Rhopressa™

Netarsudil ophthalmic solution 0.02%

CDER
Dermatologic and Ophthalmic Drugs Advisory Committee

October 13, 2017
Aerie Pharmaceuticals, Inc.

Introduction

Marvin Garrett

Vice President, Regulatory Affairs and Quality Assurance

Aerie Pharmaceuticals, Inc.

Aerie Pharmaceuticals

- 2005: Aerie founded as a spin-out from Duke University:
  - Dr. Eric Toone
  - Dr. Casey Kopczynski
  - Dr. David Epstein
  - Dr. Epstein's goal from the beginning:
    Develop a therapy that targeted the diseased tissue in glaucoma, the trabecular outflow pathway
- 2006: Aerie discovered its first Rho kinase inhibitor
- 2009: Aerie invented netarsudil
- 2012: Netarsudil 1st clinical study
- 2017: NDA filed

Netarsudil: A New Drug Class for Lowering IOP

We are requesting a recommendation for approval of netarsudil ophthalmic solution 0.02% for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension given one drop QD

Agenda

Unmet Medical Needs	***Richard A. Lewis, MD*** Chief Medical Officer Aerie Pharmaceuticals, Inc. Past President, American Glaucoma Society
Program Design and Efficacy	***Casey Kopczynski, PhD*** Chief Scientific Officer Aerie Pharmaceuticals, Inc.
Safety	***Theresa Heah, MD, MBA*** VP Clinical Research and Medical Affairs Aerie Pharmaceuticals, Inc.
Benefits and Risks	***Janet Serle, MD*** Professor of Ophthalmology Glaucoma Fellowship Director Icahn School of Medicine at Mount Sinai

List of Expert Responders

- **Cynthia Mattox, MD**
  - Associate Professor of Ophthalmology,
    Tufts University School of Medicine
  - Current President, American Glaucