studies. Cornea verticillata was observed only upon biomicroscopy, appeared to be similar in appearance to cornea verticillata associated with the approved anti-arrhythmic agent amiodarone, and was generally scored as mild in comparison to amiodarone, although less distinct. A follow-up

non-interventional study (OBS01) was conducted of 45 subjects who had ongoing cornea verticillata AEs when they exited from CS302. At the completion of this study, cornea verticillata had resolved in all except 3 subjects (4 out of 6 eyes). After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes). No clinically meaningful changes in visual function were observed upon resolution of the cornea verticillata as measured by visual acuity, contrast sensitivity, or visual function questionnaire results, indicating that there was no relationship between visual function and the presence of cornea verticillata in this study.

The other frequent ocular TEAE was conjunctival hemorrhage (QD 17.2%, BID: 19.0% in the pooled Phase 3 studies), which was typically mild in severity.

The incidence of treatment-related non-ocular AEs was low, most likely due to the lack of measurable systemic absorption of netarsudil.

SAEs were almost all non-ocular and were reported in 3.3%, 2.8% and 3.2% of subjects in the netarsudil QD, BID and timolol groups, respectively, in the pooled analysis. None of the SAEs was considered by the Sponsor to be treatment-related.

Two SAEs were considered by the Investigator to be related to study medication: exacerbation of coronary artery disease in a single subject in the netarsudil QD group and iridocyclitis in the netarsudil BID group.

Only one other serious TEAE was ocular, namely, worsening cataract requiring surgical intervention in the netarsudil QD group. The event was considered not related to treatment.

In the pooled analysis, discontinuations of study medication due to TEAEs were highest in the netarsudil BID group (54.3%) followed by netarsudil QD group (19.3%) and timolol group (1.7%). The majority of discontinuations in the netarsudil QD and BID groups were associated with ocular events, whereas the majority of discontinuations in the timolol groups were associated with non-ocular events.

Ocular tolerability was assessed at each 8 AM visit by querying subjects whether they experienced any discomfort when placing the drops in their eyes. Over 90% of subjects in the netarsudil QD and timolol groups reported no or mild ocular discomfort.

Mean changes from baseline in visual acuity were small, similar among all treatment groups, and not clinically relevant. An analysis of worst change from baseline in visual acuity demonstrated that the majority of subjects had a worst change of less than a 1-line loss of vision. The incidence of visual acuity reduced reported as a TEAE in the pooled Phase 3 studies was 5.2% of subjects in the netarsudil QD group, 8.0% of subjects in the netarsudil BID group, and 1.5% in the timolol group.

In the completed Phase 3 studies, an evaluation of the mean heart rate (HR) changes in the timolol group demonstrated statistically significant reductions from baseline at all 6 study visits in the pooled analyses (mean changes from -3.0 to -2.0 bpm). Except for a mean

reduction of 1.3 bpm at a single visit (Month 12 in the netarsudil QD group), there were no significant reductions in mean HR changes in the netarsudil groups.

Conclusions

Netarsudil represents a new class of ocular hypotensive agent with unique pharmacological mechanisms of action. Based on nonclinical and clinical studies, netarsudil appears to reduce IOP by increasing trabecular outflow facility, reducing EVP, and decreasing production of aqueous humor.

In the Phase 3 efficacy studies, individually and in the pooled analysis, treatment with netarsudil ophthalmic solution 0.02% QD demonstrated clinically relevant and statistically significant reductions in IOP from baseline that were non-inferior to timolol.

Among the most frequent ocular AEs, conjunctival hyperemia and conjunctival hemorrhage are related to the vasoactive effects of ROCK inhibition. Cornea verticillata, which is likely due to netarsudil-induced phospholipidosis, resolved or improved by the end of a non-interventional follow-up study and was not associated with any clinically meaningful impact on visual function.

Topical ocular administration of netarsudil ophthalmic solution 0.02% QD in humans produced little or no quantifiable systemic exposure to the parent compound or its primary metabolite. This lack of measurable systemic absorption is consistent with minimal netarsudil-related systemic adverse events in the clinical studies, and represents a safety benefit relative to other commonly used therapeutic classes of ocular hypotensive medication that have known significant systemic AEs.

Aerie believes that the benefits of netarsudil ophthalmic solution 0.02% QD as an ocular hypotensive agent for the treatment of OHT and OAG outweigh the potential risks when prescribing this medication.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse event
AM	Morning
AR-13324	Netarsudil mesylate (drug substance) Netarsudil ophthalmic solution (drug product)
AR-13503	Esterase metabolite of AR-13324
BID	Twice daily
BOCF	Baseline observation carried forward
bpm	Beats per minute
CAI	Carbonic anhydrase inhibitor
CI	Confidence intervals
ECD	Endothelial cell density
EVP	Episcleral venous pressure
FDA	Food and Drug Administration
HR	Heart rate
ICH	International Conference on Harmonization
IOP	Intraocular pressure
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
LOCF	Last observation carried forward
LLOQ	Lower limit of quantitation
MCMC	Monte-Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
NET	Norepinephrine transporter
NOAEL	No-observed-adverse-effect level
OAG	Open-angle glaucoma
OHT	Ocular hypertension
PG324	Fixed-dose combination of netarsudil 0.02% and latanoprost 0.005%
PGA	Prostaglandin analogue
PM	Evening
POAG	Primary open-angle glaucoma
PP	Per protocol
PT	Preferred term
QD	Once daily
ROCK	Rho kinase
S9	Supernatant fraction of an organ (usually liver) tissue homogenate obtained by centrifuging at 9000 G for 20 minutes

SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
US	United States
VA	Visual acuity
VF	Visual field

1. BACKGROUND AND SCIENTIFIC RATIONALE FOR THE DEVELOPMENT OF RHOPRESSA™

Glaucoma is a leading cause of irreversible blindness that affects more than 60 million people worldwide (Alward 1998, Casson 2012). Glaucoma can arise through various etiologies but vision loss is ultimately due to the progressive death of retinal ganglion cells and related damage to the optic nerve (Vrabec 2007). Open-angle glaucoma (OAG) is the most common form of glaucoma. OAG is defined as the ocular condition where the anterior chamber angle is open upon gonioscopic observation, there is some evidence of optic nerve damage or dysfunction (eg, visual field loss), and patients frequently exhibit elevated intraocular pressure (IOP). A second disease condition, ocular hypertension (OHT), has been identified as one for which patients have an elevated IOP compared to population-based cut-off values in the absence of apparent optic nerve damage (Kass 2002). Currently, the only modifiable risk factor for glaucomatous visual field loss is IOP. The standard of care for treating patients with OAG and OHT is reduction of IOP (Schwartz 2004).

The two primary mechanisms to lower IOP include decreasing the amount of aqueous humor production in the eye and increasing the outflow of aqueous humor from the eye. Aqueous humor flows out of the eye by two independent pathways, one of which is sensitive to eye pressure (trabecular outflow pathway), while the other operates independently of eye pressure (uveoscleral outflow).

In a healthy eye, IOP is maintained within a narrow range through pressure-sensitive regulation of aqueous outflow through the trabecular outflow pathway. In a glaucomatous eye, IOP becomes elevated due to an abnormally high resistance to outflow in the trabecular pathway (Stamer 2012). The causes of increased outflow resistance are not fully understood but it appears to involve an increase in the contractile tone and stiffness of the trabecular meshwork, changes in extracellular matrix deposition and composition, and changes in the permeability of the endothelial cell lining of Schlemm's canal (Stamer 2012, Zhou 2012, Keller 2013).

Several available classes of ocular hypotensive medications are differentiated by their mechanism of action at the cellular/molecular level. These include miotics, beta-adrenergic receptor antagonists (beta -blockers), carbonic anhydrase inhibitors (CAIs), alpha-adrenergic receptor agonists (α-agonists), and prostaglandin analogues (PGAs). The pharmacodynamic effects of these medications can differ substantially, as some affect aqueous humor production (beta-blockers, alpha-agonists, and CAIs) while others affect aqueous humor outflow (miotics, PGAs, and alpha-agonists).

From a clinician's perspective, the currently available treatments for glaucoma have different limitations and risks that must be considered when tailoring the choice of treatment to an individual patient's needs and preferences. Some therapeutic classes have known systemic adverse effects, for example, beta-adrenergic antagonists (with cardiovascular and respiratory effects such as bradycardia, dyspnea, and wheezing) and alpha-agonists (with CNS effects such as dry mouth, fatigue, sedation, and dizziness). Ocular side effects are common with topical agents and the acceptability of different side effects can vary by patient. With respect

to efficacy, the Baltimore Eye Survey of 5308 subjects found that 78% of 10,444 eyes with primary open-angle glaucoma (POAG) had screening IOP of < 25 mmHg (Sommer 1991), indicating the importance of achieving efficacy at these lower IOP levels. A regimen that encourages compliance is also an important consideration. Clinicians and patients would benefit from having an additional therapeutic option for individualizing glaucoma treatment.

Rho kinase (ROCK) inhibitors represent a new class of potential glaucoma medications that lower IOP by directly increasing trabecular outflow (Rao 2007, Wang 2014). The tissues of the trabecular outflow pathway are avascular and rely on aqueous humor to supply nutrients, growth factors, and antioxidants. The most commonly prescribed glaucoma medications lower IOP by shunting aqueous humor through the uveoscleral pathway or decreasing aqueous production. While these IOP-lowering mechanisms help protect the optic nerve from damage, they decrease the perfusion of aqueous humor through the trabecular meshwork, which may promote further degradation of the trabecular outflow pathway (Stamer 2012).

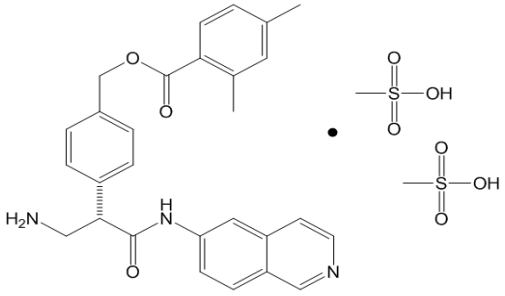
The therapeutic potential of ROCK inhibitors was initially demonstrated using the ROCK inhibitor Y-27632, which was shown to lower IOP in rabbits upon topical ocular application (Honjo 2001), relax pre-contracted trabecular meshwork tissue (Thieme 2000), and increase trabecular outflow in perfused enucleated porcine eyes (Rao 2001). Similar results have since been reported for additional ROCK inhibitors, some of which have demonstrated lowering of IOP in patients with glaucoma (Kopczynski 2014).

The ROCK inhibitor netarsudil (AR-13324) was discovered and developed by Aerie Pharmaceuticals. Netarsudil has been shown to lower IOP in studies in rabbits and monkeys (Kiel 2015, Wang 2015) and in Phase 1 and Phase 2 clinical studies (Bacharach 2015, CS201, Levy 2015, Lewis 2015). Aerie Pharmaceuticals initiated Phase 3 clinical development of netarsudil in 2014.

2. NETARSUDIL OVERVIEW

2.1 Chemical Name and Structure

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



2.2 Formulation

Rhopressa™ 0.02% is a topical ophthalmic product supplied as a sterile, isotonic, buffered aqueous solution of netarsudil mesylate with a pH of approximately 5 and an osmolality of approximately 295 mOsmol/kg. The solution contains netarsudil as the active ingredient. Benzalkonium chloride, 0.015%, is added as a preservative. The inactive ingredients are mannitol, boric acid, sodium hydroxide to adjust pH, and water for injection.

The formulation of netarsudil ophthalmic solution 0.02% was constant throughout clinical development and was the same formulation as is intended for commercialization.

2.3 Proposed Indication and Dosage

Netarsudil 0.02% is a ROCK and NET inhibitor indicated for the reduction of elevated IOP in patients with OAG or OHT.

The recommended dosage of netarsudil 0.02% is one drop in the affected eye(s) once daily (QD) in the evening (PM). If one dose is missed, treatment should continue with the next dose as normal.

The IOP-lowering effect increases gradually after initial dosing and reaches a maximum following the seventh daily dose (CS201).

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

3. NONCLINICAL EVALUATION OF NETARSUDIL

Netarsudil mesylate is a novel ROCK and NET inhibitor with ocular hypotensive activity in normotensive animals when applied to the surface of the eye. Based on nonclinical pharmacology studies, the mechanism of action for IOP lowering appears to involve increasing aqueous humor outflow through the trabecular meshwork, decreasing the production of aqueous humor and reducing episcleral venous pressure (EVP). The pharmacology of the drug is consistent with the intended commercial use.

The clinical pharmacokinetic study CS101 demonstrated that at the maximum recommended commercial dose of netarsudil 0.02% QD, systemic exposure is expected to be at least 700-fold lower than that required to evoke potential cardiovascular effects, based on the no-observed-adverse-effect level (NOAEL) of a telemetered dog study. With systemic administration of netarsudil mesylate, the expected cardiovascular effects associated with smooth muscle relaxation (vasodilation, decreased blood pressure, increased heart rate) were observed at doses of 12.5 or 25 mg netarsudil mesylate/kg.

Nonclinical topical ocular and systemic safety studies indicated that local irritation can occur with exaggerated dosing, which appeared to reduce over time with continued use. Netarsudil mesylate was not genotoxic, either in vitro or in vivo. Systemic administration of netarsudil mesylate in studies of embryo-fetal effects in rats and rabbits indicated that the drug is

embryotoxic and fetotoxic. However, netarsudil mesylate did not cause fetal abnormalities at plasma exposures that were at least 40 times (rat) and 1330 times (rabbit) higher than the human plasma exposure with topical ocular dosing of netarsudil 0.02% QD, based on calculations assuming total systemic absorption of the drug. Since plasma concentrations of netarsudil have been reported to be below 0.100 ng/mL in a clinical study, the actual safety multiplier based on plasma exposure could be far greater.

4. CLINICAL DEVELOPMENT PROGRAM AND US REGULATORY HISTORY OF NETARSUDIL

4.1 Clinical Trials

Ten clinical studies have been completed for the clinical development of netarsudil ophthalmic solution. The 2 Phase 1 and 3 Phase 2 studies are shown in Table 3; the 5 Phase 3 studies, including a non-interventional observational study, are shown in Table 4; and the numbers of subjects in the safety population are summarized by treatment and study in Table 5.

For convenience, the studies are referred to here by their abbreviated number, eg, CS301 for AR-13324-CS301 and netarsudil ophthalmic solution 0.02% is referred to as netarsudil 0.02%. The Phase 3 studies have also been known as “Rocket 1” (CS301), “Rocket 2” (CS302), “Rocket 3” (CS303), and “Rocket 4” (CS304).

Aerie is also developing PG324, a fixed dose combination of netarsudil 0.02% and latanoprost 0.005%. Further information on data relevant to netarsudil from studies with PG324 are provided in Appendix 2.

All clinical studies were conducted in accordance with current standard research approaches regarding the design, conduct, and analysis of studies, including Good Clinical Practices as summarized in ICH Guidance for Industry E6 (Good Clinical Practice: Consolidated Guidance), ICH E8 (General Considerations for Clinical Trials), and ICH E9 (Statistical Principles for Clinical Trials).

4.2 Interactions with the FDA

Aerie had multiple interactions with and guidance from the FDA during the netarsudil development program.

- April 2014, End of Phase 2 meeting. The guidance received was incorporated in the Phase 3 trial designs.
- June 2015, Type C meeting. The Agency accepted a change to the primary efficacy population (to a subgroup of the per-protocol [PP] population having maximum baseline IOP < 25 mmHg) and to the statistical analysis (from concurrent to sequential [hierarchical]) for then-ongoing CS302 based on results of CS301.
- October 2015, Pre-NDA clinical meeting.

- February 2017, NDA submission refiled. This included complete clinical study reports for CS301 and CS302, 3-month interim efficacy and safety results for CS304 (interim clinical study report), 3-month interim efficacy and safety results for PG324-CS301, and unmasked safety data for all related ongoing interventional clinical studies (CS303, CS304, PG324-CS301, and PG324-CS302).

- June 2017, 4-month safety update. This included final unmasked safety data for CS303, the complete clinical study report for CS304, the complete clinical study report for the non-interventional cornea verticillata observational study (AR-13324-OBS01) and masked results for PG324-CS301 and PG324-CS302.

- July 2017, NDA amendment. This included an updated integrated summary of efficacy across the 3 pooled Phase 3 efficacy studies and integrated summary of safety across the 4 pooled Phase 3 studies.

Table 3 Netarsudil Phase 1 and Phase 2 Studies

Study ID Phase	No. of Study Centers, Location	Study Start[1] Status	Design Control Type	Study Objective	Treatment Groups and Regimen	Subjects Planned/ Completed[2]	Treatment Duration	Gender, Mean Age (Range)	Key Inclusion Criteria
AR-13324-CS101 Phase 1	1 US	October-2013 Completed	Prospective, open-label, single-arm, uncontrolled	Ocular and systemic safety; systemic absorption	Netarsudil 0.02% QD AM	16/18	8 days	4M, 14F 47.6 yrs (24-74)	Healthy subjects with IOP 14 to 20 mmHg
AR-13324-CS102 Phase 1	1 US	May-2015 Completed	Prospective, randomized, double-masked, vehicle-controlled	Aqueous humor dynamics; ocular and systemic safety	Netarsudil 0.02% (1 eye) Vehicle (contralateral eye) QD AM	10/11	7 days	1M, 10F 38.6 yrs (21-56)	Healthy subjects with IOP 14 to 21 mmHg
AR-13324-CS201 Phase 2	12 US	March-2012 Completed	Prospective, randomized, double-masked, vehicle-controlled, parallel-group	IOP-lowering efficacy; ocular and systemic safety	Netarsudil 0.01% QD AM Netarsudil 0.02% QD AM Netarsudil 0.04% QD AM Vehicle QD AM one eye treated	80/85	7 days	34M, 51F 64.0 yrs (27-88)	OAG or OHT with IOP ≥ 24 mmHg at 08:00; ≥ 21 mmHg at 10:00, 12:00, & 16:00; ≤ 36 mmHg
AR-13324-CS202 Phase 2	23 US	November-2012 Completed	Prospective, randomized, double-masked, active-controlled, parallel-group	IOP-lowering efficacy; ocular and systemic safety	Netarsudil 0.01% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	210/224	28 days	92M, 132F 65.1 yrs (19-90)	OAG or OHT with IOP ≥ 24 mmHg at 08:00; ≥ 22 mmHg at 10:00 & 16:00; ≤ 36 mmHg
AR-13324-CS204 Phase 2	1 US	September-2016 Completed	Double-masked, vehicle-controlled, parallel-group	IOP-lowering efficacy over 24-hour period; ocular and systemic safety	Netarsudil 0.02% QD PM Vehicle QD PM	12/12	7 days	6M, 6F 65.4 yrs (47-75)	OAG or OHT with IOP > 17 mmHg and < 30 mmHg at Qualification

AM = morning; F = females; IOP = intraocular pressure; M = males; OAG = open-angle glaucoma; OHT = ocular hypertension; PM = evening; QD = once daily; US = United States

[1] First subject screened.

[2] Number of subjects included in the safety analyses.

Table 4 Netarsudil Phase 3 Studies

Study ID Phase	No. of Study Centers, Location	Study Start[1] Status	Design Control Type	Study Objectives	Treatment Groups and Regimen	Subjects Planned/ Completed[2]	Treatment Duration	Gender, Mean Age (Range)	Key Inclusion Criteria
AR-13324-CS301 Phase 3	37 US	June-2014 Completed	Prospective, randomized, double-masked, active-controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.02% QD PM Timolol 0.5% BID	400/411[3]	3 months	161M, 250F 65.0 yrs (20-96)	≥ 18 years; OAG or OHT with IOP > 21 mmHg at 08:00; > 17 mmHg at 10:00 & 16:00; < 27 mmHg; pediatric 0-2 years
AR-13324-CS302 Phase 3	62 US	June-2014 Completed	Prospective, randomized, double-masked, active-controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.02% QD PM Netarsudil 0.02% BID Timolol 0.5% BID	690/755[4,5]	12 months	293M, 463F 64.1 yrs (11-92)	≥ 18 years; OAG or OHT with IOP > 21 mmHg at 08:00; > 17 mmHg at 10:00 & 16:00; < 27 mmHg; pediatric 0-2 years
AR-13324-CS303 Phase 3	25 Canada	August-2014 Completed	Prospective, randomized, double-masked, active-controlled	Ocular and systemic safety	Netarsudil 0.02% QD PM Netarsudil 0.02% BID Timolol 0.5% BID	240/93[6]	12 months	49M, 44F 63.8 yrs (26-84)	≥ 19 years; OAG or OHT with IOP > 21 mmHg at 08:00; > 17 mmHg at 10:00 & 16:00; < 27 mmHg
AR-13324-CS304 Phase 3	63 US	August-2015 Completed	Prospective, randomized, double-masked, active-controlled	Ocular hypotensive efficacy; ocular and systemic safety	Netarsudil 0.02% QD PM Timolol 0.5% BID	700/708	6 months	263M, 455F 64.3 yrs (18-91)	≥ 18 years; OAG or OHT with IOP > 21 mmHg at 08:00; > 17 mmHg at 10:00 & 16:00; < 30 mmHg

Table 4 Netarsudil Phase 3 Studies (continued)

Study ID Phase	No. of Study Centers, Location	Study Start[1] Status	Design Control Type	Study Objectives	Treatment Groups and Regimen	Subjects Planned/ Completed[2]	Treatment Duration	Gender, Mean Age (Range)	Key Inclusion Criteria
AR-13324-OBS01 Phase 3	10 US	April-2016 Completed	Prospective, targeted, non-interventional observational	Evaluation of visual function in subjects with cornea verticillata	Not applicable	150/45	No active treatment. Subjects assessed monthly (for 3 months) and then bi-monthly until resolution of cornea verticillata	22M, 23F 69.4 yrs (50-83)	Previous subjects from studies CS301 or CS302 who had corneal verticillata ongoing at study exit

BID = twice daily; F = females; IOP = intraocular pressure; M = males; OAG = open-angle glaucoma; OHT = ocular hypertension; PM = evening; QD = once daily; US = United States

1. First subject screened.
2. Number of subjects included in the safety analyses.
3. No pediatric subjects were enrolled.
4. Two pediatric subjects were enrolled, one age 11 and one age 14.
5. 756 subjects randomized but only 755 in safety analyses since 1 subject who randomized never dosed.
6. Study was discontinued after 93 subjects were enrolled due to slow enrollment.

Table 5 Overview of Subject Exposure to Study Medication by Study and Treatment Group in Netarsudil Studies

Protocol Number	Safety N	Netarsudil				Timolol	Latanoprost	Vehicle
		0.01% QD[1] (N=97)	0.02% QD[2] (N=662)	0.02% BID (N=253)	0.04% QD (N=19)	0.5% BID (N=459)	0.005% QD (N=150)	QD (N=38)
Phase 1 and 2 Studies								
CS101	18		18					
CS102	11[3]		11					11[3]
CS201	85	22	21		19			23
CS202	224	75	72				77	
CS204	12		8					4
Subtotal	**350**	**97**	**130**		**19**		**77**	**38**
Phase 3 Studies								
CS301	411		203			208		
CS302	755		251	253		251		
CS303	93		34	36		23		
CS304	708		351			357		
Subtotal	**1967**		**839**	**289**		**839**		
Total	**2317**	**97**	**969**	**289**	**19**	**839**	**77**	**38**

BID = twice daily; QD = once daily
[1.] 0.01% QD includes AM and PM dosing groups.
[2.] 0.02% QD includes AM and PM dosing groups.
[3.] Vehicle dosed in the fellow eye. The safety N reflects only 11 subjects since both eyes were dosed concurrently.
Note: This table does not include the non-interventional observational study OBS01.

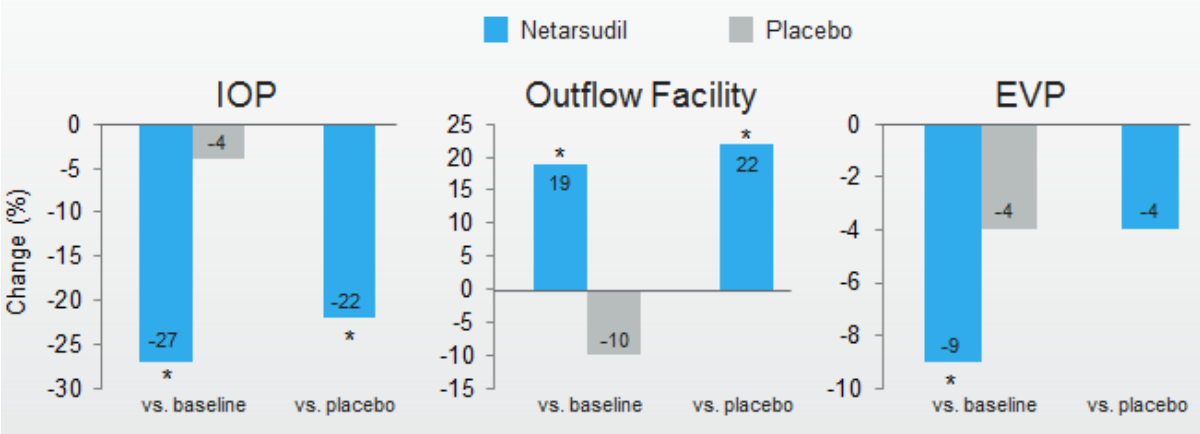
5. CLINICAL PHARMACOLOGY

5.1 Mechanism of Action

Netarsudil is a potent ROCK inhibitor for both isoforms of human Rho kinase (ROCK1 and ROCK2) and a NET inhibitor. A clinical study of aqueous humor dynamics and a mechanism of action study using enucleated human donor eyes support nonclinical studies demonstrating that netarsudil lowers IOP by increasing trabecular outflow, decreasing EVP (Kiel 2015), and decreasing aqueous humor production (Wang 2015). This combination of mechanisms is unique for an ocular hypotensive medication, as most currently used glaucoma medications reduce IOP by either reducing the production of aqueous humor or by improving the drainage of this fluid through the non-conventional uveoscleral pathway.

CS102 was a double-masked, randomized, paired-comparison, vehicle-controlled study in 11 healthy subjects with baseline IOPs of 14 to 21 mmHg to evaluate aqueous humor dynamics and safety of netarsudil 0.02% administered QD AM in one eye with vehicle in the contralateral eye for 7 days. At baseline and after completion of the 7 days of dosing subjects underwent non-invasive measurements of aqueous humor dynamics in each eye, including IOP, EVP, tonography, and aqueous flow as determined by fluorophotometry. Relative to baseline, netarsudil lowered IOP by 27%, increased outflow facility by 19%, and lowered EVP by 9% (all $p < 0.05$; Figure 1). A 16% reduction in aqueous production relative to baseline was also demonstrated but did not reach statistical significance ($p = 0.08$).

Figure 1 Mechanism of Action of Netarsudil Demonstrated in Healthy Subjects (CS102)



* $p < 0.05$

The netarsudil active metabolite AR-13503 was evaluated for its effects on trabecular outflow facility and tissue morphology in perfused human eye anterior segments (IPH05). AR-13503 caused significant increases in outflow facility compared to control eyes from 30 minutes through 3 hours post-treatment (the final timepoint). Fluorescent imaging and histological analysis showed that AR-13503 increased the area of actively filtering tissue in the trabecular outflow pathway, expanded the trabecular meshwork tissue, and caused dilation of episcleral veins in normal human eyes.

The combination of mechanisms demonstrated with netarsudil is unique for an ocular hypotensive medication as most currently used glaucoma medications reduce IOP by either reducing the production of aqueous humor or by improving the drainage of this fluid through the non-conventional uveoscleral pathway.

5.2 Pharmacokinetics

Absorption: After administration of netarsudil 0.02% QD AM for 8 days (CS101), no observed netarsudil plasma concentrations were above the lower limit of quantitation (LLOQ, 0.100 ng/mL) at any timepoint in any subject. Only 1 plasma sample from 1 subject (out of 251 samples analyzed) had a concentration above the LLOQ for the primary metabolite AR-13503 (0.11 ng/mL). Given these low plasma concentrations, and the fact that netarsudil and AR-13503 are highly protein-bound in plasma (IPK01), it is unlikely that netarsudil would have any systemic pharmacological effects after topical ocular dosing in humans, nor the potential for systemic drug-drug interactions.

Distribution: *In vitro*, netarsudil is highly protein-bound in human plasma. The active metabolite AR-13503 binds less extensively to plasma proteins but was at least 60% bound.

Clearance, Metabolism, and Elimination: Studies investigating the *in vitro* metabolism of netarsudil using corneal tissue from humans, human plasma, and human liver microsomes and microsomal S9 fractions demonstrated that netarsudil metabolism occurs through esterase activity. Subsequent metabolism of the esterase metabolite AR-13503 was not detectable. Esterase metabolism in human plasma was not detected during a 3-hour incubation.

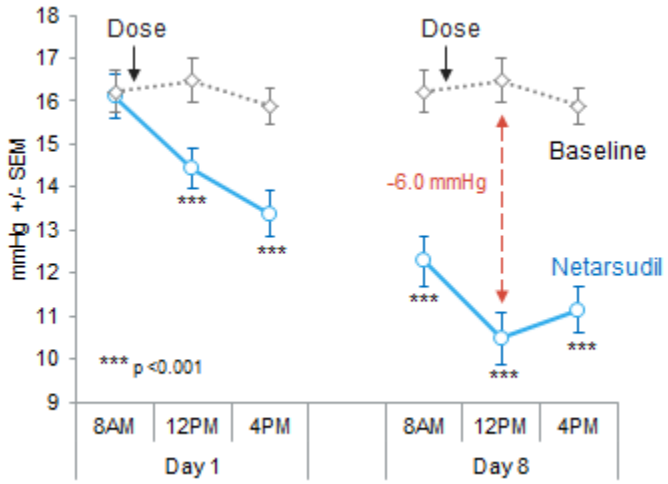
6. PHASE 1 AND PHASE 2 STUDIES

Phase 1 and Phase 2 netarsudil studies laid the foundation for Phase 3 study design.

6.1 IOP-lowering in Healthy Subjects (CS101

This open-label study in 18 healthy subjects (with baseline IOP of 14 to 20 mmHg) evaluated ocular and systemic safety and systemic absorption following administration of netarsudil 0.02% QD AM in both eyes for 8 days. In addition to the PK results (Section 5.2), this study measured IOP at 30 minutes predose (8 AM) and 4 and 8 hours postdose (12 PM and 4 PM) on Days 1 and 8. Netarsudil produced substantial reductions from baseline IOP ($p < 0.001$) at all postdose timepoints, reaching a maximum reduction of 6 mmHg (Figure 2). The magnitude of effect was greater than that seen historically with other IOP-lowering medications, e.g., Xalatan (3 mmHg; Linden 1997). The results were similar to the IOP reduction seen in normotensive primate studies, and supported the potential efficacy of netarsudil in glaucoma patients with lower baseline IOPs.

Figure 2 Netarsudil Efficacy in Normotensive Volunteers (CS101)



Baseline measurements of mean IOP (Day -1) were taken at the same time of day as the postdose measurement. For each subject at each timepoint, the value was the average IOP from both eyes.

6.2 Dose Response and IOP-lowering Across Baseline IOPs (CS201, CS202)

Two Phase 2 randomized, double-masked, vehicle- or active-controlled dose-response studies established the optimal netarsudil concentration. Subjects in both trials were ≥ 18 years old with a diagnosis of OAG or OHT in at least 1 eye. Subjects were not eligible if their glaucoma or OHT had a pseudoexfoliation or pigment dispersion component, they had a history of angle closure or narrow angles, or they had previous glaucoma intraocular surgery or glaucoma laser procedures in either eye (study eye only for CS201). In CS201, IOP entry criteria (following washout from prior IOP-lowering medications, if applicable) were: IOP ≥ 24 mmHg at 08:00 hours and ≥ 21 mmHg at 10:00, 12:00, and 16:00 hours (and < 36 mmHg at all qualification timepoints). In CS202, IOP entry criteria (following washout from prior IOP-lowering medications, if applicable) were: IOP ≥ 24 mmHg at 08:00 hours and ≥ 22 mmHg at 10:00 and 16:00 hours (and < 36 mmHg at all qualification timepoints).

In CS201, netarsudil 0.01%, 0.02%, and 0.04% and vehicle were dosed QD AM for 7 days. Significantly greater IOP reductions were observed with netarsudil compared to vehicle at all timepoints, with the largest reductions in IOP with netarsudil on Day 8. On the morning of Day 8 (24 hours after the 6th dose), mean IOP change from baseline was -5.6, -5.9, -6.3, and -2.3 mmHg for netarsudil 0.01%, 0.02%, 0.04%, and vehicle, respectively. At 16:00 hours on Day 8, mean IOP change from baseline was -6.1, -6.9, -7.2, and -1.8 mmHg for netarsudil 0.01%, 0.02%, 0.04%, and vehicle, respectively. Based upon mean reduction in IOP from baseline, netarsudil 0.01% was less effective than 0.02% and 0.04%, and netarsudil 0.02% had similar efficacy and superior tolerability compared to 0.04%. Given the 24-hour efficacy and a reduced incidence of conjunctival hyperemia at 8 hours and 24 hours after dosing compared to 2 hours after dosing, it was concluded that a QD PM dosing regimen of netarsudil 0.02% would have the potential to provide similar efficacy to QD AM dosing with a lower incidence of hyperemia during the day.

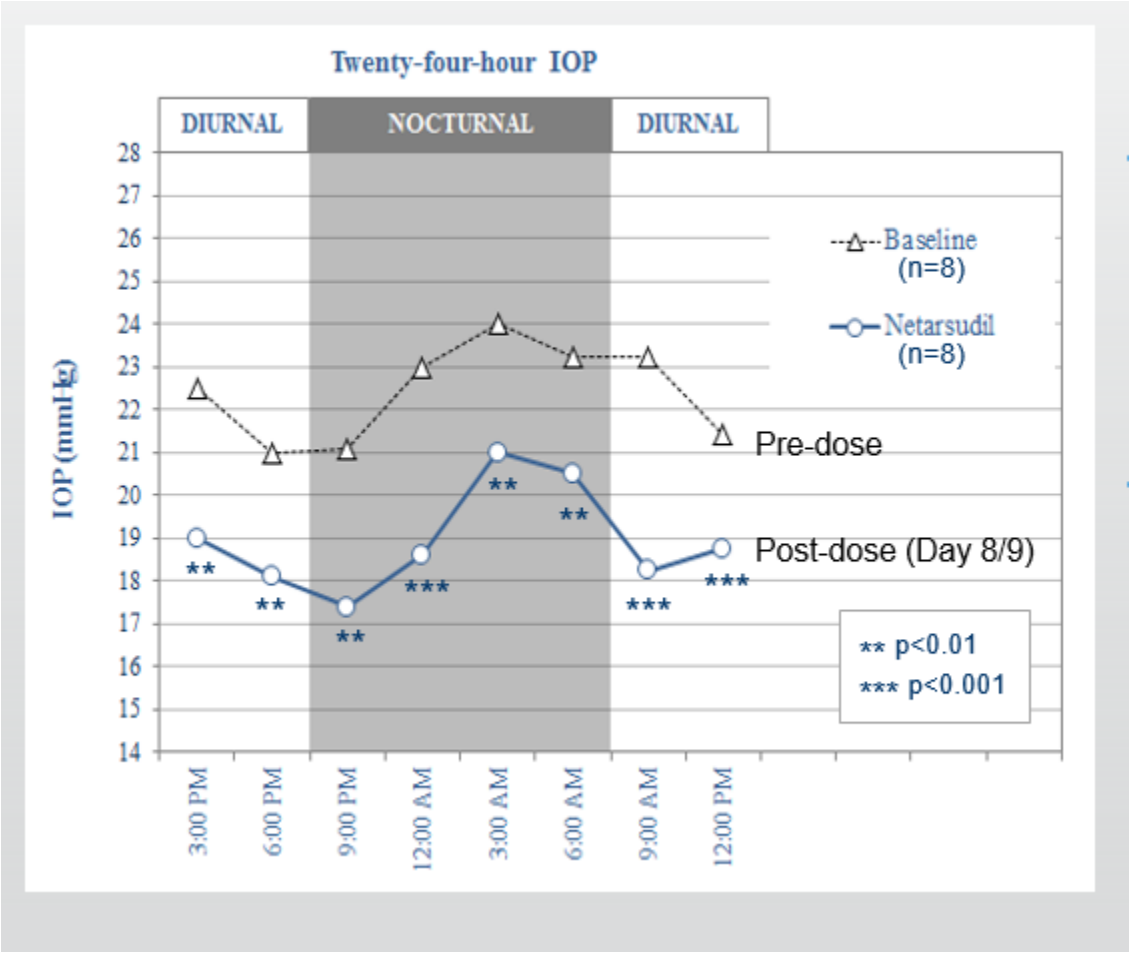
In CS202, netarsudil 0.01% and 0.02% were dosed QD PM and compared to latanoprost ophthalmic solution 0.005% QD PM after dosing for 28 days. Netarsudil 0.01% and 0.02% produced clinically relevant and statistically significant changes from baseline in IOP ranging from -5.2 to -6.6 mmHg across the 9 post-treatment timepoints. The 0.02% concentration was numerically more effective than 0.01% at 8 of the 9 timepoints.

In the total CS202 study population with baseline IOP of 22 to 36 mmHg, netarsudil 0.02% was approximately 1 mmHg less effective than latanoprost in mean diurnal IOP (mean change of -5.7 and -6.8 mmHg, respectively, at Day 28); however, netarsudil and latanoprost were statistically equivalent in the pre-specified analysis of subjects with baseline IOP of 22 to 26 mmHg, with mean changes from baseline IOP of -5.7 and -6.0 mmHg, respectively. In contrast to the baseline-dependent efficacy of latanoprost, IOP reductions with netarsudil were similar in subgroups with lower and higher baseline IOP.

6.3 Nocturnal IOP-lowering (CS204)

Current glaucoma medications either have no efficacy at night (beta-blockers, alpha-agonists) or reduced efficacy at night (PGAs, CAIs). CS204 was a pilot double-masked, vehicle-controlled study to evaluate IOP-lowering over 24 hours. Netarsudil 0.02% was dosed QD PM to 8 subjects with baseline IOP > 17 and < 30 mmHg in both eyes and compared to vehicle (4 subjects) after dosing for 7 days. Netarsudil demonstrated statistically significant mean change from nocturnal baseline IOP of -3.5 mmHg ($p < 0.0001$; Figure 3), which was equivalent to the mean change from baseline IOP during the diurnal period (-3.5 mmHg). Changes from baseline in the netarsudil group were statistically significant at all timepoints throughout the 24-hour period. In contrast, change from baseline in the vehicle group was -0.4 mmHg in the nocturnal period and -0.9 mmHg in the diurnal period. While this pilot study was small in sample size and short in treatment duration, the data were nevertheless compelling with respect to demonstrating equivalent efficacy of netarsudil 0.02% during nocturnal and daytime hours.

Figure 3 Twenty-four-hour IOP in Subjects Treated with Netarsudil (CS204)



6.4 Summary of Phase 1 and Phase 2 Findings

- Netarsudil 0.02% increases trabecular outflow and decreases EVP in humans. A numerical decrease in aqueous production was also observed but did not reach statistical significance.
- Netarsudil 0.02% produces large IOP reductions in normotensive subjects with low baseline IOPs.
- In contrast to the baseline-dependent efficacy of latanoprost, IOP reductions (mmHg) with netarsudil 0.02% are similar in subjects with lower and higher baseline IOP.
- Netarsudil 0.02% provides equal diurnal and nocturnal IOP-lowering in subjects with OAG or OHT.

- Netarsudil 0.02% is more effective than 0.01% and has similar efficacy and better tolerability than 0.04%.

- A QD PM dosing regimen provides similar efficacy to QD AM dosing with a lower incidence of hyperemia during the day.

Based on the results of these studies, the Phase 3 studies evaluated netarsudil 0.02%. Both QD and BID regimens were evaluated in Phase 3 studies and, as described below, the discontinuation rate due to AEs with the BID regimen led to the decision to pursue marketing approval solely for the QD dosing regimen.

7. PHASE 3 STUDIES

7.1 Clinical Trial Design and Population

CS301, CS302, and CS304 were double-masked, randomized, multicenter, active-controlled, parallel-group Phase 3 trials designed to confirm the safety and IOP-lowering efficacy of netarsudil 0.02% dosed QD PM over a 3-month period. CS303 was a double-masked, randomized, multicenter, active-controlled, parallel-group Phase 3 trial designed to confirm the safety of netarsudil 0.02% dosed QD PM over a 12-month period. CS302 and CS303 also included a treatment arm in which netarsudil 0.02% was dosed BID (AM and PM). An overview of the studies is shown in Table 6.

Treatment duration was 3 months in CS301, 6 months in CS304, and 12 months in CS302 and CS303. IOP was measured as the efficacy variable in CS301, CS302, and CS304 for 3 months, as a safety variable after 3 months in CS302 and CS304, and as a safety variable in CS303. The 3 efficacy trials had equal randomization to the treatment arms.

Table 6 Overview of Phase 3 Interventional Study Design

Study	Treatment	Baseline IOP (08:00 hours)
CS301 90-day safety and efficacy	Once-daily (PM) netarsudil 0.02% (n = 202) Twice-daily timolol (n = 209)	> 20 to < 27 mmHg
CS302 12-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 251) Twice-daily netarsudil 0.02% (n = 254) Twice-daily timolol (n = 251)	> 20 to < 27 mmHg
CS304 6-month safety, 3-month primary efficacy	Once-daily (PM) netarsudil 0.02% (n = 351) Twice-daily timolol (n = 357)	> 20 to < 30 mmHg
CS303 12-month safety[1]	Once-daily (PM) netarsudil 0.02% (n = 34) Twice-daily netarsudil 0.02% (n = 36) Twice-daily timolol (n = 23)	> 20 to < 27 mmHg

IOP = intraocular pressure; PM = evening
[1] Study CS303 was discontinued after 93 subjects were enrolled due to slow enrollment.

Subjects in these studies dosed both eyes, although one eye was designated as the study eye based on protocol-specified criteria.

Timolol maleate ophthalmic solution 0.5% BID was chosen as the control because it is an acceptable clinical and regulatory benchmark for demonstration of equivalency of proposed IOP-lowering agents due to well-known benefits and risks. To maintain masking, subjects in the netarsudil 0.02% QD arm received vehicle solution to dose in the AM.

Subjects were required to have a diagnosis of OAG or OHT in both eyes and were not eligible if their glaucoma or OHT had a pseudoexfoliation or pigment dispersion component, they had a history of angle closure or narrow angles, or they had previous glaucoma intraocular surgery or glaucoma laser procedures in either eye. Subjects who had a known hypersensitivity or contraindication to beta-adrenoceptor antagonists were excluded. Required washout periods for ocular hypotensive medications were specified. In CS301, CS302, and CS303, IOP after washout from prior IOP-lowering medications, if applicable, was required to be > 20 mmHg at 08:00 hours and > 17 mmHg at 10:00 and 16:00 hours. Additionally, IOP had to be < 27 mmHg in both eyes at all qualification timepoints. In CS304, IOP after washout from prior IOP-lowering medications, if applicable, was required to be > 20 mmHg and < 30 mmHg at 08:00 hours and > 17 mmHg and < 30 mmHg at 10:00 and 16:00 hours. Randomization in CS304 stratified subjects by site and maximum baseline IOP (< 25 mmHg and ≥ 25 mmHg).

CS301 had 6 visits: Screening, Qualification #1, Day 1/Qualifying #2, Day 15, Day 43, and Day 90. For visits at Day 1, Day 15, Day 43, and Day 90, subjects were evaluated at 08:00, 10:00, and 16:00 hours within the visit day. The total treatment period was 90 days. Compared to CS301, CS302 had additional visits at Month 6, Month 9, and Month 12, when subjects were evaluated at 8:00 hours only, and CS304 had additional visits at Month 4, Month 5, and Month 6, with evaluations at the 3 timepoints within each visit day. The total treatment period was 365 days for CS302 and 180 days for CS304. In safety study CS303, which had a treatment period of 365 days, subjects were evaluated at the same visit days as CS302 but only at 08:00 hours on each visit day after the qualifying visits.

The primary efficacy endpoint in each of the Phase 3 efficacy studies (CS301, CS302, and CS304) was mean IOP at 08:00, 10:00, and 16:00 hours at Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90). Mean IOP assessed at 9 timepoints over a 3-month period has previously served as the primary efficacy endpoint in Phase 3 trials for IOP-lowering products approved in the US. The assessment timepoints included the expected peak and trough times for netarsudil and timolol. The Week 2 assessment allowed for evaluation of early onset of efficacy and safety and the Month 3 assessment served to establish long-term efficacy and safety.

7.2 Disposition

Across the 4 Phase 3 studies, the pooled safety population of all subjects who were randomized and treated (analyzed by the treatment received) included 839, 289, and 839 in the netarsudil QD, netarsudil BID, and timolol groups, respectively. An overview of subject disposition in the pooled analysis of the safety population is presented in Table 7. The

proportion of subjects who discontinued the studies was 31.5% with netarsudil QD, 68.5% with netarsudil BID, and 12.6% with timolol. In the netarsudil treatment arms, the most frequent reason for discontinuation was AEs, which are discussed in Section 9.4.3.

Table 7 Subject Disposition in Pooled Safety Analysis (Safety Population in CS301, CS302, CS303, and CS304)

	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5% BID (N = 839) n (%)
Analysis Populations			
Safety	839 (100.0)	289 (100.0)	839 (100.0)
Intent to Treat (ITT)[1]	804 (95.8)	253 (87.5)	817 (97.4)
Per Protocol (PP)[1]	694 (82.7)	209 (72.3)	721 (85.9)
Discontinued from Study[2]	264 (31.5)	198 (68.5)	106 (12.6)
Reason for Discontinuation[2]			
Adverse Event(s)	174 (20.7)	161 (55.7)	28 (3.3)
Withdrawal of Consent	24 (2.9)	13 (4.5)	28 (3.3)
Non-Compliant	4 (0.5)	1 (0.3)	6 (0.7)
Lost to Follow-up	2 (0.2)	3 (1.0)	4 (0.5)
Lack of Efficacy	26 (3.1)	3 (1.0)	3 (0.4)
Disallowed Concurrent Medication	4 (0.5)	2 (0.7)	8 (1.0)
Investigator Decision	5 (0.6)	4 (1.4)	7 (0.8)
Protocol Violation	15 (1.8)	7 (2.4)	19 (2.3)
Death	3 (0.4)	0	0
Other	7 (0.8)	4 (1.4)	3 (0.4)

BID = twice daily; QD = once daily

1. CS303 (N = 93) did not define ITT and PP populations and those subjects are only counted here in the safety population.
2. Percentage is based on the number of subjects treated in each group.

Source: ISS Table 14.1.2.2.

The pooled efficacy population of subjects with maximum baseline IOP < 25 mmHg included 1163 subjects who were randomized and treated in CS301, CS302, and CS304: 494, 159, and 510 in the netarsudil QD, netarsudil BID, and timolol groups, respectively. Of these, 1010 subjects (86.8%) completed 3 months of treatment (Table 8). The proportion of subjects who discontinued before Month 3 was 13.4% with netarsudil QD, 37.1% with netarsudil BID, and 5.5% with timolol. In the netarsudil treatment arms, the most frequent reason for discontinuation was AEs, which are discussed in Section 9.4.3.

Table 8 Subject Disposition in Pooled Efficacy Analysis (Randomized Population -- Subjects with Baseline IOP < 25 mmHg in CS301, CS302, and CS304)

	Netarsudil 0.02% QD (N = 494) n (%)	Netarsudil 0.02% BID (N = 159) n (%)	Timolol 0.5% BID (N = 510) n (%)	All Subjects (N = 1163) n (%)
Number of Randomized Subjects	494	159	510	1163
Analysis Populations[1]				
Safety	494 (100.0)	159 (100.0)	510 (100.0)	1163 (100.0)
Intent-to-Treat (ITT)	494 (100.0)	159 (100.0)	510 (100.0)	1163 (100.0)
Per Protocol (PP)	428 (86.6)	132 (83.0)	453 (88.8)	1013 (87.1)
Completion of 3-Month Treatment				
Completed	428 (86.6)	100 (62.9)	482 (94.5)	1010 (86.8)
Discontinued	66 (13.4)	59 (37.1)	28 (5.5)	153 (13.2)
Reason for Subject Discontinuation[2]				
Adverse Event(s)	44 (8.9)	44 (27.7)	8 (1.6)	96 (8.3)
Withdrawal of Consent	7 (1.4)	5 (3.1)	4 (0.8)	16 (1.4)
Non-Compliant	2 (0.4)	1 (0.6)	1 (0.2)	4 (0.3)
Lost to Follow-up	0	1 (0.6)	0	1 (0.1)
Lack of Efficacy	1 (0.2)	1 (0.6)	0	2 (0.2)
Disallowed Concurrent Medication	1 (0.2)	1 (0.6)	1 (0.2)	3 (0.3)
Investigator Decision	2 (0.4)	0	1 (0.2)	3 (0.3)
Protocol Violation	7 (1.4)	4 (2.5)	13 (2.5)	24 (2.1)
Death	1 (0.2)	0	0	1 (0.1)
Other	1 (0.2)	2 (1.3)	0	3 (0.3)
Protocol Deviations[3]				
Any Deviations	220 (44.5)	77 (48.4)	203 (39.8)	500 (43.0)
Major Deviations	66 (13.4)	27 (17.0)	57 (11.2)	150 (12.9)
Minor Deviations	184 (37.2)	65 (40.9)	175 (34.3)	424 (36.5)

BID = twice daily; QD = once daily

[1] For the treatment assignments, ITT uses as randomized; Safety and PP use as treated.

[2] Percentage is based on the number of subjects treated in each group.

[3] Magnitude of the deviations were assigned by the Sponsor in writing prior to database lock and unmasking. Deviations are summarized as treated.

Source: ISE Table 14.1.2.1

7.3 Demographics and Baseline Characteristics

The overall demographics and baseline disease characteristics of the pooled Phase 3 safety population are representative of the OAG or OHT patients who would be expected to receive the drug product once marketed. The pooled population included 1967 subjects ranging in age from 11 to 96 years with a mean age of 64.3 years. Overall, no clinically relevant differences were observed between the treatment groups in the assessment of any demographic or baseline characteristics (Table 9). Subgroup analyses of efficacy and safety by demographic subgroup are discussed in Section 8.3 and Section 9.3.4, respectively.

The original Phase 3 protocols permitted enrollment of subjects 2 years of age or older but no subjects < 18 years of age were enrolled in CS301 and only 2 subjects < 18 years of age (11 and 14 years old) were enrolled in CS302.

No clinically relevant differences were observed between treatment groups for concomitant disorders, or prior or concomitant medications. Additionally, the most common disorders and medications are typical of the aging population in the US that would use the drug product once marketed.

Table 9 Subject Demographics in Pooled Safety Analysis (Safety Population in CS301, CS302, CS303, and CS304)

	Netarsudil 0.02% QD (N = 839)	Netarsudil 0.02% BID (N = 289)	Timolol 0.5% BID (N = 839)
Sex, n (%)			
Male	349 (41.6)	107 (37.0)	309 (36.8)
Female	490 (58.4)	182 (63.0)	530 (63.2)
Age (years)			
Mean (SD)	64.9 (11.4)	64.2 (12.0)	63.9 (11.4)
Min, Max	(14, 96)	(18, 92)	(11, 91)
Age (years), n (%)			
< 65	371 (44.2)	139 (48.1)	407 (48.5)
≥ 65	468 (55.8)	150 (51.9)	432 (51.5)
Race, n (%)			
Native Hawaiian or Other Pacific Islander	0	0	1 (0.1)
Asian	11 (1.3)	7 (2.4)	19 (2.3)
Black or African American	199 (23.7)	70 (24.2)	203 (24.2)
Native American	2 (0.2)	0	0
White	625 (74.5)	211 (73.0)	611 (72.8)
Multiple/Other	2 (0.2)	1 (0.3)	5 (0.6)
Iris Color, n (%)			
Blue/Grey/Green	214 (25.5)	76 (26.3)	225 (26.8)
Brown/Black	521 (62.1)	178 (61.6)	538 (64.1)
Hazel	103 (12.3)	35 (12.1)	76 (9.1)
Other	1 (0.1)	0	0
Study Eye Diagnosis, n (%)			
Ocular Hypertension	299 (35.6)	120 (41.5)	283 (33.7)
Open Angle Glaucoma	540 (64.4)	169 (58.5)	556 (66.3)

BID = twice daily; QD = once daily; SD = standard deviation
Percentages are based on the number of subjects (N) in a given treatment group for the population being analyzed.
Source: ISS Table 14.1.1.2.

In the pooled efficacy population of subjects with maximum baseline IOP < 25 mmHg, the demographic characteristics were generally similar among the treatment groups (Table 10) and were similar to those in the pooled safety population.

Table 10 Subject Demographics in Pooled Efficacy Analysis (Randomized Population -- Subjects with Baseline IOP < 25 mmHg in CS301, CS302, and CS304)

	Netarsudil 0.02% QD (N = 494)	Netarsudil 0.02% BID (N = 159)	Timolol 0.5% BID (N = 510)	All Subjects (N = 1163)
Sex, n (%)				
Male	202 (40.9)	49 (30.8)	188 (36.9)	439 (37.7)
Female	292 (59.1)	110 (69.2)	322 (63.1)	724 (62.3)
Age (years)				
Mean (SD)	64.9 (12.21)	64.4 (12.92)	63.8 (11.65)	64.4 (12.07)
Min, Max	(14, 96)	(18, 92)	(11, 91)	(11, 96)
Age (years), n (%)				
< 65	212 (42.9)	76 (47.8)	243 (47.6)	531 (45.7)
≥ 65	282 (57.1)	83 (52.2)	267 (52.4)	632 (54.3)
Race, n (%)				
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2)	1 (0.1)
Asian	9 (1.8)	4 (2.5)	12 (2.4)	25 (2.1)
Black or African American	115 (23.3)	44 (27.7)	120 (23.5)	279 (24.0)
Native American	1 (0.2)	0	0	1 (0.1)
White	369 (74.7)	111 (69.8)	374 (73.3)	854 (73.4)
Multiple	0	0	2 (0.4)	2 (0.2)
Other	0	0	1 (0.2)	1 (0.1)
Ethnicity, n (%)				
Hispanic or Latino	97 (19.6)	34 (21.4)	104 (20.4)	235 (20.2)
Not Hispanic or Latino	397 (80.4)	125 (78.6)	406 (79.6)	928 (79.8)
Iris Color Study Eye, n (%)				
Blue/Grey/Green	127 (25.7)	32 (20.1)	129 (25.3)	288 (24.8)
Brown/Black	303 (61.3)	110 (69.2)	340 (66.7)	753 (64.7)
Hazel	62 (12.6)	17 (10.7)	41 (8.0)	120 (10.3)
Other	2 (0.4)	0	0	2 (0.2)

BID = twice daily; QD = once daily; SD = standard deviation
Percentages are based on the number of subjects (N) in a given treatment group for the population being analyzed.
Source: ISE Table 14.1.1.1

In the pooled efficacy population of subjects with maximum baseline IOP < 25 mmHg, there were no statistically significant differences between the treatment groups for any of the baseline disease characteristics in the pooled population. The study eye diagnosis was OAG for 65.9% of subjects and OHT for 33.9% (3 subjects, 1 in the netarsudil BID group and 2 in the timolol BID group, did not have a study eye diagnosis), and the mean time since diagnosis averaged 357.9 weeks, or approximately 7.0 years (Table 11).

Prior hypotensive therapy was used by 63.0% of subjects, the most common being prostaglandin monotherapy (45.7%). In the study eye, the unmedicated mean diurnal IOP (average of all measurements on Day 1 prior to study medication) was 21.4, 21.5, and

21.4 mmHg in the netarsudil QD, netarsudil BID, and timolol BID treatment groups, respectively.

Table 11 Baseline Disease Characteristics and Prior Treatment in Pooled Efficacy Analysis (Randomized Population -- Subjects with Baseline IOP < 25 mmHg in CS301, CS302, and CS304)

	Netarsudil 0.02% QD (N = 494)	Netarsudil 0.02% BID (N = 159)	Timolol 0.5% BID (N = 510)	All Subjects (N = 1163)
Study Eye Diagnosis, n (%)				
Ocular Hypertension	174 (35.2)	57 (35.8)	163 (32.0)	394 (33.9)
Open Angle Glaucoma	320 (64.8)	101 (63.5)	345 (67.6)	766 (65.9)
Time Since Current OHT or OAG Diagnosis (Weeks)				
N	493	157	507	1157
Mean (SD)	370.8 (346.90)	318.2 (313.10)	357.5 (319.77)	357.9 (330.89)
Median	278.0	227.0	272.0	268.0
Min, Max	(1, 2141)	(1, 1750)	(1, 1817)	(1, 2141)
Prior Hypotensive Therapy, n (%)				
Combination Therapy	34 (6.9)	15 (9.4)	35 (6.9)	84 (7.2)
Prostaglandins (Monotherapy)	234 (47.4)	65 (40.9)	232 (45.5)	531 (45.7)
Other (Monotherapy)	51 (10.3)	14 (8.8)	53 (10.4)	118 (10.1)
No Prior Therapy[1]	175 (35.4)	65 (40.9)	190 (37.3)	430 (37.0)
Prior Hypotensive Therapy, n (%)				
Prior Prostaglandin Therapy	252 (51.0)	74 (46.5)	256 (50.2)	582 (50.0)
No Prior Prostaglandin Therapy	242 (49.0)	85 (53.5)	254 (49.8)	581 (50.0)
Time on Current Hypotensive Therapy (Weeks)				
N	319	93	319	731
Mean (SD)	136.0 (191.81)	148.6 (198.06)	132.5 (183.21)	136.1 (188.73)
Median	53.0	67.0	59.0	59.0
Min, Max	(2, 1322)	(3, 886)	(-26, 1673)	(-26, 1673)
Mean Diurnal IOP on Day 1 (mmHg)				
N	494	159	510	1163
Mean (SD)	21.383 (1.1920)	21.476 (1.1995)	21.397 (1.2119)	21.402 (1.2011)
Median	21.333	21.500	21.333	21.333
Min, Max	(18.17, 24.17)	(18.67, 24.00)	(18.17, 24.50)	(18.17, 24.50)

BID = twice daily; OAG = open-angle glaucoma; OHT = ocular hypertension; QD = once daily; SD = standard deviation
Percentages are based on the number of subjects (N) in a given treatment group for the population being analyzed.
[1] Subjects were not on IOP-lowering therapy at screening and did not require a washout.
Source: ISE Table 14.1.1.1

8. EFFICACY OF NETARSUDIL

8.1 Efficacy Endpoints and Statistical Methods

The primary efficacy endpoint was mean IOP at 08:00, 10:00, and 16:00 hours at Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90). The primary analysis of mean IOP was completed using individual 2-sample 95% t-distribution confidence intervals (CIs) for each comparison of netarsudil QD to timolol at each timepoint. If the upper 95% confidence limit for the difference (netarsudil – timolol) was within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority of timepoints (at least 5 of 9), then netarsudil was to be considered clinically non-inferior to timolol. For CS302, which included a netarsudil BID treatment arm, the primary analysis was hierarchical to preserve alpha, first testing netarsudil QD to timolol then, if QD demonstrated clinical non-inferiority, secondarily testing netarsudil BID for non-inferiority to timolol.

Secondary analyses included mean change from diurnally adjusted baseline IOP at each timepoint (08:00, 10:00, and 16:00 hours at Week 2, Week 6, and Month 3); mean diurnal IOP at Week 2, Week 6, and Month 3; mean change from baseline for mean diurnal IOP at Week 2, Week 6, and Month 3; and mean percent change from diurnally adjusted baseline IOP at each timepoint at Week 2, Week 6, and Month 3.

The intent-to-treat (ITT) population was all randomized subjects who received at least 1 dose of study medication. The PP population was a subset of the ITT population that included subjects (and their visits) who did not have a major protocol violation likely to seriously affect the primary outcome of the study as judged by a masked evaluation prior to the unmasking of the study treatment. In addition to inclusion/exclusion criteria violations, the types of protocol deviations that may have been considered major included out-of-window visit, incorrect study drug assignment or instillation, subject failure to follow instructions, and use of prohibited concomitant medication.

The PP populations served as the primary analysis set for these trials because the studies were designed to demonstrate non-inferiority to an active comparator. The primary analysis population was the overall PP population with maximum baseline IOP < 27 mmHg in CS301 (with a post hoc analysis conducted on the PP population subset with maximum baseline IOP < 25 mmHg) and the PP population with maximum baseline IOP < 25 mmHg in CS302 and CS304. Secondary analyses were also conducted on the ITT population. Sensitivity analyses were conducted for the PP and ITT populations using various methods to impute missing data, including last observation carried forward (LOCF), baseline observation carried forward (BOCF), and Monte Carlo Markov Chain (MCMC). In CS304, secondary endpoints included subjects with maximum baseline IOP < 26 mmHg and < 27 mmHg.

In addition, an integrated analysis of efficacy (ISE) was performed on data pooled across the 3 efficacy studies. The primary efficacy outcome was mean IOP at 08:00, 10:00, and 16:00 hours at the Day 15 (Week 2), Day 43 (Week 6), and Day 90 (Month 3) study visits in subjects whose study eyes had maximum baseline IOP < 25 mmHg.

8.2 Efficacy Results in the Individual Phase 3 Efficacy Studies

In Phase 2 studies CS201 and CS202, netarsudil 0.02% QD provided clinically relevant and statistically significant reduction in mean IOP from baseline in subjects with baseline IOP up to 36 mmHg (Section 6.2). In each of the Phase 3 efficacy studies, netarsudil 0.02% QD provided clinically relevant and statistically significant ($p < 0.001$) reductions in mean IOP from baseline in subjects with baseline IOP up to <27 mmHg (CS301, CS302) and <30 mmHg (CS304). In these studies, netarsudil QD has been demonstrated to be non-inferior to timolol in subjects with baseline IOP up to < 30 mmHg (in CS304, which was the only study to include subjects with maximum baseline IOP ≥27 mmHg and < 30 mmHg) and up to < 25 mmHg (in CS301, CS302 and CS304, Table 12).

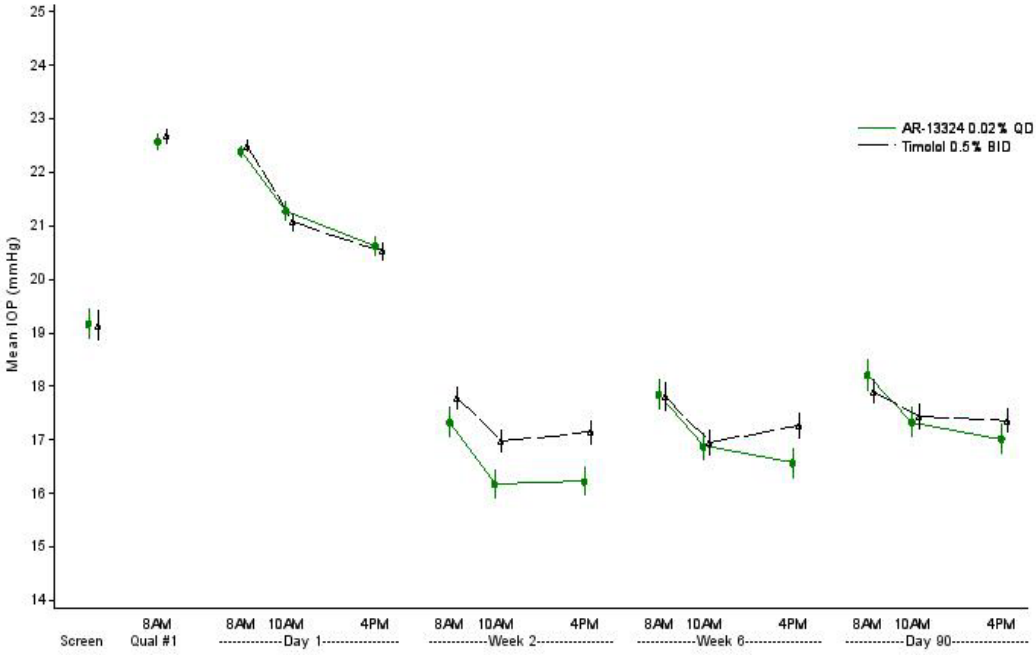
Table 12 Efficacy of Netarsudil 0.02% QD PM Demonstrated in Studies CS301, CS302, and CS304

Efficacy Endpoint	CS301 3-Month Efficacy	CS302 3-Month Efficacy	CS304 3-Month Efficacy
Non-inferiority vs timolol in patients with baseline IOP < 25 mmHg	Met Post hoc	Met Primary analysis	Met Primary analysis
Non-inferiority vs timolol in patients with baseline IOP ≤ 23 mmHg	Met Pre-specified	Not assessed	Not assessed
Non-inferiority vs timolol in patients with baseline IOP < 27 mmHg	Not met Primary analysis	Not met Pre-specified	Met Pre-specified
Non-inferiority vs timolol in patients with baseline IOP < 30 mmHg	Not assessed	Not assessed	Met Pre-specified

8.2.1 Mean IOP and Mean Change from Baseline IOP

In CS301 in the primary analysis of subjects in the PP population with maximum baseline IOP < 27 mmHg (full PP population), mean IOP is shown by visit in Table 13. Mean IOP changes from diurnally adjusted baseline with netarsudil QD across the 9 observation timepoints ranged from -3.3 to -5.0 mmHg and those for timolol BID ranged from -3.7 to -5.1 mmHg. In the secondary analysis of the PP population of subjects with maximum baseline IOP < 25 mmHg, mean IOP is shown by visit in Table 13 and Figure 4. Mean IOP changes from baseline with netarsudil QD across the 9 timepoints ranged from -3.7 to -5.1 mmHg and those for timolol BID ranged from -3.2 to -4.7 mmHg. Detailed results for change from baseline are shown in Appendix 1, Table 36.

Figure 4 Study CS301: Mean IOP (±1 SE) in the Study Eye by Visit and Timepoint (PP Population with Maximum Baseline IOP < 25 mmHg)



Source: CS301, Figure 5

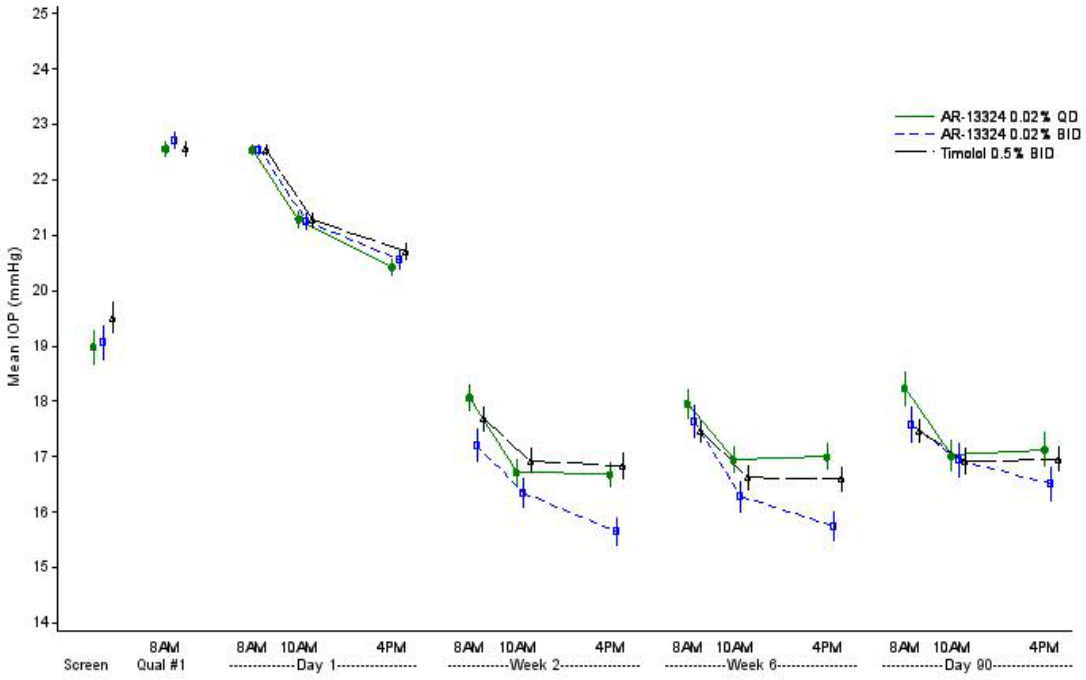
Table 13 Study CS301: Mean IOP Over Time for Netarsudil QD and Timolol (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil QD (N = 182)	Timolol (N = 188)	Mean Difference[1]	95% CI	Netarsudil QD (N = 113)	Timolol (N = 124)	Mean Difference[1]	95% CI
Baseline (Visit 3) 08:00	23.42 (N = 182)	23.37 (N = 188)	--	--	22.39 (N = 113)	22.50 (N = 124)	--	--
10:00	22.28 (N = 182)	21.92 (N = 188)	--	--	21.28 (N = 113)	21.07 (N = 124)	--	--
16:00	21.78 (N = 182)	21.45 (N = 188)	--	--	20.62 (N = 113)	20.52 (N = 124)	--	--
Day 15 08:00	18.68 (N = 177)	18.33 (N = 187)	035	(-0.27, 0.96)	17.34 (N = 108_	17.78 (N = 123)	-0.44	(-1.10, 0.22)
10:00	17.29 (N = 176)	17.55 (N = 186)	-0.26	(-0.87, 0.36)	16.18 (N = 107)	16.98 (N = 122)	-0.81	(-1.44, -0.17)
16:00	17.24 (N = 176)	17.70 (N = 186)	-0.45	(-1.08, 0.17)	16.22 (N = 107)	17.14 (N = 122)	-0.92	(-1.58, -0.26)
Day 43 08:00	19.35 (N = 170)	18.24 (N = 184)	1.11	(0.42, 1.80)	17.85 (N = 105)	17.81 (N = 121)	0.05	(-0.68, 0.77)
10:00	18.14 (N = 170)	17.44 (N = 184)	0.70	(0.04, 1.36)	16.88 (N = 105)	16.96 (N = 121)	-0.08	(-0.74, 0.58)
16:00	17.86 (N = 170)	17.71 (N = 183)	0.15	(-0.52, 0.83)	16.57 (N = 105)	17.26 (N = 120)	-0.69	(-1.40, 0.02)
Day 90 08:00	19.81 (N = 157)	18.47 (N = 181)	1.33	(0.64, 2.03)	18.22 (N = 99)	17.91 (N = 119)	0.31	(-0.40, 1.02)
10:00	18.92 (N = 158)	17.96 (N = 181)	0.96	(0.26, 1.66)	17.34 (N = 99)	17.43 (N = 119)	-0.09	(-0.82, 0.63)
16:00	18.48 (N = 158)	17.74 (N = 181)	0.74	(0.07, 1.42)	17.02 (N = 99)	17.37 (N = 119)	-0.35	(-1.03, 0.34)

CI = confidence interval; QD = once daily
[1] Difference from timolol and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil QD vs timolol.
Source: CS301 Tables 14.2.1.1 and 14.2.1.1.99.13

In CS302 in the primary analysis of subjects in the PP population with maximum baseline IOP < 25 mmHg, mean IOP is shown by visit for the netarsudil and timolol groups in Table 14 (netarsudil QD), Table 15 (netarsudil BID), and Figure 5. Mean IOP changes from diurnally adjusted baseline across the 9 timepoints in subjects with maximum baseline IOP < 25 mmHg ranged from -3.3 to -4.6 mmHg for netarsudil QD, -3.7 to -5.1 mmHg for timolol, and -4.1 to -5.4 mmHg for netarsudil BID. In the secondary analysis of the PP population of subjects with maximum baseline IOP < 27 mmHg (full PP population), mean IOP is shown by visit for the netarsudil and timolol groups in Table 14 (netarsudil QD) and Table 15 (netarsudil BID). Mean IOP changes from diurnally adjusted baseline with netarsudil QD across the 9 timepoints ranged from -3.6 to -4.6 mmHg for netarsudil QD, -4.3 to -5.3 mmHg for netarsudil BID, and -3.9 to -5.4 mmHg for timolol. Detailed results for change from baseline are shown in Appendix 1, Table 37.

Figure 5 Study CS302: Mean IOP (±1 SE) in the Study Eye by Visit and Timepoint (PP Population with Maximum Baseline IOP < 25 mmHg)



Source: CS302, Figure 1

Table 14 Study CS302: Mean IOP Over Time for Netarsudil QD and Timolol (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil QD (N = 206)	Timolol (N = 217)	Mean Difference[1]	95% CI	Netarsudil QD (N = 129)	Timolol (N = 142)	Mean Difference[1]	95% CI
Baseline (Visit 3) 08:00	23.51 (N = 206)	23.45 (N = 217)	--	--	22.54 (N = 129)	22.54 (N = 142)	--	--
10:00	22.31 (N = 206)	22.18 (N = 217)	--	--	21.29 (N = 129)	21.27 (N = 142)	--	--
16:00	21.56 (N = 206)	21.61 (N = 217)	--	--	20.43 (N = 129)	20.71 (N – 142)	--	--
Day 15 08:00	19.02 (N = 201)	18.25 (N = 217)	0.77	(0.22, 1.32)	18.07 (N = 127)	17.69 (N = 142)	0.37	(-0.25, 0.99)
10:00	17.74 (N = 199)	17.49 (N = 215)	0.25	(-0.33, 0.82)	16.72 (N = 126)	16.93 (N = 141)	-0.21	(-0.82, 0.41)
16:00	17.37 (N = 200)	17.59 (N = 215)	-0.22	(-0.78, 0.34)	16.68 (N = 126)	16.83 (N = 141)	-0.15	(-0.75, 0.46)
Day 43 08:00	19.37 (N = 193)	18.08 (N = 215)	1.29	(0.66, 1.93)	17.95 (N = 122)	17.46 (N = 141)	0.49	(-0.13, 1.12)
10:00	18.11 (N = 187)	17.31 (N = 215)	0.80	(0.19, 1.41)	16.95 (N = 120)	16.63 (N = 141)	0.32	(-0.31, 0.95)
16:00	17.88 (N = 187)	17.25 (N = 215)	0.63	(0.07, 1.19)	17.00 (N = 120)	16.60 (N = 141)	0.40	(-0.22, 1.02)
Day 90 08:00	19.43 (N = 177)	18.21 (N = 214)	1.21	(0.54, 1.89)	18.24 (N = 116)	17.47 (N = 140)	0.77	(0.03, 1.50)
10:00	18.18 (N = 173)	17.52 (N = 213)	0.66	(0.01, 1.31)	17.03 (N = 114)	16.92 (N = 140)	0.10	(-0.59, 0.80)
16:00	17.73 (N = 170)	17.67 (N = 212)	0.06	(-0.58, 0.70)	17.13 (N = 114)	16.95 (N = 139)	0.18	(-0.55, 0.91)

CI = confidence interval; QD = once daily
[1] Difference from timolol and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil QD vs timolol.
Source: CS302 Tables 14.2.1.1.1 and 14.2.1.1.2

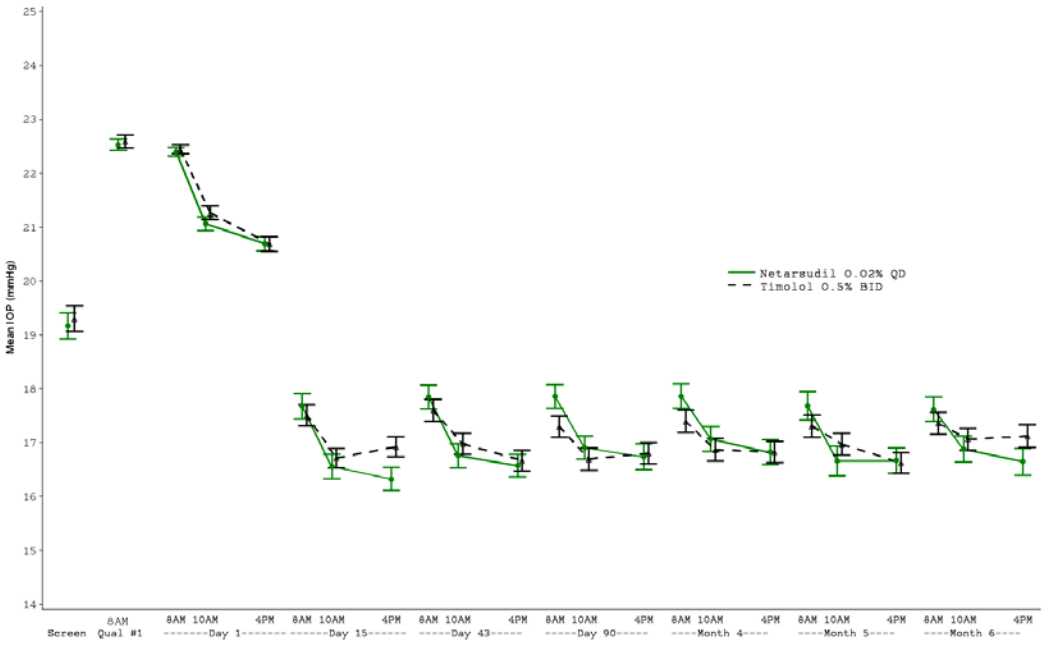
Table 15 Study CS302: Mean IOP Over Time for Netarsudil BID and Timolol (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil BID (N = 209)	Timolol (N = 217)	Mean Difference[1]	95% CI	Netarsudil BID (N = 132)	Timolol (N = 142)	Mean Difference[1]	95% CI
Baseline (Visit 3) 08:00	23.50 (N = 209)	23.45 (N = 217)	--	--	22.55 (N = 132)	22.54 (N = 142)	--	--
10:00	22.26 (N = 209)	22.18 (N = 217)	--	--	21.27 (N = 132)	21.27 (N = 142)	--	--
16:00	21.49 (N = 209)	21.61 (N = 217)	--	--	20.56 (N = 132)	20.71 (N – 142)	--	--
Day 15 08:00	18.20 (N = 191)	18.25 (N = 217)	-0.05	(-0.67, 0.56)	17.21 (N = 122)	17.69 (N = 142)	-0.48	(-1.19, 0.22)
10:00	16.91 (N = 185)	17.49 (N = 215)	-0.58	(-1.17, 0.00)	16.35 (N = 120)	16.93 (N = 141)	-0.57	(-1.24, 0.09)
16:00	16.28 (N = 183)	17.59 (N = 215)	-1.31	(-1.89, -0.73)	15.65 (N = 118)	16.83 (N = 141)	-1.18	(-1.82, -0.54)
Day 43 08:00	18.57 (N = 169)	18.08 (N = 215)	0.49	(-0.11, 1.08)	17.64 (N = 111)	17.46 (N = 141)	0.17	(-0.51, 0.86)
10:00	17.09 (N = 162)	17.31 (N = 215)	-0.22	(-0.82, 0.38)	16.28 (N = 106)	16.63 (N = 141)	-0.34	(-1.02, 0.33)
16:00	16.58 (N = 162)	17.25 (N = 215)	-0.67	(-1.28, -0.06)	15.75 (N = 106)	16.60 (N = 141)	-0.85	(-1.53, -0.17)
Day 90 08:00	18.66 (N = 138)	18.21 (N = 214)	0.45	(-0.24, 1.14)	17.58 (N = 91)	17.47 (N = 140)	0.11	(-0.64, 0.86)
10:00	17.81 (N = 131)	17.52 (N = 213)	0.28	(-0.40, 0.97)	16.94 (N = 88)	16.92 (N = 140)	0.02	(-0.72, 0.77)
16:00	17.08 (N = 131)	17.67 (N = 212)	-0.59	(-1.25, 0.08)	16.51 (N = 88)	16.95 (N = 139)	-0.44	(-1.16, 0.27)

CI = confidence interval; QD = once daily
[1] Difference from timolol and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil QD vs timolol.
Source: CS302 Tables 14.2.1.1.1 and 14.2.1.1.2

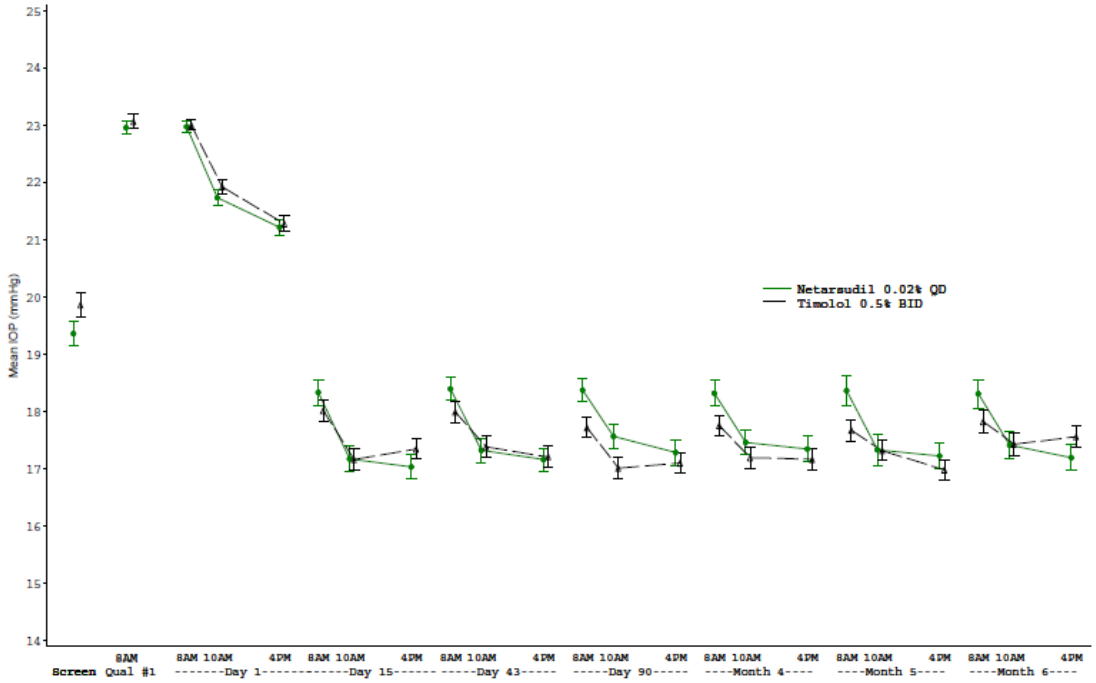
In CS304 in the primary analysis of subjects in the PP population with maximum baseline IOP < 25 mmHg, mean IOP is shown by visit in Table 16 and Figure 6. Mean IOP changes from diurnally adjusted across the 9 timepoints in subjects with maximum baseline IOP < 25 mmHg ranged from -3.9 to -4.7 mmHg for netarsudil QD and -3.8 to -5.2 mmHg for timolol. In the secondary analysis of subjects with maximum baseline IOP < 27 mmHg, mean IOP is shown by visit in Table 16 and Figure 7. Mean IOP changes from diurnally adjusted baseline IOP across the 9 timepoints ranged from -3.9 to -4.7 mmHg for netarsudil QD and -3.9 to -5.3 mmHg for timolol. In the secondary analysis of subjects with maximum baseline IOP < 30 mmHg (full PP population), mean IOP is shown by visit in Table 17. Mean IOP changes from diurnally adjusted baseline IOP across the 9 timepoints ranged from -4.0 to -4.7 mmHg for netarsudil QD and -4.1 to -5.5 mmHg for timolol. Detailed results for change from baseline are shown in Appendix 1, Table 39.

Figure 6 **Study CS304: Mean IOP (±1SE) in the Study Eye by Visit and Timepoint (PP Population -- Subjects with Maximum Baseline IOP < 25 mmHg)**



Source: CS304, Figure 14.2.1

Figure 7 **Study CS304: Mean IOP (± 1 SE) in the Study Eye by Visit and Timepoint (PP Population-- Subjects with Maximum Baseline IOP < 27 mmHg)**



Source: CS304, Figure 14.2.3

Table 16 Study CS304: Mean IOP Over Time for Netarsudil QD and Timolol (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil QD (N = 240)	Timolol (N = 248)	Mean Difference[1]	95% CI	Netarsudil QD (N = 186)	Timolol (N = 186)	Mean Difference[1]	95% CI
Baseline (Visit 3) 08:00	22.98 (N = 240)	23.01 (N = 248)	--	--	22.40 (N = 186)	22.44 (N = 186)	--	--
10:00	21.74 (N = 240)	21.92 (N = 248)	--	--	21.06 (N = 186)	21.27 (N = 186)	--	--
16:00	21.22 (N = 240)	21.28 (N = 248)	--	--	20.69 (N = 186)	20.69 (N = 186)	--	--
Day 15 08:00	18.34 (N = 237)	18.02 (N = 245)	0.32	(-0.25, 0.89)	17.68 (N = 184)	17.51 (N = 183)	0.17	(-0.43, 0.77)
10:00	17.17 (N = 233)	17.17 (N = 245)	0.00	(-0.55, 0.56)	16.55 (N = 181)	16.71 (n = 183)	-0.16	(-0.73, 0.41)
16:00	17.04 (N = 233)	17.35 (N = 245)	-0.31	(-0.85, 0.23)	16.32 (N = 181)	16.92 (N = 183)	-0.60	(-1.16, -0.04)
Day 43 08:00	18.40 (N = 228)	18.00 (N = 245)	0.40	(-0.14, 0.94)	17.84 (N = 177)	17.60 (N – 183)	0.25	(-0.34, 0.83)
10:00	17.33 (N = 227)	17.39 (N = 244)	-0.06	(-0.61, 0.49)	16.75 (N = 177)	16.98 (N = 182)	-0.22	(-0.82, 0.37)
16:00	17.16 (N = 226)	17.21 (N = 244)	-0.05	(-0.58, 0.49)	16.57 (N = 176)	16.67 (N = 182)	-0.10	(-0.66, 0.46)
Day 90 08:00	18.38 (N = 214)	17.72 (N = 239)	0.65	(0.11, 1.19)	17.86 (N = 167)	17.29 (N = 179)	0.56	(-0.02, 1.15)
10:00	17.57 (N = 212)	17.01 (N = 238)	0.55	(-0.01, 1.12)	16.90 (N = 166)	16.69 (N = 179)	0.21	(-0.37, 0.79)
16:00	17.29 (N = 211)	17.11 (N = 238)	0.18	(-0.38, 0.75)	16.73 (N = 165)	16.80 (N = 179)	-0.07	(-0.68, 0.55)

CI = confidence interval; QD = once daily
[1] Difference from timolol and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil QD vs timolol.
Source: CS304 Tables 14.2.1.1.1, 14.2.1.2.10

Table 17 Study CS304: Mean IOP Over Time (PP Population with Baseline IOP < 30 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg			
	Netarsudil QD (N = 306)	Timolol (N = 316)	Mean Difference[1]	95% CI
Baseline (Visit 3) 08:00	23.93 (N = 306)	23.89 (N = 316)	--	--
10:00	22.67 (N = 306)	22.77 (N = 316)	--	--
16:00	22.17 (N = 306)	22.04 (N = 316)	--	--
Day 15 08:00	19.20 (N = 302)	18.60 (N = 312)	0.60	(0.02, 1.17)
10:00	17.93 (N = 297)	17.80 (N = 312)	0.13	(-0.42, 0.69)
16:00	17.76 (N = 297)	17.85 (N = 312)	-0.09	(-0.62, 0.44)
Day 43 08:00	19.45 (N = 289)	18.52 (N = 310)	0.93	(0.35, 1.52)
10:00	18.12 (N = 286)	17.89 (N = 309)	0.23	(-0.31, 0.78)
16:00	17.89 (N = 285)	17.88 (N = 309)	0.01	(-0.54, 0.56)
Day 90 08:00	19.24 (N = 261)	18.35 (N = 300)	0.89	(0.30, 1.49)
10:00	18.30 (N = 259)	17.60 (N = 299)	0.70	(0.13, 1.27)
16:00	18.02 (N = 258)	17.66 (N = 299)	0.36	(-0.20, 0.93)

CI = confidence interval; QD = once daily
[1] Difference from timolol and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil QD vs timolol.
Source: CS304 Table 14.2.1.2.1

8.2.2 Non-Inferiority to Timolol in Subjects with Baseline IOP < 25 mmHg

Based on the non-inferiority definition for these studies, if the upper 95% confidence limit for the difference (netarsudil – timolol) was within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority of timepoints (at least 5 of 9), then netarsudil was to be considered clinically non-inferior to timolol.

In CS301, netarsudil did not meet the pre-specified statistical criteria for demonstrating non-inferiority to timolol in the full PP population of subjects with baseline IOP < 27 mmHg. In a pre-specified secondary analysis of subjects with maximum baseline IOP ≤ 23 mmHg, netarsudil met the requirement for clinical non-inferiority to timolol and showed greater IOP lowering compared to timolol in mean IOP values at all 9 timepoints (data not shown). Based on these results and the results of the Phase 2b study CS202, additional post hoc analyses were conducted to further explore the effect of baseline IOP. These post hoc analyses showed that netarsudil also met the criteria for non-inferiority to timolol in the PP subgroup with maximum baseline IOP < 25 mmHg. Results were within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at 8 of 9 timepoints. The differences in mean IOP for netarsudil and timolol (expressed as [netarsudil – timolol]) ranged from -0.9 to +0.3 mmHg across the 9 timepoints (Table 18).

Additionally, post hoc analyses of the PP subgroups with maximum baseline IOP ≤ 22, ≤ 24, and ≤ 25 mmHg all met the criteria for non-inferiority of netarsudil to timolol (data not shown).

Results of the PP and ITT analyses conducted using observed data only were generally consistent with the results obtained using different methods for imputing missing data, both for the primary efficacy endpoint and for the prospectively defined secondary efficacy endpoints. In CS302, both dosing regimens met the pre-specified criteria for non-inferiority to timolol in the primary efficacy population (PP population with maximum baseline IOP < 25 mmHg); the upper limit of the 95% CIs was within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority of the 9 timepoints. The differences in mean IOP for netarsudil vs timolol (expressed as [netarsudil – timolol]) ranged from -0.2 to +0.8 mmHg for netarsudil QD (Table 18) and -1.2 to +0.2 mmHg for netarsudil BID (Table 19).

The robustness of the non-inferiority result was also demonstrated in sensitivity analyses performed on the PP and ITT populations using various methods to impute missing data (LOCF with time-relevant measures, BOCF with time-relevant measures, or a MCMC multiple imputation method). For subjects with baseline IOP < 25 mmHg, non-inferiority to timolol was demonstrated for all analyses populations with the exception of the PP and ITT populations using BOCF to impute missing data.

In CS304, netarsudil QD met the pre-specified criteria for non-inferiority to timolol BID in the primary efficacy population (PP population with maximum baseline IOP < 25 mmHg); the upper limits of the 95% CIs were within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at 8 of the 9 timepoints. The differences in mean IOP for netarsudil QD vs timolol (expressed as [netarsudil – timolol]) ranged from -0.6 to +0.6 mmHg (Table 18).

The robustness of the non-inferiority result was demonstrated in sensitivity analyses performed on the PP and ITT populations using various methods to impute missing data (LOCF with time-relevant measures, BOCF with time-relevant measures, or a MCMC multiple imputation method).

Table 18 Studies CS301, CS302, and CS304: Mean IOP Difference from Timolol by Study for QD Regimen (PP Population with Baseline IOP < 25 mmHg)

Study Visit and Timepoint	CS301			CS302			CS304		
	Netarsudil 0.02% QD			Netarsudil 0.02% QD			Netarsudil 0.02% QD		
	N	Diff.	95% CI	N	Diff.	95% CI	N	Diff.	95% CI
Day 15 08:00	108	-0.44	(-1.10, 0.22)	127	0.37	(-0.25, 0.99)	184	0.17	(-0.43, 0.77)
10:00	107	-0.81	(-1.44, -0.17)	126	-0.21	(-0.82, 0.41)	181	-0.16	(-0.73, 0.41)
16:00	107	-0.92	(-1.58, -0.26)	126	-0.15	(-0.75, 0.46)	181	-0.60	(-1.16, -0.04)
Day 43 08:00	105	0.05	(-0.68, 0.77)	122	0.49	(-0.13, 1.12)	177	0.25	(-0.34, 0.83)
10:00	105	-0.08	(-0.74, 0.58)	120	0.32	(-0.31, 0.95)	177	-0.22	(-0.82, 0.37)
16:00	105	-0.69	(-1.40, 0.02)	120	0.40	(-0.22, 1.02)	176	-0.10	(-0.66, 0.46)
Day 90 08:00	99	0.31	(-0.40, 1.02)	116	0.77	(0.03, 1.50)	167	0.56	(-0.02, 1.15)
10:00	99	-0.09	(-0.82, 0.63)	114	0.10	(-0.59, 0.80)	166	0.21	(-0.37, 0.79)
16:00	99	-0.35	(-1.03, 0.34)	114	0.18	(-0.55, 0.91)	165	-0.07	(-0.68, 0.55)

CI = confidence interval; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference = netarsudil – timolol
Difference from timolol 0.5% and two-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil 0.02% QD vs timolol 0.5% BID.
Source: CS301 Table 14.2.1.1.99.13; CS302 Table 14.2.1.1.1; CS304 Table 14.2.1.1.1

Table 19 Study CS302: Netarsudil 0.02% BID Mean IOP Difference from Timolol (PP Population with Baseline IOP < 25 mmHg)

Study Visit and Timepoint	CS302		
	Netarsudil 0.02% BID		
	N	Diff.	95% CI
Day 15 08:00	122	-0.48	(-1.19, 0.22)
10:00	120	-0.57	(-1.24, 0.09)
16:00	118	-1.18	(-1.82, -0.54)
Day 43 08:00	111	0.17	(-0.51, 0.86)
10:00	106	-0.34	(-1.02, 0.33)
16:00	106	-0.85	(-1.53, -0.17)
Day 90 08:00	91	0.11	(-0.64, 0.86)
10:00	88	0.02	(-0.72, 0.77)
16:00	88	-0.44	(-1.16, 0.27)

BID = twice daily; CI = confidence interval; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference = netarsudil – timolol
Difference from timolol 0.5% and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil 0.02% BID vs timolol 0.5% BID.
Source: CS302 Table 14.2.1.1.1

8.2.3 Non-Inferiority to Timolol with Baseline IOP < 27 mmHg and < 30 mmHg

In CS301, netarsudil did not meet the pre-specified statistical criteria for demonstrating non-inferiority to timolol in the full PP population of subjects with maximum baseline IOP < 27 mmHg (all 9 timepoints had upper 95% CI limits for the difference [netarsudil – timolol] within 1.0 mmHg). Results for that population were within 1.5 mmHg at 6 of the 9 timepoints and within 1.0 mmHg at 4 of 9 timepoints. The differences in mean IOP for netarsudil and timolol (expressed as [netarsudil – timolol]) ranged from -0.5 to +1.3 mmHg across the 9 timepoints (Table 20).

In CS302, netarsudil BID but not QD met the criteria for non-inferiority to timolol in the secondary analysis of the PP population of subjects with maximum baseline IOP < 27 mmHg (Table 20).

In CS304, netarsudil QD met the criteria for non-inferiority to timolol in the secondary analyses of the PP populations of subjects with maximum baseline IOP < 27 mmHg and < 30 mmHg (Table 21). This was the only study among the 3 efficacy studies that included subjects with maximum baseline IOP ≥ 27 and < 30 mmHg.

Table 20 Studies CS301 and CS302: Mean IOP Difference from Timolol by Study (PP Population with Baseline IOP < 27 mmHg)

Study Visit and Timepoint	CS301			CS302					
	Netarsudil 0.02% QD			Netarsudil 0.02% QD			Netarsudil 0.02% BID		
	N	Diff.	95% CI	N	Diff.	95% CI	N	Diff.	95% CI
Day 15 08:00	177	0.35	(-0.27, 0.96)	201	0.77	(0.22, 1.32)	191	-0.05	(-0.67, 0.56)
10:00	176	-0.26	(-0.87, 0.36)	199	0.25	(-0.33, 0.82)	185	-0.58	(-1.17, 0.00)
16:00	176	-0.45	(-1.08, 0.17)	200	-0.22	(-0.78, 0.34)	183	-1.31	(-1.89, -0.73)
Day 43 08:00	170	1.11	(0.42, 1.80)	193	1.29	(0.66, 1.93)	169	0.49	(-0.11, 1.08)
10:00	170	0.70	(0.04, 1.36)	187	0.80	(0.19, 1.41)	162	-0.22	(-0.82, 0.38)
16:00	170	0.15	(-0.52, 0.83)	187	0.63	(0.07, 1.19)	162	-0.67	(-1.28, -0.06)
Day 90 08:00	157	1.33	(0.64, 2.03)	177	1.21	(0.54, 1.89)	138	0.45	(-0.24, 1.14)
10:00	158	0.96	(0.26, 1.66)	173	0.66	(0.01, 1.31)	131	0.28	(-0.40, 0.97)
16:00	158	0.74	(0.07, 1.42)	170	0.06	(-0.58, 0.70)	131	-0.59	(-1.25, 0.08)

BID = twice daily; CI = confidence interval; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference = netarsudil – timolol
Difference from timolol 0.5% and 2-sided CIs and p-values are based on 2-sample t-tests comparing netarsudil 0.02% QD and BID vs timolol 0.5%.
Source: CS301 Table 14.2.1.1; CS302 Table 14.2.1.1.2

Table 21 Study CS304: Mean IOP Difference from Timolol for Subjects with Maximum Baseline IOP < 27 mmHg and < 30 mmHg (PP Population)

Study Visit, Timepoint		Netarsudil 0.02% QD (< 27 mmHg)			Netarsudil 0.02% QD (< 30 mmHg)		
		N	Diff.	95% CI	N	Diff.	95% CI
Day 15	08:00	237	0.32	(-0.25, 0.89)	302	0.60	(0.02, 1.17)
	10:00	233	0.00	(-0.55, 0.56)	297	0.13	(-0.42, 0.69)
	16:00	233	-0.31	(-0.85, 0.23)	297	-0.09	(-0.62, 0.44)
Day 43	08:00	228	0.40	(-0.14, 0.94)	289	0.93	(0.35, 1.52)
	10:00	227	-0.06	(-0.61, 0.49)	286	0.23	(-0.31, 0.78)
	16:00	226	-0.05	(-0.58, 0.49)	285	0.01	(-0.54, 0.56)
Day 90	08:00	214	0.65	(0.11, 1.19)	261	0.89	(0.30, 1.49)
	10:00	212	0.55	(-0.01, 1.12)	259	0.70	(0.13, 1.27)
	16:00	211	0.18	(-0.38, 0.75)	258	0.36	(-0.20, 0.93)

CI = confidence interval; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference = netarsudil – timolol
Difference from timolol 0.5% and 2-sided CIs are based on 2-sample t-tests comparing netarsudil 0.02% QD vs timolol 0.5% BID.
Source: CS304 Table 14.2.1.2.10 and Table 14.2.1.2.1

8.3 Efficacy Results of the Pooled Analysis

The pooled populations for netarsudil QD provided larger sample sizes for the various subgroup analyses than available from the individual studies. In general, the subgroup analysis results for the pooled population agreed with the results obtained in each individual Phase 3 study.

In the pooled efficacy analysis of PP subjects with maximum baseline IOP < 25 mmHg, netarsudil 0.02% QD produced clinically relevant and statistically significant ($p < 0.0001$) reductions in mean IOP from baseline at all timepoints studied. Mean IOP changes from baseline with netarsudil across the 9 observation timepoints ranged from -3.6 to -4.8 mmHg and those for timolol ranged from -3.7 to -5.0 mmHg. Netarsudil met the criteria for non-inferiority to timolol, with differences in mean IOP for netarsudil vs timolol (expressed as [netarsudil – timolol]) ranging from -0.5 to +0.6 mmHg.

Non-inferiority of netarsudil was confirmed in the ITT population and the robustness of the analysis was confirmed by multiple forms of data imputation including last observation carried forward (LOCF) and Monte-Carlo Markov Chain (MCMC).

In addition, netarsudil QD showed clinically relevant reductions from mean baseline IOP at all treatment timepoints for subgroups based on age (< 65 years; ≥ 65 years), sex (male; female), race (Caucasian; non-Caucasian), iris color (blue/grey/green; black/brown). IOP reductions in subgroups were generally similar to those in the primary PP population with maximum baseline IOP < 25 mmHg.

Analyses of mean IOP and mean change from baseline IOP were performed for the following additional maximum baseline IOP categories within the PP population: < 22, < 23, ≤ 23, < 24, < 26 mmHg, < 27 mmHg (ad hoc ISE Table 14.2.99.21.1), and < 30 mmHg. Netarsudil QD demonstrated non-inferiority to timolol in all maximum baseline IOP populations.

Mean baseline IOP was similar between the netarsudil and timolol treatment groups within each population defined by maximum baseline IOP. With netarsudil QD treatment, the mean change from baseline IOP was similar in each population, ranging from -3.6 to -4.9 mmHg, -3.6 to -4.8 mmHg, -3.6 to -4.7 mmHg, -3.7 to -4.7 mmHg, and -3.7 to -4.8 mmHg in the populations with maximum baseline IOP of < 22 mmHg, < 24 mmHg, < 26 mmHg, < 27 mmHg, and < 30 mmHg, respectively. In contrast, treatment with timolol produced smaller mean changes from baseline IOP in the lower baseline IOP populations and larger changes in the higher baseline IOP populations, ranging from -2.8 to -4.3 mmHg, -3.5 to -4.8 mmHg, -3.8 to -5.1 mmHg, -3.9 to -5.2 mmHg, and -4.0 to -5.3 mmHg in the populations with maximum baseline IOP of < 22 mmHg, < 24 mmHg, < 26 mmHg, < 27 mmHg, and < 30 mmHg, respectively.

The trend for timolol producing larger IOP reductions at higher baseline IOPs compared to lower baseline IOPs, while netarsudil produced similar IOP reductions across all baseline IOP subgroups, was evident in a comparison of Day 90 mean diurnal IOP (Figure 8). Netarsudil also demonstrated statistically significant greater efficacy relative to timolol at lower baseline IOPs when comparing the proportion of subjects who achieved a ≥ 20% IOP reduction from baseline (Figure 9).

Analyses of mean IOP and mean change from baseline IOP were performed for the following pre-study medication use categories within the primary PP population of subjects with maximum baseline IOP < 25 mmHg: prior prostaglandin use, no prior prostaglandin use, and no prior ocular hypotensive therapy. For all subgroups, netarsudil showed a clinically relevant and statistically significant reduction from mean baseline IOP at all on-treatment timepoints.

Figure 8 **Pooled Analysis: Change in Day 90 Mean Diurnal IOP (± 1 SE) in the Study Eye Relative to Maximum Baseline IOP (PP Population)**

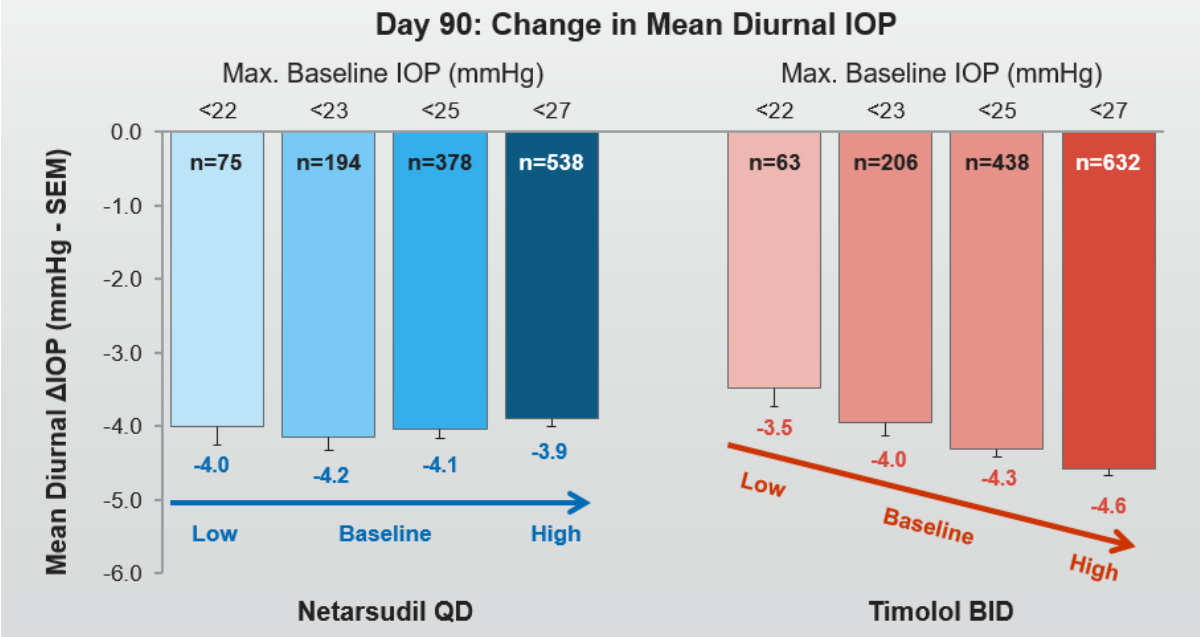
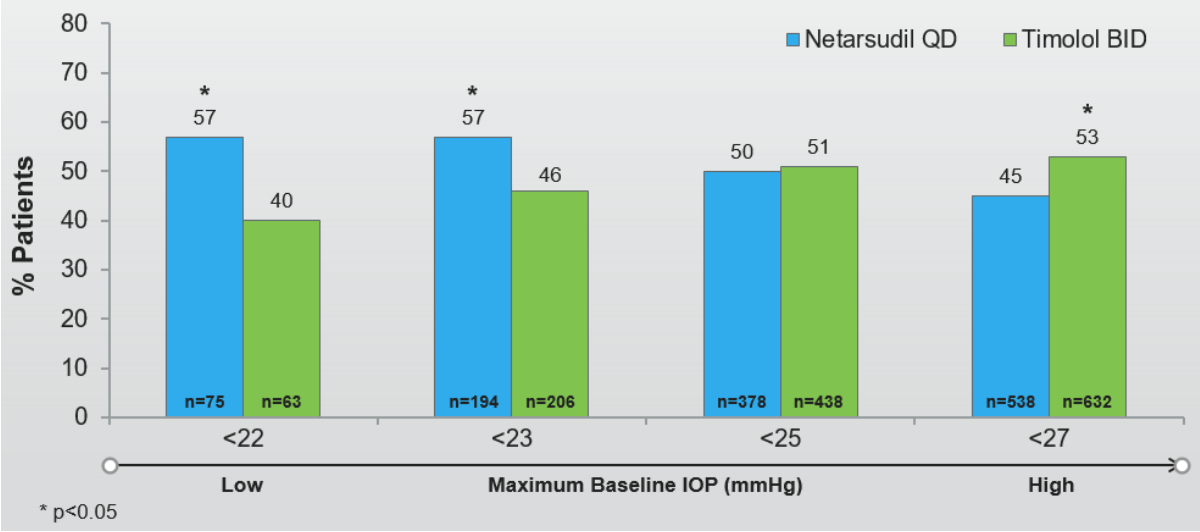


Figure 9 **Pooled Analysis: Proportion of Subjects Achieving ≥20% IOP Reduction at Day 90 by Baseline IOP**

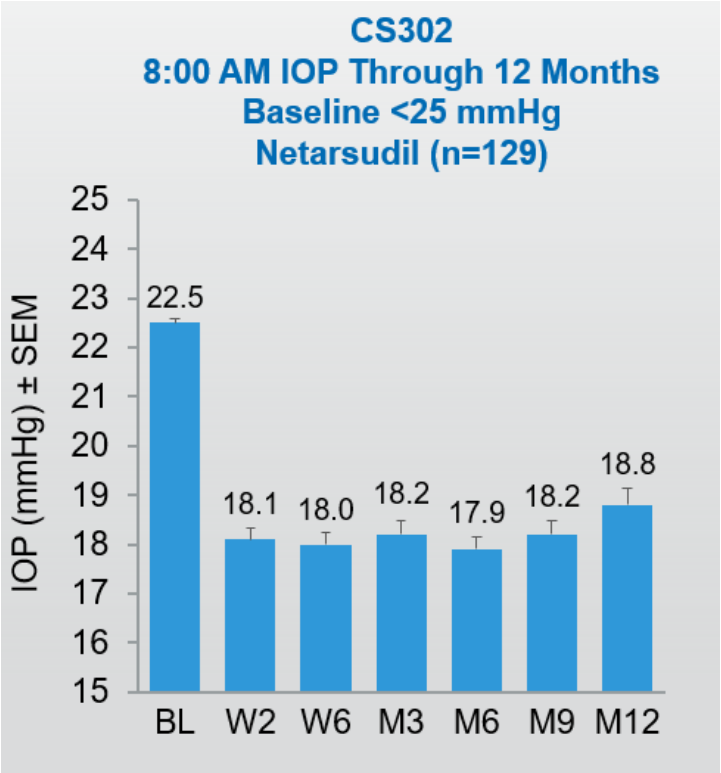


8.4 Efficacy Over 12 Months

In CS302, IOP was measured at 08:00 hours throughout the 12-month duration of the trial. For subjects with maximum baseline IOP < 25 mmHg, mean IOP at 08:00 hours ranged from

17.9 to 18.8 mmHg for netarsudil dosed QD, demonstrating persistence of ocular hypotensive efficacy (Figure 10).

Figure 10 Study CS302: Mean IOP (±1 SE) in the Study Eye by Visit Over 12 Months (PP Population with Maximum Baseline IOP < 25 mmHg)



Note: IOP was measured only at 08:00 hours as a safety measure at Months 6, 9, and 12

8.5 Efficacy Conclusions

In the Phase 3 efficacy studies, individually and in the pooled analysis, treatment with netarsudil ophthalmic solution 0.02% QD demonstrated clinically relevant and statistically significant reductions in IOP from baseline that were non-inferior to timolol. Efficacy was stable over 12 months.

9. SAFETY OF NETARSUDIL

9.1 Safety Evaluation Plan

The safety of netarsudil was evaluated in each study and in a pooled analysis across the 4 Phase 3 studies (CS301, CS302, CS303, and CS304). The safety evaluation was conducted on all subjects who were randomized into a study and received at least 1 dose of study medication. The safety parameters in these studies provided a comprehensive assessment of the ocular and systemic safety of netarsudil and included extent of exposure, adverse events (AEs), visual acuity, biomicroscopy, ophthalmoscopy, cup to disc ratio, comfort assessment, pupil size, visual fields, specular microscopy, pachymetry, IOP, vital signs, and clinical laboratory testing.

The only major limitations of the safety database were the exclusion of pregnant or nursing women in the clinical studies and the small number of pediatric subjects (n=2; one 11 years old and one 14 years old) in the Phase 3 studies.

Subject disposition and demographics for the pooled safety population are summarized in Section 7.2 and Section 7.3, respectively.

9.2 Exposure

The numbers of subjects treated in the netarsudil studies are summarized by treatment and study in Table 5. Across the Phase 1 and Phase 2 studies, 130 subjects received netarsudil 0.02%, 97 received netarsudil 0.01%, and 19 received netarsudil 0.04%, all administered QD. Across the Phase 3 studies, 839 subjects received netarsudil 0.02% QD, the concentration and dosing frequency for which this application seeks approval. In addition, 289 subjects received netarsudil BID and 839 subjects received timolol.

The duration of treatment with netarsudil 0.02% QD across the 4 Phase 3 studies was ≥ 365 days for 38 subjects, 181 to 364 days for 257 subjects, 91 to 180 days for 340 subjects, 31 to 90 days for 152 subjects, and 1 to 30 days for 52 subjects (Table 22). The duration of treatment with netarsudil 0.02% BID was ≥ 365 days for 15 subjects, 181 to 364 days for 98 subjects, 91 to 180 days for 58 subjects, 31 to 90 days for 68 subjects, and 1 to 30 days for 50 subjects. The duration of exposure to netarsudil 0.02% QD and BID in these studies met the numbers needed for completion of 12 months of therapy as discussed at the Pre-NDA Meeting.

Table 22 Treatment Duration in Phase 3 Studies

Treatment	Total N	Number (%) of Subjects				
		1 to 30 days	31 to 90 days	91 to 180 days	181 to 364 days	≥ 365 days
Netarsudil 0.02% QD						
CS301	203	12	72	119	0	0
CS302	251	17	29	34	136	35
CS303	34	2	6	8	15	3
CS304	351	21	45	179	106	0
Total	**839**	**52**	**152**	**340**	**257**	**38**
Netarsudil 0.02% BID						
CS302	253	41	55	48	94	15
CS303	36	9	13	10	4	0
Total	**289**	**50**	**68**	**58**	**98**	**15**
Timolol						
CS301	208	6	75	127	0	0
CS302	251	6	5	18	177	45
CS303	23	1	1	2	13	6
CS304	357	9	14	206	128	0
Total	**839**	**22**	**95**	**353**	**318**	**51**

Source: New ISS Table 14.3.12.9.1.99

9.3 Adverse Events

9.3.1 Overview of Adverse Events

AEs were obtained both as solicited comments from subjects and as observations by the investigators. AEs were to be reported for any change (expected or unexpected) in a subject's ocular and/or systemic health that occurred after initiation of study treatment. As such, all AEs are considered to be treatment-emergent AEs (TEAEs). Any changes in any safety parameters (visual acuity, biomicroscopy and ophthalmoscopy parameters, pachymetry, visual field, heart rate, and blood pressure) were reported as TEAEs based upon assessment by the investigator. The coding of TEAEs was standardized using a MedDRA dictionary and reported using Preferred Terms (PTs) grouped by System Organ Class (SOC). The pooled analysis was based on coding of the TEAEs with MedDRA version 19.0.

In the pooled population, the number of subjects that experienced TEAEs was higher in the netarsudil groups (QD: 83.3%; BID: 90.3%) compared to timolol (60.3%). A similar pattern was observed in ocular TEAEs with higher incidences in the netarsudil groups (QD: 79.3%; BID: 89.3%) compared to timolol (49.3%) (Table 23).

Of the subjects who experienced a TEAE, the majority in the netarsudil QD (58.5%; 409/699) and timolol (73.3%; 371/506) groups experienced TEAEs that were mild in intensity. However, a higher incidence of netarsudil BID subjects (46.4%; 121/261) experienced TEAEs of moderate intensity compared to netarsudil QD (35.2%; 246/699) and timolol (21.9%; 111/506) subjects (Table 23).

A higher proportion of subjects in the netarsudil groups (QD: 73.1%; BID: 84.1%) compared to those in the timolol group (42.3%) experienced treatment-related events. Serious TEAEs were infrequent and were balanced across treatment groups. There were 2 treatment-related serious TEAEs; one each in the netarsudil QD and BID groups. The number of subjects with TEAEs resulting in discontinuation of study medication was dose frequency-related and highest in the netarsudil BID group (57.8%) followed by the QD group (22.1%) compared to timolol BID (4.1%). Serious TEAEs are described in Section 9.4.2 and TEAEs resulting in discontinuation of study medication are described in Section 9.4.3.

These results are shown by study for CS301 and CS302 in Table 24 and for CS303 and CS304 in Table 25.

Table 23 Pooled Phase 3 Safety Analysis: Overall Summary of Treatment-Emergent Adverse Events

	Netarsudil 0.02% QD (N = 839) n (%)	**Netarsudil 0.02% BID (N = 289) n (%)**	**Timolol 0.5% BID (N = 839) n (%)**
Number of TEAEs	2696	1324	1142
Number of subjects with at least one TEAE	699 (83.3)	261 (90.3)	506 (60.3)
Number of ocular TEAEs	2314	1180	752
Number of subjects with at least one ocular TEAE	665 (79.3)	258 (89.3)	414 (49.3)
Number of non-ocular TEAEs	382	144	390
Number of subjects with at least one non-ocular TEAE	221 (26.3)	77 (26.6)	223 (26.6)
Number of SAEs	36	10	37
Number of subjects with at least one SAE	28 (3.3)	8 (2.8)	27 (3.2)
Number of treatment-related TEAEs	1966	996	560
Number of subjects with at least one treatment-related TEAE	613 (73.1)	243 (84.1)	355 (42.3)
Number of treatment-related SAEs	1 (0.1)[1]	1 (0.3)[2]	0
Number of subjects with at least one treatment-related SAE	1 (0.1)	1 (0.3)	0
Number of subjects with TEAEs by maximum severity			
Mild	409 (48.7)	104 (36.0)	371 (44.2)
Moderate	246 (29.3)	121 (41.9)	111 (13.2)
Severe	44 (5.2)	36 (12.5)	24 (2.9)
Number of subjects with TEAEs resulting in test article discontinuation	185 (22.1)	167 (57.8)	34 (4.1)
Number of subjects with TEAEs resulting in death	3 (0.4)[3]	0	0

BID = twice daily; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event
[1] Study CS301: SAE was exacerbation of coronary artery disease which was reported as moderate and possibly related to investigational drug by the investigator and recovered/resolved (subject completed study). Sponsor assessed the event as not related.
[2] Study CS303: SAE was iridocyclitis which was reported as severe and possibly related by the investigator and recovered/resolved.
[3] None of the deaths were considered related to treatment.
Source: ISS Table 14.3.2.1

Table 24 Studies CS301 and CS302: Overall Summary of Treatment-Emergent Adverse Events by Study (Safety Population)

	Number (%) of Subjects				
	CS301		CS302		
	Netarsudil 0.02% QD (N = 203)	Timolol 0.5% BID (N = 208)	Netarsudil 0.02% QD (N = 251)	Netarsudil 0.02% BID (N = 253)	Timolol 0.5% BID (N = 251)
Number of TEAEs	473	193	930	1086	430
Number of subjects with at least one TEAE	165 (81.3)	112 (53.8)	220 (87.6)	225 (88.9)	159 (63.3)
Number of ocular TEAEs	413	141	762	962	248
Number of subjects with at least one ocular TEAE	156 (76.8)	92 (44.2)	209 (83.3)	222 (87.7)	124 (49.4)
Number of non-ocular TEAEs	60	52	168	124	182
Number of subjects with at least one non-ocular TEAE	41 (20.2)	40 (19.2)	81 (32.3)	68 (26.9)	82 (32.7)
Number of serious TEAEs	3	6	22	9	18
Number of subjects with at least one serious TEAE	3 (1.5)	4 (1.9)	17 (6.8)	7 (2.8)	12 (4.8)
Number of treatment-related TEAEs	367	121	630	803	167
Number of subjects with at least one treatment-related TEAE	148 (72.9)	89 (42.8)	192 (76.5)	207 (81.8)	98 (39.0)
Number of treatment-related serious TEAEs	1	0	0	0	0
Number of subjects with at least one treatment-related serious TEAE	1 (0.5)	0	0	0	0
Number of subjects with TEAEs by maximum severity					
Mild	120 (59.1)	91 (43.8)	115 (45.8)	100 (39.5)	111 (44.2)
Moderate	39 (19.2)	16 (7.7)	87 (34.7)	102 (40.3)	37 (14.7)
Severe	6 (3.0)	5 (2.4)	18 (7.2)	23 (9.1)	11 (4.4)
Number of subjects with AEs resulting in test article discontinuation	22 (10.8)	4 (1.9)	76 (30.3)	136 (53.8)	16 (6.4)
Number of subjects with AEs resulting in death	0	0	2 (0.8)	0	0

AE = adverse event; BID = twice daily; QD = once daily; TEAE = treatment-emergent adverse event
Source: CS301, Table 14.3.1.2; CS302, Table 14.3.1.2.

Table 25 Studies CS304 and CS303: Overall Summary of Treatment-Emergent Adverse Events by Study (Safety Population)

	Number (%) of Subjects				
	CS304		CS303		
	Netarsudil 0.02% QD (N = 351)	Timolol 0.5% BID (N = 357)	Netarsudil 0.02% QD (N = 34)	Netarsudil 0.02% BID (N = 36)	Timolol 0.5% BID (N = 23)
Number of TEAEs	1061	462	232	238	57
Number of subjects with at least one TEAE	281 (80.1)	215 (60.2)	33 (97.1)	36 (100.0)	20 (87.0)
Number of ocular TEAEs	938	322	201	218	41
Number of subjects with at least one ocular TEAE	267 (76.1)	180 (50.4)	33 (97.1)	36 (100.0)	18 (78.3)
Number of non-ocular TEAEs	123	140	31	20	16
Number of subjects with at least one non-ocular TEAE	82 (23.4)	91 (25.5)	17 (50.0)	9 (25.0)	10 (43.5)
Number of serious TEAEs	11	12	0	1	1
Number of subjects with at least one serious TEAE	8 (2.3)	10 (2.8)	0	1 (2.8)	1 (4.3)
Number of treatment-related TEAEs	793	247	176	193	25
Number of subjects with at least one treatment-related TEAE	241 (68.7)	152 (42.6)	32 (94.1)	36 (100.0)	16 (69.6)
Number of treatment-related serious TEAEs	0	0	0	1	0
Number of subjects with at least one treatment-related serious TEAE	0	0	0	1 (2.8)	0
Number of subjects with TEAEs by maximum severity					
Mild	164 (46.7)	157 (44.0)	10 (29.4)	4 (11.1)	12 (52.2)
Moderate	103 (29.3)	51 (14.3)	17 (50.0)	19 (52.8)	7 (30.4)
Severe	14 (4.0)	7 (2.0)	6 (17.6)	13 (6.1)	1 (4.3)
Number of subjects with TEAEs resulting in test article discontinuation	71 (20.2)	11 (3.1)	16 (47.1)	31 (86.1)	3 (13.0)
Number of subjects with AEs resulting in death	1 (0.3)	0	0	0	0

AE = adverse event; BID = twice daily; QD = once daily; TEAE = treatment-emergent adverse event
Source: CS304, Table 14.3.1.2; CS303, Table 14.3.1.2

In the Phase 2 studies, the number of subjects who experienced any TEAE was dose-related and higher in all netarsudil QD groups (0.01%: 59.1% to 66.7%; 0.02%: 69.4% to 76.9%; 0.04%: 89.5%) compared to vehicle (13.0%) and latanoprost (32.9% to 36.4%). The incidence of subjects with TEAEs judged to be treatment-related was also dose-related and higher in the netarsudil QD groups (0.01%: 54.5% to 61.3%; 0.02%: 61.5% to 66.7%; 0.04%: 89.5%) compared to vehicle (8.7%) and latanoprost (24.7% to 26.0%). No TEAEs were reported during the 7 days of treatment in CS204.

9.3.2 Analysis of Ocular Adverse Events

The most frequently reported (≥ 2%) ocular TEAEs in any group in the Phase 3 pooled population are presented in Table 26 and are shown by study in Table 27. In the pooled population, the most common ocular events (reported at an incidence ≥ 5%) in either netarsudil group included conjunctival hyperemia (QD: 54.4%; BID: 69.9%), cornea verticillata (QD: 20.9%; BID: 27.0%), conjunctival hemorrhage (QD: 17.2%; BID: 19.0%), vision blurred (QD: 7.4%; BID: 17.0%), lacrimation increased (QD: 7.2%; BID: 10.0%), erythema of eyelid (QD: 6.8%; BID: 7.6%), visual acuity reduced (QD: 5.2%; BID: 8.0%), eye pruritus (QD: 4.1%; BID: 8.0%), conjunctival edema (QD: 3.1%; BID: 7.6%), eye irritation (QD: 3.5%; BID: 5.5%), eyelid edema (QD: 3.5%; BID: 6.6%), foreign body sensation in eyes (QD: 2.5%; BID: 6.2%), corneal opacity (QD: 1.3%; BID: 5.2%), instillation site pain (QD: 19.9%; BID: 18.3%), instillation site erythema (QD: 9.1%; BID: 11.8%), and vital dye staining cornea present (QD: 9.4%; BID: 8.7%). These same events were all reported at lower incidences in the timolol group with the exception of instillation site pain (21.6%).

The incidence of most events was higher in the BID group than in the QD group of the netarsudil treatment groups.

An evaluation of ocular treatment-related events provided similar results as noted above since almost all events were judged by the investigators to be related to treatment.

Table 26 Pooled Phase 3 Safety Analysis: Ocular Treatment-Emergent Adverse Events Reported for ≥ 2.0% of Subjects by Treatment (Safety Population)

System Organ Class Preferred Term	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5% BID (N = 839) n (%)
Eye Disorders	609 (72.6)	249 (86.2)	225 (26.8)
Conjunctival Hyperemia	456 (54.4)	202 (69.9)	87 (10.4)
Cornea Verticillata	175 (20.9)	78 (27.0)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	55 (19.0)	15 (1.8)
Vision Blurred	62 (7.4)	49 (17.0)	12 (1.4)
Lacrimation Increased	60 (7.2)	29 (10.0)	5 (0.6)
Erythema of Eyelid	57 (6.8)	22 (7.6)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	23 (8.0)	13 (1.5)
Eye Pruritus	34 (4.1)	23 (8.0)	7 (0.8)
Conjunctival Edema	26 (3.1)	22 (7.6)	1 (0.1)
Eye Irritation	32 (3.8)	16 (5.5)	12 (1.4)
Eyelid Edema	29 (3.5)	19 (6.6)	6 (0.7)
Foreign Body Sensation in Eyes	21 (2.5)	18 (6.2)	6 (0.7)
Punctate Keratitis	27 (3.2)	12 (4.2)	15 (1.8)
Conjunctivitis Allergic	21 (2.5)	13 (4.5)	1 (0.1)
Eye Pain	19 (2.3)	14 (4.8)	17 (2.0)
Blepharitis	17 (2.0)	13 (4.5)	5 (0.6)
Corneal Opacity	11 (1.3)	15 (5.2)	1 (0.1)
Eyelids Pruritus	18 (2.1)	7 (2.4)	2 (0.2)
Eye Discharge	14 (1.7)	9 (3.1)	6 (0.7)
Dry Eye	18 (2.1)	4 (1.4)	15 (1.8)
Photophobia	13 (1.5)	9 (3.1)	2 (0.2)
General Disorders and Administration Site Conditions	247 (29.4)	91 (31.5)	227 (27.1)
Instillation Site Pain	167 (19.9)	53 (18.3)	181 (21.6)
Instillation Site Erythema	76 (9.1)	34 (11.8)	13 (1.5)
Instillation Site Discomfort	29 (3.5)	9 (3.1)	22 (2.6)
Investigations	118 (14.1)	37 (12.8)	86 (10.3)
Vital Dye Staining Cornea Present	79 (9.4)	25 (8.7)	64 (7.6)
Infections and Infestations	92 (11.0)	39 (13.5)	84 (10.0)
Conjunctivitis	14 (1.7)	8 (2.8)	4 (0.5)

BID = twice daily; QD = once daily
Table includes all related and not-related events reported for ≥ 2.0% of subjects in any treatment group. Events are presented by system organ class and preferred term (MedDRA Version 19.0).
Source: New ISS Table 14.3.3.1.1.

Table 27 Ocular Treatment-Emergent Adverse Events Reported for ≥ 2.0% of Subjects in Pooled Phase 3 Studies by Study (Safety Population)

System Organ Class Preferred Term	Number (%) of Subjects									
	CS301		CS302			CS304		CS303		
	Netarsudil QD (N = 203)	Timolol BID (N = 208)	Netarsudil QD (N = 251)	Netarsudil BID (N = 253)	Timolol BID (N = 251)	Netarsudil QD (N = 351)	Timolol BID (N = 357)	Netarsudil QD (N = 34)	Netarsudil BID (N = 36)	Timolol BID (N = 23)
Eye Disorders										
Conjunctival hyperemia	108 (53.2)	17 (8.2)	152 (60.6)	168 (66.4)	35 (13.9)	168 (47.9)	33 (9.2)	28 (82.4)	34 (94.4)	2 (8.7)
Cornea verticillata	12 (5.9)	0	64 (25.5)	64 (25.3)	2 (0.8)	86 (24.5)	0	13 (38.2)	14 (38.9)	0
Conjunctival hemorrhage	27 (13.3)	1 (0.5)	49 (19.5)	49 (19.4)	2 (0.8)	56 (16.0)	11 (3.1)	7 (20.6)	6 (16.7)	0
Vision blurred	11 (5.4)	1 (0.5)	27 (10.8)	44 (17.4)	7 (2.8)	22 (6.3)	4 (1.1)	2 (5.9)	5 (13.9)	0
Lacrimation increased	8 (3.9)	0	19 (7.6)	25 (9.9)	0	26 (7.4)	5 (1.4)	7 (20.6)	4 (11.1)	0
Erythema of eyelid	12 (5.9)	0	14 (5.6)	12 (4.7)	2 (0.8)	26 (7.4)	2 (0.6)	5 (14.7)	10 (27.8)	2 (8.7)
Visual acuity reduced	8 (3.9)	3 (1.4)	22 (8.8)	22 (8.7)	6 (2.4)	14 (4.0)	4 (1.1)	0	1 (2.8)	0
Eye pruritus	4 (2.0)	0	14 (5.6)	20 (7.9)	3 (1.2)	13 (3.7)	4 (1.1)	3 (8.8)	3 (8.3)	0
Conjunctival edema	4 (2.0)	0	8 (3.2)	19 (7.5)	0	11 (3.1)	1 (0.3)	3 (8.8)	3 (8.3)	0
Eye irritation	8 (3.9)	1 (0.5)	11 (4.4)	13 (5.1)	8 (3.2)	12 (3.4)	3 (0.8)	1 (2.9)	3 (8.3)	0
Foreign body sensation in eyes	2 (1.0)	1 (0.5)	7 (2.8)	14 (5.5)	1 (0.4)	12 (3.4)	4 (1.1)	0	4 (11.1)	0
Punctate keratitis	4 (2.0)	1 (0.5)	12 (4.8)	12 (4.7)	5 (2.0)	11 (3.1)	8 (2.2)	0	0	1 (4.3)
Conjunctivitis allergic	6 (3.0)	0	6 (2.4)	11 (4.3)	1 (0.4)	9 (2.6)	0	0	2 (5.6)	0
Eye pain	2 (1.0)	0	10 (4.0)	11 (4.3)	8 (3.2)	5 (1.4)	8 (2.2)	2 (5.9)	3 (8.3)	1 (4.3)
Blepharitis	4 (2.0)	2 (1.0)	4 (1.6)	8 (3.2)	1 (0.4)	7 (2.0)	2 (0.6)	2 (5.9)	5 (13.9)	0
Corneal opacity	0	0	1 (0.4)	11 (4.3)	0	5 (1.4)	1 (0.3)	5 (14.7)	4 (11.1)	0
Eyelids pruritus	3 (1.5)	0	2 (0.8)	4 (1.6)	1 (0.4)	12 (3.4)	1 (0.3)	1 (2.9)	3 (8.3)	0
Eye discharge	0	1 (0.5)	4 (1.6)	8 (3.2)	3 (1.2)	8 (2.3)	2 (0.6)	2 (5.9)	1 (2.8)	0
Dry eye	2 (1.0)	3 (1.4)	6 (2.4)	4 (1.6)	6 (2.4)	9 (2.6)	4 (1.1)	1 (2.9)	0	2 (8.7)
Photophobia	4 (2.0)	0	5 (2.0)	8 (3.2)	1 (0.4)	2 (0.6)	1 (0.3)	2 (5.9)	1 (2.8)	0

Table 27 Ocular Treatment-Emergent Adverse Events Reported for ≥ 2.0% of Subjects in Pooled Phase 3 Studies by Study (Safety Population) (continued)

System Organ Class Preferred Term	Number (%) of Subjects									
	CS301		CS302			CS304		CS303		
	Netarsudil QD (N = 203)	Timolol BID (N = 208)	Netarsudil QD (N = 251)	Netarsudil BID (N = 253)	Timolol BID (N = 251)	Netarsudil QD (N = 351)	Timolol BID (N = 357)	Netarsudil QD (N = 34)	Netarsudil BID (N = 36)	Timolol BID (N = 23)
General Disorders and Administration Site Conditions										
Instillation site pain	30 (14.8)	42 (20.2)	45 (17.9)	45 (17.8)	41 (16.3)	83 (23.6)	92 (25.8)	9 (26.5)	8 (22.2)	6 (26.1)
Instillation site erythema	24 (11.8)	4 (1.9)	14 (5.6)	32 (12.6)	5 (2.0)	36 (10.3)	4 (1.1)	2 95.9)	2 (5.6)	0
Instillation site discomfort	10 (4.9)	9 (4.3)	9 (3.6)	7 (2.8)	5 (2.0)	4 (1.1)	7 (2.0)	6 (17.6)	2 (5.6)	1 (4.3)
Investigations										
Vital dye staining cornea present	17 (8.4)	19 (9.1)	14 (5.6)	17 (6.7)	14 (5.6)	34 (9.7)	24 (6.7)	14 (41.2)	8 (22.2)	7 (30.4)
Infections and Infestations										
Conjunctivitis	2 (1.0)	0	6 (2.4)	8 (3.2)	3 (1.2)	4 (1.1)	1 (0.3)	2 (5.9)	0	0

BID = twice daily; QD = once daily

Note: Table shows by-study results for the related and not-related adverse events that were reported for > 2.0% of subjects in the pooled Phase 3 population (Table 26).

Source: CS301, up-versioned Table 14.3.3.1; CS302, Table 14.3.3.1; CS304, Table 14.3.3.1; CS303, Table 14.3.3.1

In the Phase 2 studies, the most frequently reported ocular TEAE in the netarsudil QD groups was conjunctival hyperemia. The incidences of conjunctival hyperemia were dose-related and higher following AM dosing in CS201 (QD 0.01%: 50.0%; QD 0.02%: 57.1%; QD 0.04%: 73.7%) compared to PM dosing across the other Phase 2 studies (QD 0.01%: 38.7%; QD 0.02%: 38.9% to 39.7%). The incidences of conjunctival hyperemia were lower in the vehicle (4.3%) and latanoprost (13.7% to 15.6%) groups in these studies. Almost all reports (96.0%: 120/125) of conjunctival hyperemia in all netarsudil groups across the Phase 2 studies were considered treatment-related.

The most frequently reported non-ocular TEAEs across all netarsudil groups in the Phase 2 studies included headache (1.3% to 4.8%) and nasopharyngitis (1.4% to 3.8%), which were similar to the incidences in the latanoprost group (1.4 to 2.6%).

9.3.2.1 Conjunctival Hyperemia

In the Phase 3 studies, the presence of conjunctival hyperemia was documented as the result of either an investigator-reported biomicroscopy finding or a subject-reported symptom. Per the protocols, any change from baseline in hyperemia grade was recorded as an AE, regardless of the investigator's decision about the clinical significance of the biomicroscopy finding. The incidence of treatment-related conjunctival hyperemia AEs with netarsudil QD was 50.1% across the pooled Phase 3 studies (Table 28).

Additional analyses were performed on the netarsudil QD arms to evaluate subject-reported hyperemia (verbatim term contained "subject/patient reported") separately from investigator-reported hyperemia observed via slit-lamp examination. For this analysis, if the verbatim contained "subject/patient reported," the conjunctival hyperemia AE was categorized as subject-reported hyperemia. Otherwise, if the date of the AE covered a visit, the event was categorized as investigator-reported; if the AE started and ended between visits, it was categorized as subject-reported. Conjunctival hyperemia data for the netarsudil QD arm for each study and combined data from all studies are summarized in Table 28. Subject-reported conjunctival hyperemia was noted in 9.9% of subjects across the pooled Phase 3 studies.

Post-treatment biomicroscopy findings of conjunctival hyperemia were also evaluated relative to the baseline visit, which occurred after ocular hypotensive medication washout, and to the screening visit, at which time the subject's standard ocular hypotensive medication was being used. The screening visit comparison evaluates the change in conjunctival hyperemia from the subject's standard ocular hypotensive medication.

The incidence of investigator-reported conjunctival hyperemia in the netarsudil QD arm across the pooled Phase 3 studies was 46.2%. A 2-point or more increase in post-treatment conjunctival hyperemia grade was reported in 16.9% of subjects (n = 142) in comparison with the baseline visit (post-washout, if needed) and 15.6% of subjects (n = 131) in comparison with the screening visit (pre-washout; Table 29).

Overall, the results indicate that the majority of the netarsudil QD subjects did not report noticing a change in eye redness (hyperemia) associated with netarsudil treatment during the

studies. The majority of hyperemia findings were reported by investigators based on ocular examinations using a slit lamp biomicroscope.

Table 28 Number (%) of Subjects Treated with Netarsudil 0.02% QD with Treatment-related Conjunctival Hyperemia

	CS301 (N = 203)	CS302 (N = 251)	CS303 (N = 34)	CS304 (N = 351)	Pooled (N = 839)
Total reported conjunctival hyperemia	105 (51.7)	139 (55.4)	25 (73.5)	151 (43.0)	420 (50.1)
Discontinuation due to conjunctival hyperemia	1 (0.5)	30 (12.0)	4 (11.8)	14 (4.0)	49 (5.8)
Subject-reported conjunctival hyperemia	22 (10.8)	25 (10.0)	6 (17.6)	30 (8.5)	83 (9.9)
Discontinuation due to subject-reported conjunctival hyperemia	0	2 (0.8)	1 (2.9)	1 (0.3)	4 (0.5)
Investigator-reported conjunctival hyperemia	93 (45.8)	129 (51.4)	23 (67.6)	143 (40.7)	388 (46.2)
Discontinuation due to investigator-reported conjunctival hyperemia	1 (0.5)	28 (11.2)	3 (8.8)	13 (3.7)	45 (5.4)

Source: Unmasked NDA Safety Table 9.1

Table 29 Number (%) of Subjects with Treatment-related Conjunctival Hyperemia Reported by Subject or Investigator (Pooled Phase 3 Studies)

	Netarsudil QD (N = 839)	Netarsudil BID (N = 289)	Timolol BID (N = 839)
Subject-reported conjunctival hyperemia	83 (9.9)	44 (15.2)	17 (2.0)
Investigator-reported conjunctival hyperemia	388 (46.2)	172 (59.5)	60 (7.2)
Maximum change from baseline[1]			
0	20 (2.4)	7 (2.4)	6 (0.7)
1	226 (26.9)	74 (25.6)	49 (5.8)
2	126 (15.0)	67 (23.2)	5 (0.6)
3	16 (1.9)	24 (8.3)	0
Maximum change from screening[1]			
0	30 (3.6)	9 (3.1)	7 (0.8)
1	227 (27.1)	76 (26.3)	49 (5.8)
2	116 (13.8)	64 (22.1)	4 (0.5)
3	15 (1.8)	23 (8.0)	0

[1] Screening was before washout and baseline was after washout of prior ocular hypotensive medication.
Source: Unmasked NDA Safety Table 8

9.3.2.2 Cornea Verticillata

Corneal verticillata (corneal deposits) were not observed in the 7-day or 28-day Phase 2 studies and were first detected in the Phase 3 studies after 6 weeks of dosing.

This event, observed by the investigators only upon biomicroscopy, was generally scored as mild. The term “cornea verticillata” refers to a whorl-like pattern of deposits typically

localized to the basal corneal epithelium (Mantyjarvi 1998; Hollander 2004). The events in these studies appeared to be similar in appearance to cornea verticillata associated with the approved anti-arrhythmic agent amiodarone. A variety of drugs that are both cationic and amphiphilic are known to induce cornea verticillata, which arise due to the lysosomal accumulation of phospholipids within corneal epithelial cells through a process called phospholipidosis. Netarsudil is a cationic amphiphilic drug and Aerie has shown that netarsudil can induce phospholipidosis in Chinese hamster ovary cells (IPH07), suggesting that the etiology of the netarsudil-induced corneal deposits is phospholipidosis. It is unusual for cornea verticillata to result in reduction of visual acuity or ocular symptoms and the deposits typically resolve with discontinuation of the drug (Mantyjarvi 1998).

In the Phase 3 studies, cornea verticillata occurred at a higher incidence in 12-month CS302 (QD: 25.5%; BID: 25.3%), 12-month CS303 (QD: 38.2%; BID: 38.9%), and 6-month CS304 (QD: 24.5%) than in 3-month CS301 (QD: 5.9%). In the timolol group, this event was reported in CS302 at an incidence of 0.8% and 0% in the other 3 studies (Table 27).

OBS01 was an observational follow-on study to evaluate visual function in subjects who were reported with ongoing cornea verticillata (or corneal deposits) AEs at the time of exit from either CS301 or CS302. Subjects with corneal verticillata were followed until resolution (corneal verticillata grading of 0) or stabilization, which was defined as no worsening of the corneal verticillata grading.

Forty-five (45) subjects at 10 investigative sites from CS302 were enrolled in this study and included in the analysis population.

At the completion of this study, cornea verticillata had resolved in all except 3 subjects (4 out of 6 eyes). After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes). There were no changes from the start to the end of the study in visual function as measured by visual acuity, contrast sensitivity, and a visual function questionnaire. The findings indicate that the presence of corneal verticillata did not cause any clinically meaningful impact on visual function.

In CS304, cornea verticillata was reported in 86 (24.5%) subjects in the netarsudil group and 0 subjects in the timolol group. Cornea verticillata were predominantly bilateral and of mild severity, with earliest onset occurring at Day 30 and resolution approximately 87 days on average after discontinuing study medication. Of the subjects in the netarsudil group, 4.0% (14/351), discontinued study medication due to cornea verticillata.

In CS303, cornea verticillata was reported in 38.2% (13/34), 38.9% (14/36), and 0 (0%) of subjects in the netarsudil QD, netarsudil BID, and timolol groups, respectively. The AE was considered to be treatment-related in all of the netarsudil QD and the netarsudil BID subjects. Of the subjects in the netarsudil groups, 11.8% (4/34) in the QD group and 16.7% (6/36) in the BID group discontinued study medication due to cornea verticillata.

9.3.2.3 Conjunctival Hemorrhage

Conjunctival hemorrhage is related to the vasodilatory mechanism of ROCK inhibitors. In the pooled analysis, the incidence of conjunctival hemorrhage was higher in the netarsudil groups (QD: 17.2%; BID: 19.0%) than in the timolol group (1.8%). When present, conjunctival hemorrhage was typically considered mild, treatment-related, and was self-resolving.

In the pooled analysis, conjunctival hemorrhage was associated with discontinuation of study medication in 0.6% (5/839) and 2.4% (7/289) of netarsudil QD and BID subjects, respectively, and no timolol-treated subjects.

9.3.3 Analysis of Non-Ocular Adverse Events

In the pooled analysis, the most frequently reported non-ocular AEs in the netarsudil treatment groups were upper respiratory infection (QD: 1.8%; BID: 3.1%), headache (QD: 1.5%; BID: 4.5%) and dermatitis allergic (QD: 0.5%; BID: 2.8%). Similarly, low incidences of these events were seen in the timolol group (Table 30). Results are shown by study in Table 31.

Table 30 Pooled Phase 3 Safety Analysis: Non-Ocular Adverse Events Reported in ≥ 2.0% of Subjects by Treatment Group (Safety Population)

	Pooled Phase 3 Studies		
Preferred Term	**Netarsudil 0.02% QD (N = 839) n (%)**	**Netarsudil 0.02% BID (N = 289) n (%)**	**Timolol 0.5% BID (N = 839) n (%)**
Upper respiratory tract infection	15 (1.8)	9 (3.1)	23 (2.7)
Headache	13 (1.5)	13 (4.5)	16 (1.9)
Dermatitis Allergic	4 (0.5)	8 (2.8)	0

Events are presented by system organ class and preferred term (MedDRA Version 19.0).
Source: New ISS Table 14.3.3.1.1.

Treatment-related non-ocular TEAEs were reported in single subjects within a group with the exception of dermatitis allergic (netarsudil QD: 3 subjects, 0.4%; BID: 7 subjects, 2.4%), dermatitis contact (netarsudil QD: 5 subjects, 0.6%; BID: 3 subjects, 1.0%), headache (netarsudil QD: 6 subjects, 0.7%; BID: 4 subjects, 1.4%; timolol 2 subjects, 0.2%), dizziness (netarsudil BID: 2 subjects, 0.7%), dysgeusia (timolol: 3 subjects, 0.4%), bradycardia (timolol: 2 subjects, 0.2%), nausea (timolol: 2 subjects, 0.2%), hypersensitivity (netarsudil QD: 2 subjects, 0.2%) and dyspnea (timolol: 3 subjects, 0.4%).

Table 31 Studies CS301, CS302, CS304, and CS303: Most Frequently Reported Non-Ocular Treatment-Emergent Adverse Events by Study (Safety Population)

	Number (%) of Subjects									
	CS301		CS302			CS304		CS303		
Preferred Term	Netarsudil QD (N = 203)	Timolol BID (N = 208)	Netarsudil QD (N = 251)	Netarsudil BID (N = 253)	Timolol BID (N = 251)	Netarsudil QD (N = 351)	Timolol BID (N = 357)	Netarsudil QD (N = 34)	Netarsudil BID (N = 36)	Timolol BID (N = 23)
Upper respiratory tract infection	0	2 (1.0)	5 (2.0)	9 (3.6)	7 (2.8)	10 (2.8)	14 (3.9)	0	0	0
Headache	0	1 (0.5)	6 (2.4)	10 (4.0)	9 (3.6)	6 (1.7)	5 (1.4)	1 (2.9)	3 (8.3)	1 (4.3)
Dermatitis allergic	0	0	2 (0.8)	6 (2.4)	0	2 (0.6)	0	0	2 (5.6)	0

Note: Table includes all related and not-related PTs reported for > 2.0% of subjects in any treatment group within a study.
Source: CS301, up-versioned Table 14.3.3.1; CS302, Table 14.3.3.1; CS304, Table 14.3.3.1; CS303 Table 14.3.3.1

9.3.4 Adverse Events in Demographic Subgroups

Analyses of AEs by demographic subgroups (age, race, sex, and iris color) were conducted with pooled data from the Phase 3 studies. The key findings were as follows:

- Whites had a higher incidence of overall TEAEs and ocular TEAEs compared to subjects of other races. The comparative incidences (white vs other races) of ocular events by treatment were: netarsudil QD 85.3% vs 61.7%; netarsudil BID 92.9% vs 79.5%; and timolol 54.3% vs 36.0%.
- An analysis of TEAE severity indicated that in the netarsudil groups, white subjects had greater incidences of moderate and severe TEAEs (overall TEAEs and events in the Eye Disorders SOC) compared to subjects of other races.
- Higher incidences of conjunctival hyperemia occurred in the netarsudil QD and BID groups in males versus females (QD: 60.5% vs 50.0%; BID: 74.8% vs 67.0%) and in white versus other races (QD: 61.3% vs 34.1%; BID: 75.4% vs 55.1%).
- Higher incidences of cornea verticillata occurred in the netarsudil QD and BID groups in elderly (≥ 65 years) versus non-elderly (< 65 years) (QD: 24.8% vs 15.9%; BID: 30.7% vs 23.0%), in males versus females (QD: 24.4% vs 18.4%; BID: 31.8% vs 24.2%), and in white versus other races (QD: 25.6% vs 7.0%; BID: 32.7% vs 11.5%).

9.4 Deaths, Serious Adverse Events, and Discontinuations Due to Adverse Events

9.4.1 Deaths

Four deaths in the netarsudil groups were reported during the completed netarsudil clinical studies: 2 due to myocardial infarctions (CS302), 1 due to cardiac arrest (CS304), and 1 due to leukemia (CS202). These events were assessed as severe and not related to study medication.

9.4.2 Serious Adverse Events (SAEs)

SAEs were almost all non-ocular and were reported in 3.3%, 2.8% and 3.2% of subjects in the netarsudil QD, BID and timolol groups, respectively, in the pooled analysis (Table 32). None of the SAEs were considered by the Sponsor to be treatment-related.

Two SAEs were considered by the Investigator to be related to study medication: exacerbation of coronary artery disease in a single subject in the netarsudil QD group and iridocyclitis in the netarsudil BID group.

Only one other serious TEAE was ocular, namely, worsening cataract requiring surgical intervention in the netarsudil QD group. The event was considered not related to treatment.

Table 32 Pooled Phase 3 Safety Analysis: All Serious Adverse Events by Treatment (Safety Population)

System Organ Class Preferred Term	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5%BID (N = 839) n (%)
Any Serious Adverse Event	28 (3.3)	8 (2.8)	27 (3.2)
Cardiac Disorders	10 (1.2)	2 (0.7)	4 (0.5)
Coronary Artery Disease	3 (0.4)	1 (0.3)	1 (0.1)
Myocardial Infarction	3 (0.4)	1 (0.3)	1 (0.1)
Atrial Fibrillation	2 (0.2)	0	1 (0.1)
Atrial Flutter	1 (0.1)	0	0
Bradycardia	1 (0.1)	0	0
Cardiac Arrest	1 (0.1)	0	0
Cardiac Failure Congestive	0	0	1 (0.1)
Cardiomegaly	0	0	1 (0.1)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts and Polyps)	8 (1.0)	0	3 (0.4)
Prostate Cancer	2 (0.2)	0	0
Bladder Cancer Recurrent	1 (0.1)	0	0
Breast Cancer	1 (0.1)	0	1 (0.1)
Chronic Myeloid Leukemia	1 (0.1)	0	0
Malignant Melanoma in Situ	1 (0.1)	0	0
Myelodysplastic Syndrome	1 (0.1)	0	0
Papillary Thyroid Cancer	1 (0.1)	0	0
Invasive Ductal Breast Carcinoma	0	0	1 (0.1)
Uterine Leiomyoma	0	0	1 (0.1)
Injury, Poisoning and Procedural Complications	1 (0.1)	2 (0.7)	5 (0.6)
Foot Fracture	0	1 (0.3)	0
Postoperative Ileus	1 (0.1)	0	0
Road Traffic Accident	0	1 (0.3)	0
Fall	0	0	2 (0.3)
Hip Fracture	0	0	1 (0.1)
Ligament Rupture	0	0	1 (0.1)
Radius Fracture	0	0	1 (0.1)
Tendon Rupture	0	0	1 (0.1)
Nervous System Disorders	3 (0.4)	0	5 (0.6)
Cerebrovascular Accident	1 (0.1)	0	1 (0.1)
Embolic Stroke	1 (0.1)	0	0
Transient Ischemic Attack	1 (0.1)	0	1 (0.1)
Carotid Artery Stenosis	0	0	1 (0.1)
Facial Paralysis	0	0	1 (0.1)
Hypoesthesia	0	0	1 (0.1)

Table 32 Pooled Phase 3 Safety Analysis: All Serious Adverse Events by Treatment (Safety Population) (continued)

System Organ Class Preferred Term	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5%BID (N = 839) n (%)
Respiratory, Thoracic and Mediastinal Disorders	2 (0.2)	1 (0.3)	2 (0.2)
Epistaxis	0	1 (0.3)	0
Pneumonia Aspiration	1 (0.1)	0	0
Pulmonary Artery Stenosis	1 (0.1)	0	0
Acute Respiratory Failure	0	0	1 (0.1)
Pulmonary Embolism	0	0	1 (0.1)
Vascular Disorders	2 (0.2)	1 (0.3)	1 (0.1)
Accelerated Hypertension	1 (0.1)	0	0
Hypertension	1 (0.1)	0	0
Internal Hemorrhage	0	1 (0.3)	0
Peripheral Artery Occlusion	0	0	1 (0.1)
Gastrointestinal Disorders	1 (0.1)	1 (0.3)	2 (0.2)
Abdominal Pain	0	1 (0.3)	0
Gastric Volvulus	1 (0.1)	0	0
Hiatus Hernia	1 (0.1)	0	0
Abdominal Discomfort	0	0	1 (0.1)
Gastric Ulcer Perforation	0	0	1 (0.1)
Musculoskeletal and Connective Tissue Disorders	2 (0.2)	0	1 (0.1)
Back Pain	1 (0.1)	0	0
Osteoarthritis	1 (0.1)	0	0
Synovial Cyst	0	0	1 (0.1)
Renal and Urinary Disorders	1 (0.1)	1 (0.3)	2 (0.2)
Acute Kidney Injury	0	1 (0.3)	1 (0.1)
Bladder Prolapse	1 (0.1)	0	0
Renal Failure	0	0	1 (0.1)
Eye Disorders	0	1 (0.3)	1 (0.1)
Iridocyclitis	0	1 (0.3)	0
Cataract	0	0	1 (0.1)
Hepatobiliary Disorders	1 (0.1)	0	1 (0.1)
Cholelithiasis	1 (0.1)	0	0
Cholecystitis	0	0	1 (0.1)
Infections and Infestations	1 (0.1)	0	4 (0.5)
Cellulitis	1 (0.1)	0	0
Peritonitis Bacterial	0	0	1 (0.1)
Pneumonia	0	0	3 (0.4)
Urinary Tract Infection	0	0	1 (0.1)

Table 32 Pooled Phase 3 Safety Analysis: All Serious Adverse Events by Treatment (Safety Population) (continued)

System Organ Class Preferred Term	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5%BID (N = 839) n (%)
Metabolism and Nutrition Disorders	1 (0.1)	0	0
Fluid Overload	1 (0.1)	0	0
Reproductive System and Breast Disorders	1 (0.1)	0	1 (0.1)
Cervical Dysplasia	1 (0.1)	0	0
Adenomyosis	0	0	1 (0.1)
Skin and Subcutaneous Tissue Disorders	0	1 (0.3)	0
Angioedema	0	1 (0.3)	0
Investigations	0	0	1 (0.1)
Prostatic Specific Antigen Increased	0	0	1 (0.1)
Psychiatric Disorders	0	0	1 (0.1)
Mental Status Changes	0	0	1 (0.1)

BID = twice daily; QD = once daily
Events are presented by system organ class and preferred term (MedDRA Version 19.0).
Source: ISS Table 14.3.3.2.1

No SAEs were reported in the Phase 1 studies. In the Phase 2 studies, 6 SAEs were reported among 3 subjects and were equally distributed among several SOCs. Most (66.7%) of the SAEs were in the latanoprost group. All SAEs were non-ocular and no SAE was considered to be treatment-related.

9.4.3 Discontinuations Due to Adverse Events

In the pooled analysis, discontinuations of study medication due to TEAEs were highest in the netarsudil BID group (54.3%) followed by netarsudil QD group (19.3%) and timolol group (1.7%). The majority of discontinuations in the netarsudil QD and BID groups were associated with ocular events, whereas the majority of discontinuations in the timolol groups were associated with non-ocular events.

The most frequently reported TEAEs associated with study medication discontinuation and reported in ≥ 5% of subjects in the netarsudil groups were conjunctival hyperemia (QD: 6.0%; BID: 27.0%), cornea verticillata (QD: 3.7%; BID: 10.4%), and vision blurred (QD: 1.5%; BID: 7.6%) (Table 33). Less common TEAEs associated with study medication discontinuation in the netarsudil QD group (> 1.0% and < 2.0%) included eyelid edema, lacrimation increased, eye irritation, conjunctivitis allergic, erythema of eyelid, instillation site pain, IOP increased, visual acuity reduced, conjunctival edema, and eye pruritus.

Table 33 Pooled Phase 3 Safety Analysis: Adverse Events Associated with Discontinuations in ≥ 5.0% of Subjects (Safety Population)

System Organ Class Preferred Term	Pooled Phase 3 Studies		
	Netarsudil 0.02% QD (N = 839) n (%)	Netarsudil 0.02% BID (N = 289) n (%)	Timolol 0.5% BID (N = 839) n (%)
Any TEAEs Resulting in Test Agent Discontinuation	185 (22.1)	167 (57.8)	34 (4.1)
Eye Disorders			
Conjunctival Hyperemia	50 (6.0)	78 (27.0)	0
Cornea Verticillata	31 (3.7)	30 (10.4)	0
Vision Blurred	13 (1.5)	22 (7.6)	2 (0.2)

BID = twice daily; QD = once daily
Events are presented by system organ class and preferred term (MedDRA Version 19.0).
Source: New ISS Table 14.3.3.4.1

In the Phase 2 studies, the overall rate of subject discontinuation due to a TEAE across all treatment groups was low in the netarsudil (0 to 2.8%) and latanoprost (2.6%) groups. No subject discontinued due to a TEAE in the Phase 1 studies or Phase 2 study CS204. Most events that resulted in discontinuation of study medication or study participation in the Phase 2 studies were ocular and included isolated reports of IOP fluctuation, IOP increased, conjunctival hyperemia, conjunctival hemorrhage, and ulcerative keratitis. The non-ocular events included drug hypersensitivity and pneumonia.

9.5 Other Observations Related to Safety

Additional safety-related assessments included visual acuity, biomicroscopy, ophthalmoscopy, cup to disc ratio, comfort assessment, pupil size, visual fields, specular microscopy, pachymetry, IOP, vital signs, and clinical laboratory testing. There were no clinically relevant differences in these parameters comparing the netarsudil and control groups (vehicle, latanoprost, and timolol) except for visual acuity, biomicroscopy parameters, and vital signs, which are discussed below for the pooled analysis.

9.5.1 Visual Acuity

In the pooled analysis, the worst change in visual acuity scores at any post-treatment visit is summarized in Table 34. The majority of subjects had a visual acuity loss of < 1 line in the study eye: netarsudil QD (54.1%), netarsudil BID (52.4%), and timolol (66.9%). Sixty-eight subjects experienced a ≥ 3-line loss of vision in the study eye with higher incidences in the netarsudil QD (3.8%) and netarsudil BID (7.3%) groups compared to timolol (1.8%). TEAEs of visual acuity reduced were reported with higher incidences in the netarsudil QD (5.2%) and netarsudil BID (8.0%) groups compared to timolol (1.5%) (Table 26). Sixteen subjects discontinued study medication or study participation with visual acuity reduced as an AE at the time of discontinuation, with higher incidences in the netarsudil QD (1.0%) and netarsudil BID (2.8%) groups vs timolol (0%).

Table 34 Pooled Phase 3 Safety Analysis: Worst Change in Visual Acuity Scores (logMAR) at Any Post-Treatment Visit (Safety Population)

	Netarsudil 0.02% QD N = 839 n (%)	Netarsudil 0.02% BID N = 289 n (%)	Timolol 0.5% BID N = 839 n (%)
Study Eye, n	837	286	837
0 or less	187 (22.3)	57 (19.9)	247 (29.5)
> 0 to +0.09	266 (31.8)	93 (32.5)	313 (37.4)
+0.10 to 0.19	275 (32.9)	80 (28.0)	223 (26.6)
+0.20 to 0.29	77 (9.2)	35 (12.2)	39 (4.7)
+0.30 or more	32 (3.8)	21 (7.3)	15 (1.8)

BID = twice daily; QD = once daily
Worst change is the largest positive logMAR unit change from baseline considering all post-treatment visits.
Source: ISS Table 14.3.5.1.1

9.5.2 Biomicroscopy

In the pooled analysis, the most frequent clinically significant finding in the netarsudil groups was conjunctival hyperemia, observed in up to 12.9% of netarsudil QD subjects and 18.7% of BID subjects compared with 0.6% of timolol subjects. Eyelid erythema (QD: 1.8%; BID 5.0%), eyelid edema (QD: 1.7%; BID: 1.8%), conjunctival edema (QD: 2.2%; BID: 4.0%), and corneal staining (QD: 2.2%; BID: 3.1%) were also reported as clinically significant findings in the netarsudil groups and at higher rates than in the timolol group.

In the pooled analysis, a ≥ 1 severity grade increase from baseline for conjunctival hyperemia in the study eyes of subjects was observed across any visit in 62.8% of netarsudil QD subjects and 72.9% of netarsudil BID subjects versus 14.6% of timolol subjects. Lower incidences were reported at the final visit in the netarsudil groups (QD: 30.0%; BID: 32.3%) and timolol group (3.6%). Other parameters for which netarsudil QD or BID had a higher incidence of a ≥1 severity grade increase compared to timolol across any visit included eyelid erythema (QD: 10.2%, BID: 14.2%; timolol: 1.0%); eyelid edema (QD: 4.8%; BID: 9.4%; timolol: 0.8%); conjunctival edema (QD: 5.3%; BID: 14.9%; timolol: 0.5%), corneal staining (QD: 13.0%; BID: 16.0%; timolol: 10.8%), and corneal edema (QD: 0.7%; BID: 2.8%; timolol: 0%).

Adverse events consistent with the slit-lamp findings in the netarsudil groups were reported in the pooled analysis for conjunctival hyperemia (QD: 54.4%; BID: 69.9%), erythema of eyelid (QD 6.8%, BID: 7.6%), conjunctival edema (QD: 3.1%; BID: 7.6%), eyelid edema (QD: 3.5%, BID: 6.6%), and vital dye staining cornea present (QD: 9.4%; BID 8.7%) (Table 26).

9.5.3 Corneal Endothelial Cell Evaluation

Specular microscopy was performed in subjects in 12-month CS302 to evaluate corneal endothelial cell density over 3 months. A centralized reading center confirmed no cell loss with netarsudil treatment. The mean changes from baseline in cell density were small and not

clinically relevant: +1.7 cells/mm^2 (0.4% increase) with netarsudil QD, +16.8 cells/mm^2 (0.1% increase) with netarsudil BID, and -1.1 cells/mm^2 (0.2% decrease) with timolol.

9.5.4 Subject-reported Ocular Discomfort

Ocular discomfort was assessed at each 8 AM visit by querying subjects whether they experienced any discomfort when placing the drops in their eyes. Subjects' responses were recorded using a standardized scale (none, mild, moderate, severe). Over 90% of subjects in the netarsudil QD and timolol groups reported no or mild ocular discomfort (Table 35). Instillation site pain and discomfort were reported as TEAEs for a similar incidence of subjects with each treatment.

Table 35 Pooled Phase 3 Safety Analysis: Ocular Discomfort

	Ocular Discomfort[1]	Adverse Events Reflecting Ocular Discomfort with Drop Instillation[2]	
Treatment	Ocular Discomfort "None" or "Mild"	Instillation Site Pain	Instillation Site Discomfort
Netarsudil QD	92.5% to 99.6%	19.9%	3.5%
Netarsudil BID	86.0% to 99.0%	18.3%	3.1%
Timolol BID	97.4% to 100%	21.6%	2.6%

BID = twice daily; QD = once daily

[1] Percentages calculated based on number of respondents at each visit.

[2] Percentages calculated based on number of subjects in the safety population.

Source: New ISS Tables 14.3.7.1, 14.3.3.1.1

9.5.5 Vital Signs

In the pooled analysis for all subjects, the mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate (HR) were generally small and not clinically relevant except for greater HR reductions in the timolol group. The timolol group had statistically significant reductions from baseline in mean HR changes at all 6 study visits in the pooled analysis, with mean changes ranging from -3.0 to -2.0 bpm. Except for a mean reduction of 1.3 bpm at a single visit (Month 12 in the netarsudil QD group), there were no significant reductions in mean HR changes in the netarsudil groups (QD and BID) at the same study visits.

9.5.6 Clinical Laboratory Evaluations

Clinical laboratory testing was performed in Phase 1, 2, and 3 studies at the screening and exit visits. If subjects discontinued from the study prematurely, laboratory testing was done at the time of the exit visit. Centralized laboratories were used to provide supplies, coordinate shipment of the samples, and analyze the samples in the Phase 2 and 3 studies.

For the most part, there were no clinically significant changes in clinical chemistry or hematology in subjects exposed to netarsudil for up to 12 months. There were selected, sporadic AEs regarding abnormal values. A single subject treated with netarsudil was discontinued from the study due to an abnormal laboratory value (hypoglycemia). That

subject's discontinuation was judged as not related to study medication. There was no evidence of clinical laboratory or hematology safety issues with netarsudil treatment.

10. BENEFITS AND RISK CONCLUSIONS

Netarsudil represents a new class of ocular hypotensive agent, a ROCK and NET inhibitor, with unique pharmacological mechanisms of action. Based on nonclinical and clinical studies, netarsudil appears to reduce IOP by increasing trabecular outflow facility, reducing EVP, and decreasing production of aqueous humor.

Netarsudil 0.02% QD provided clinically relevant and statistically significant reduction in mean IOP from baseline for subjects with baseline IOP of 24 to 36 mmHg in Phase 2 studies. In the Phase 3 efficacy studies, netarsudil 0.02% QD provided clinically relevant and statistically significant reductions in mean IOP from baseline in subjects with baseline IOP up to < 27 mmHg (CS301, CS302) and < 30 mmHg (CS304). In these studies, netarsudil QD was demonstrated to be non-inferior to timolol in subjects with baseline IOP up to < 30 mmHg (in CS304, which was the only study to include subjects with baseline IOP ≥ 27 mmHg and < 30 mmHg) and up to < 25 mmHg (in CS301, CS302, and CS304). Stable efficacy has been demonstrated through 12 months of treatment.

In a pilot study, netarsudil QD has been shown to have equivalent efficacy during nocturnal and daytime hours. Currently used glaucoma medications provide no IOP lowering at night (beta blockers, alpha agonists) or reduced IOP lowering at night (PGAs, CAIs).

The optimal dosing regimen for netarsudil from an efficacy and safety perspective has been established as 0.02% dosed QD PM. A QD PM dosing regimen has the benefit of convenience for patients, which may improve compliance. The majority of patients are on a PGA medication, which are also dosed QD PM.

Topical ocular administration of netarsudil ophthalmic solution 0.02% QD in humans produced little or no quantifiable systemic exposure to the parent compound or its primary metabolite. This lack of measurable systemic absorption is consistent with minimal netarsudil-related systemic TEAEs in the clinical studies, and it represents a safety benefit relative to other therapeutic classes of products commonly used to treat elevated IOP that have known significant systemic adverse effects. These include beta-adrenergic antagonists (with cardiovascular and respiratory effects such as bradycardia, dyspnea, and wheezing) and alpha-agonists (with CNS effects such as dry mouth, fatigue, sedation, and dizziness).

The pooled safety analysis across the 4 Phase 3 safety studies (including safety study CS303) included 839, 289, and 839 subjects treated with netarsudil QD, netarsudil BID, or timolol, respectively. A higher proportion of netarsudil QD subjects (79.3%) compared to timolol subjects (49.3%) reported ocular TEAEs. The most common TEAE in the netarsudil QD group was conjunctival hyperemia (54.4%), an expected primary pharmacological effect of ROCK inhibitors, which act as vasodilators. The TEAEs of conjunctival hemorrhage (17.2%) and erythema of the eyelid (6.8%) may also be related to the vasoactive effects of ROCK inhibition. The majority of these TEAEs were reported as mild in severity. In the 12-month study CS302, the discontinuation rates associated with these TEAEs were 6.8% for

hyperemia (6.0% scored as moderate, 0.8% severe) and 2.8% for conjunctival hemorrhage (mild).

Cornea verticillata was observed only in the Phase 3 studies. The term "cornea verticillata" refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium. A variety of cationic, amphiphilic drugs are known to induce cornea verticillata, which arise due to the accumulation of phospholipids within corneal epithelial cells through phospholipidosis. A nonclinical cell-based assay confirmed that netarsudil induces phospholipidosis, supporting the conclusion that the etiology of netarsudil-induced cornea verticillata is phospholipidosis.

It is unusual for drug-induced cornea verticillata to result in reduction of visual acuity or ocular symptoms, and the lipid deposits typically resolve with discontinuation of the drug. Among the 45 subjects who had ongoing cornea verticillata when they exited from CS302 and were followed until resolution (corneal verticillata grading of 0) or stabilization (no worsening of the corneal verticillata grading), cornea verticillata had resolved in all except 3 subjects (4 out of 6 eyes) at study completion. After study completion, cornea verticillata resolved in 1 of these subjects and had improved in the other 2 subjects (3 out of 4 eyes). The finding of corneal verticillata due to netarsudil did not demonstrate any clinically meaningful impact on visual function.

Mean changes from baseline in visual acuity were small, similar among all treatment groups, and not clinically relevant. An analysis of worst change from baseline in visual acuity demonstrated that the majority of subjects had a worst change of less than a 1-line loss of vision. In addition, the incidence of visual acuity reduced reported as a TEAE was 5.2% of subjects in the netarsudil QD group and 1.5% of subjects in the timolol group.

Netarsudil ophthalmic solution 0.02% offers potential benefits as a novel therapeutic for the reduction of elevated IOP. Topical pharmacotherapy for ocular hypertension and OAG in the US includes molecules in a number of classes. While eye care professionals and their patients may select from agents that decrease aqueous humor production or increase uveoscleral outflow, no commonly used agents act primarily to increase outflow through the trabecular outflow pathway, the site of the pathology that causes elevated IOP. One class of agent, the beta-adrenoceptor antagonists, was a major therapeutic advance when introduced as a topical ocular hypotensive medication in the 1980s. Nonetheless, even in carefully selected patients, systemic beta-blockade and its sequelae continue to be an important safety issue for that drug class. Netarsudil provides similar ocular hypotensive efficacy as the beta-adrenoceptor antagonist class of ocular hypotensive medication without the systemic beta-blockade safety risk.

Netarsudil has proven to be effective at lowering IOP in patients with OAG and OHT. Due to its unique mechanism of action, Aerie believes that netarsudil will provide added efficacy when used in combination with currently used topical agents, as has been shown in a Phase 2 study of a fixed-dose combination of netarsudil plus latanoprost. Although netarsudil produces a higher incidence of ocular AEs than timolol, the ocular side effects are generally mild, not associated with loss of visual function, and are reversible upon cessation of treatment.

Based on the study results, Aerie believes that the benefits of netarsudil ophthalmic solution 0.02% QD as an ocular hypotensive agent for the treatment of OHT and OAG outweigh the potential risks when prescribing this medication.

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Appendix 1 Mean Change from Diurnally Adjusted Baseline IOP

Table 36 Study CS301: Mean IOP and Mean Change from Diurnally Adjusted Baseline (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil 0.02% QD				Netarsudil 0.02% QD			
	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	177	18.68	-4.77	<0.0001	108	17.34	-5.06	<0.0001
10:00	176	17.29	-5.03	<0.0001	107	16.18	-5.11	<0.0001
16:00	176	17.24	-4.59	<0.0001	107	16.22	-4.42	<0.0001
Day 43 08:00	170	19.35	-4.06	<0.0001	105	17.85	-4.50	<0.0001
10:00	170	18.14	-4.16	<0.0001	105	16.88	-4.40	<0.0001
16:00	170	17.86	-3.96	<0.0001	105	16.57	-4.08	<0.0001
Day 90 08:00	157	19.81	-3.59	<0.0001	99	18.22	-4.18	<0.0001
10:00	158	18.92	-3.33	<0.0001	99	17.34	-3.94	<0.0001
16:00	158	18.48	-3.31	<0.0001	99	17.02	-3.65	<0.0001
	Timolol BID				Timolol BID			
	N		Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	187	18.33	-5.05	<0.0001	123	17.78	-4.74	<0.0001
10:00	186	17.55	-4.39	<0.0001	122	16.98	-4.09	<0.0001
16:00	186	17.70	-3.78	<0.0001	122	17.14	-3.41	<0.0001
Day 43 08:00	184	18.24	-5.14	<0.0001	121	17.81	-4.71	<0.0001
10:00	184	17.44	-4.49	<0.0001	121	16.96	-4.12	<0.0001
16:00	183	17.71	-3.75	<0.0001	120	17.26	-3.25	<0.0001
Day 90 08:00	181	18.47	-4.93	<0.0001	119	17.91	-4.61	<0.0001
10:00	181	17.96	-3.99	<0.0001	119	17.43	-3.66	<0.0001
16:00	181	17.74	-3.73	<0.0001	119	17.37	-3.19	<0.0001

BID = twice daily; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test
Source: CS301 Table 14.2.1.1, Table 14.2.1.1.99.13

Table 37 Study CS302: Mean IOP and Mean Change from Diurnally Adjusted Baseline for Netarsudil QD (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil 0.02% QD				Netarsudil 0.02% QD			
	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	201	19.02	-4.50	<0.0001	127	18.07	-4.50	<0.0001
10:00	199	17.74	-4.57	<0.0001	126	16.72	-4.60	<0.0001
16:00	200	17.37	-4.21	<0.0001	126	16.68	-3.79	<0.0001
Day 43 08:00	193	19.37	-4.13	<0.0001	122	17.95	-4.59	<0.0001
10:00	187	18.11	-4.20	<0.0001	120	16.95	-4.41	<0.0001
16:00	187	17.88	-3.64	<0.0001	120	17.00	-3.47	<0.0001
Day 90 08:00	177	19.43	-4.00	<0.0001	116	18.24	-4.30	<0.0001
10:00	173	18.18	-4.00	<0.0001	114	17.03	-4.25	<0.0001
16:00	170	17.73	-3.68	<0.0001	114	17.13	-3.30	<0.0001
	Timolol BID				Timolol BID			
	N		Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	217	18.25	-5.20	<0.0001	142	17.69	-4.85	<0.0001
10:00	215	17.49	-4.70	<0.0001	141	16.93	-4.35	<0.0001
16:00	215	17.59	-4.02	<0.0001	141	16.83	-3.88	<0.0001
Day 43 08:00	215	18.08	-5.38	<0.0001	141	17.46	-5.09	<0.0001
10:00	215	17.31	-4.88	<0.0001	141	16.63	-4.66	<0.0001
16:00	215	17.25	-4.36	<0.0001	141	16.60	-4.11	<0.0001
Day 90 08:00	214	18.21	-5.25	<0.0001	140	17.47	-5.09	<0.0001
10:00	213	17.52	-4.69	<0.0001	140	16.92	-4.38	<0.0001
16:00	212	17.67	-3.94	<0.0001	139	16.95	-3.74	<0.0001

BID = twice daily; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test
Source: CS302 Table 14.2.1.1.2, Table 14.2.1.1.1

Table 38 Study CS302: Mean IOP and Mean Change from Diurnally Adjusted Baseline for Netarsudil BID (PP Populations with Baseline IOP < 27 mmHg and < 25 mmHg)

Study Visit and Timepoint	Baseline IOP < 27 mmHg				Baseline IOP < 25 mmHg			
	Netarsudil 0.02% BID				Netarsudil 0.02% BID			
	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	191	18.20	-5.31	<0.0001	122	17.21	-5.36	<0.0001
10:00	185	16.91	-5.33	<0.0001	120	16.35	-4.99	<0.0001
16:00	183	16.28	-5.17	<0.0001	118	15.65	-4.92	<0.0001
Day 43 08:00	169	18.57	-4.88	<0.0001	111	17.64	-4.92	<0.0001
10:00	162	17.09	-5.13	<0.0001	106	16.28	-5.06	<0.0001
16:00	162	16.58	-4.89	<0.0001	106	15.75	-4.83	<0.0001
Day 90 08:00	138	18.66	-4.77	<0.0001	91	17.58	-4.96	<0.0001
10:00	131	17.81	-4.36	<0.0001	88	16.94	-4.47	<0.0001
16:00	131	17.08	-4.34	<0.0001	88	16.51	-4.09	<0.0001
	Timolol BID				Timolol BID			
	N		Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	217	18.25	-5.20	<0.0001	142	17.69	-4.85	<0.0001
10:00	215	17.49	-4.70	<0.0001	141	16.93	-4.35	<0.0001
16:00	215	17.59	-4.02	<0.0001	141	16.83	-3.88	<0.0001
Day 43 08:00	215	18.08	-5.38	<0.0001	141	17.46	-5.09	<0.0001
10:00	215	17.31	-4.88	<0.0001	141	16.63	-4.66	<0.0001
16:00	215	17.25	-4.36	<0.0001	141	16.60	-4.11	<0.0001
Day 90 08:00	214	18.21	-5.25	<0.0001	140	17.47	-5.09	<0.0001
10:00	213	17.52	-4.69	<0.0001	140	16.92	-4.38	<0.0001
16:00	212	17.67	-3.94	<0.0001	139	16.95	-3.74	<0.0001

BID = twice daily; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test
Source: CS302 Table 14.2.1.1.2, Table 14.2.1.1.1

Table 39 Study CS304: Mean IOP and Mean Change from Diurnally Adjusted Baseline (PP Populations with Baseline IOP < 25 mmHg, < 27 mmHg, and < 30 mmHg)

Study Visit and Timepoint	Baseline IOP < 25 mmHg				Baseline IOP < 27 mmHg				Baseline IOP < 30 mmHg			
	Netarsudil 0.02% QD				Netarsudil 0.02% QD				Netarsudil 0.02% QD			
	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	184	17.68	-4.74	<0.0001	237	18.34	-4.65	<0.0001	302	19.20	-4.74	<0.0001
10:00	181	16.55	-4.51	<0.0001	233	17.17	-4.57	<0.0001	297	17.93	-4.74	<0.0001
16:00	181	16.32	-4.37	<0.0001	233	17.04	-4.17	<0.0001	297	17.76	-4.39	<0.0001
Day 43 08:00	177	17.84	-4.55	<0.0001	228	18.40	-4.56	<0.0001	289	19.45	-4.45	<0.0001
10:00	177	16.75	-4.27	<0.0001	227	17.33	-4.36	<0.0001	286	18.12	-4.47	<0.0001
16:00	176	16.57	-4.09	<0.0001	226	17.16	-4.03	<0.0001	285	17.89	-4.20	<0.0001
Day 90 08:00	167	17.86	-4.52	<0.0001	214	18.38	-4.57	<0.0001	261	19.24	-4.52	<0.0001
10:00	166	16.90	-4.10	<0.0001	212	17.57	-4.08	<0.0001	259	18.30	-4.13	<0.0001
16:00	165	16.73	-3.88	<0.0001	211	17.29	-3.87	<0.0001	258	18.02	-3.95	<0.0001
	Timolol BID				Timolol BID				Timolol BID			
	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value	N	Mean	Diff.	p-value
Day 15 08:00	183	17.51	-4.94	<0.0001	245	18.02	-5.00	<0.0001	312	18.60	-5.30	<0.0001
10:00	183	16.71	-4.55	<0.0001	245	17.17	-4.76	<0.0001	312	17.80	-4.97	<0.0001
16:00	183	16.92	-3.77	<0.0001	245	17.35	-3.94	<0.0001	312	17.85	-4.19	<0.0001
Day 43 08:00	183	17.60	-4.85	<0.0001	245	18.00	-5.02	<0.0001	310	18.52	-5.37	<0.0001
10:00	182	16.98	-4.29	<0.0001	244	17.39	-4.54	<0.0001	309	17.89	-4.87	<0.0001
16:00	182	16.67	-4.01	<0.0001	244	17.21	-4.08	<0.0001	309	17.88	-4.14	<0.0001
Day 90 08:00	179	17.29	-5.17	<0.0001	239	17.72	-5.31	<0.0001	300	18.35	-5.52	<0.0001
10:00	179	16.69	-4.56	<0.0001	238	17.01	-4.91	<0.0001	299	17.60	-5.11	<0.0001
16:00	179	16.80	-3.89	<0.0001	238	17.11	-4.14	<0.0001	299	17.66	-4.27	<0.0001

BID = twice daily; Diff. = difference; IOP = intraocular pressure; PP = per-protocol; QD = once daily
Difference from baseline is Visit Value - Baseline Value and is tested against 0 within treatment with a 2-tailed 1-sample t-test
Source: CS304 Table 14.2.1.1.1, Table 14.2.1.2.10, and Table 14.2.1.2.1

Appendix 2 PG324 (Netarsudil and Latanoprost Combination)

In addition to netarsudil, Aerie is also developing PG324, a fixed dose combination of netarsudil 0.02% and latanoprost 0.005%. Data relevant to netarsudil monotherapy are available from a completed 4-arm Phase 2 study (PG324-CS201) with PG324 ophthalmic solution compared to its individual active components, netarsudil ophthalmic solution 0.02% and latanoprost ophthalmic solution 0.005%. Data are also available from 2 Phase 3 trials with PG324 ophthalmic solution (PG324-CS301 and PG324-CS302) with the same comparator arms that were ongoing at the time of the safety update: unmasked 3-month efficacy data for PG324-CS301 and masked safety data for PG324-CS301 and PG324-CS302. The 3 studies for the PG324 combination program are shown in Table 40.

Efficacy of Netarsudil

Results from the planned 3-month interim analysis are available for this double-masked, randomized, multicenter, active-controlled, parallel-group, 12-month study assessing the safety and ocular hypotensive efficacy of PG324 ophthalmic solution compared to its active constituents - netarsudil ophthalmic solution 0.02% and latanoprost ophthalmic solution 0.005% - in subjects with elevated IOP (PG324-CS301). Enrollment had been completed with 718 subjects with OAG or OHT and the study was ongoing at the time of the netarsudil NDA submission.

Mean baseline IOP was similar across the groups and ranged from 22.4 to 24.8 mmHg. During the 3-month treatment period described in this summary, mean IOP ranged from 14.8 to 16.2 mmHg, 17.2 to 19.0 mmHg, and 16.7 to 17.8 mmHg in the PG324, netarsudil, and latanoprost groups, respectively, representing a mean change from baseline IOP of -7.2 to -9.2 mmHg, -5.1 to -6.1 mmHg, and -5.3 to -7.1 mmHg. There was a clinically and statistically significant reduction from baseline in all treatment groups. Mean IOP in the PG324 group was 1.8 to 3.0 mmHg greater than in the netarsudil group ($p < 0.0001$), and 1.3 to 2.4 mmHg greater than in the latanoprost group ($p \leq 0.0002$). At Month 3, 43.5% (87/200) of PG324 subjects achieved mean diurnal IOPs of ≤ 15 mmHg compared to 22.7% (45/198) and 24.7% (55/223) of netarsudil 0.02% and latanoprost 0.005% subjects, respectively ($p < 0.0001$).

Non-inferiority of netarsudil 0.02% to latanoprost 0.005% was demonstrated in a post hoc analysis (PP population with maximum baseline IOP < 25 mmHg). The upper 95% confidence limit for the differences in mean IOP between netarsudil 0.02% and latanoprost 0.005% was within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at 6 of the 9 timepoints, meeting the criteria for non-inferiority as pre-specified in prior netarsudil Phase 3 studies. The difference in means between treatments (netarsudil - latanoprost) ranged from -0.45 to +0.79 mmHg.

Safety

Studies PG324-CS301 and PG324-CS302 were ongoing as of the cutoff date for the netarsudil NDA 4-month safety update. Each of these studies was designed to evaluate the

safety and efficacy of PG324 in comparison with its individual components over a 3-month (PG324-CS302) or 12-month (PG324-CS301) treatment period. The masked safety data from the combined studies through 20 April 2017 were summarized in the safety update. Since that cutoff date, study PG324-CS302 has completed and the clinical study report is in progress.

Demographics: A total of 1468 subjects were randomized and treated in PG324-CS301 (718 subjects) and PG324-CS302 (750 subjects); enrollment in each study is closed. As of the 20 April 2017 cutoff date for the safety update, 1176 subjects had completed the studies.

A total of 1963 subjects were screened, ranging in age from 18 to 99 years (mean 64.4 to 65.0). In PG324-CS301 and PG324-CS302, respectively, there were similar numbers of elderly subjects (≥ 65 years: 56.8% and 54.9%) and non-elderly subjects (≥ 18 to < 65 years: 43.2% and 45.1%). Most subjects were white (68.7% and 66.3%). These 2 studies included a higher percentage of females (56.9% and 56.4%) compared to males (43.1% and 43.6%).

Adverse Events: In PG324-CS301 and PG324-CS302, the proportion of subjects who experienced TEAEs was 63.5% and 53.6%, respectively. The most frequently reported ocular TEAEs included conjunctival hyperemia (44.4% and 37.7%), instillation site pain (18.4% in PG324-CS301 only), conjunctival hemorrhage (10.7% and 6.8%), eye irritation (2.8% and 9.5%), cornea verticillata (9.5% and 7.6 %) eye pruritus (7.0% and 2.5%), and punctate keratitis (5.2% and 2.4%).

No new safety issues relating to netarsudil 0.02% have been identified in these studies. However, it was noted that corneal disorder was reported in 26 subjects (3.5%) in PG324-CS302. In that study, endothelial cell counts were measured at baseline and 3 months with specular microscopy, and corneal disorder (endothelial cell pleomorphism or distortion of specular microscopy corneal endothelial cell morphology) was reported. That study had completed and was unmasked after the safety update cutoff date; however, it is known that corneal disorder was reported in 14 (5.7%) subjects in the PG324 group, 12 (4.7%) subjects in the netarsudil 0.02% group, and 0 subjects in the latanoprost 0.005% group. Nonetheless, no corneal endothelial cell density change, corneal thickness change, or corneal edema was reported.

Corneal disorder was previously reported in study CS302, which also measured endothelial cell counts at baseline and 3 months. In that study, corneal disorder was reported in 1 (0.4%) subject in the netarsudil QD group, and 0 subjects in both the netarsudil BID and timolol groups. Although corneal disorder is not a new AE, it was reported at a higher incidence rate in netarsudil– containing treatment groups in study PG324-CS302.

No treatment-related SAEs were reported as of the cutoff date; however, 2 deaths considered unrelated to the study treatment have been reported. One subject in PG324-CS301 died of atherosclerotic/hypertensive cardiovascular disease and one subject in PG324-CS302 died of cardiac arrest.

The most frequently reported ocular TEAEs causing subjects to discontinue study participation in PG324-CS301 and PG324-CS302, respectively, included conjunctival

hyperemia (5.2% and 1.6%), allergic conjunctivitis (1.4% and 0.4%), eye pruritus (1.4% and 0.1%), blurred vision (1.1% and 0.3%), corneal verticillata (1.0% and 0.3%), instillation site pain (1.3% in PG324-CS301 only), increased lacrimation (1.1% in PG324-CS301 only), and contact dermatitis (1.0% in PG324-CS301 only).

Table 40 Description of Clinical Studies in the Development of the Fixed Combination PG324 with a Netarsudil 0.02% QD Treatment Arm

Study ID (Phase)	No. of Study Centers, Location	Study Start[1] Status	Design Control Type	Study Objective	Treatment Groups and Regimen	Subjects Planned/ Completed[2]	Treatment Duration	Gender Mean Age (Range)	Key Inclusion Criteria
PG324-CS201 Phase 2	24 US	January-2014 Completed	Double-masked, randomized, active-controlled, parallel-group	IOP-lowering efficacy; ocular and systemic safety	PG324 0.01% QD PM PG324 0.02% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	280/297	28 days	123M / 175F 64.9 yrs (26, 92)	OAG or OHT; IOP: ≥ 24 mmHg at 08:00; ≥ 21 mmHg at 10:00 and 16:00; ≤ 36 mmHg
PG324-CS301 Phase 3	55 US	July-2015 Ongoing[3]	Double-masked, randomized, multi-center, active-controlled, parallel-group	IOP-lowering efficacy; ocular and systemic safety	PG324 0.02% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	690/718	12 months	Screened: 410M/ 541F Mean 65.0 yrs (18-93)	OAG or OHT; IOP: > 20 mmHg at 08:00; > 17 mmHg at 10:00 and 16:00; < 36 mmHg
PG324-CS302 Phase 3	59 US and Canada	January-2016 Completed[4]	Double-masked, randomized, multi-center, active-controlled, parallel-group	IOP-lowering efficacy; ocular and systemic safety	PG324 0.02% QD PM Netarsudil 0.02% QD PM Latanoprost 0.005% QD PM	690/750	3 months	Screened: 441M/ 571F Mean 64.4 yrs (18-99)	OAG or OHT; IOP: > 20 mmHg at 08:00; > 17 mmHg at 10:00 and 16:00; < 36 mmHg

F = females; IOP = intraocular pressure; M = males; OAG = open-angle glaucoma; OHT = ocular hypertension; PG324 = fixed-dose combination of netarsudil 0.02% and latanoprost 0.005%; PM = evening; QD = once daily; US = United States

[1] First subject screened.

[2] Number of subjects included in the safety analyses.

[3] PG324-CS301 was ongoing as of the 20 April 2017 cutoff date for the 4-month safety update. Unmasked results of the planned 3-month interim analysis were available for efficacy and masked results through 20 April 2017 were available for safety.

[4] PG324-CS302 was ongoing as of the 20 April 2017 cutoff date for the 4-month safety update. Masked safety results through 20 April 2017 were available.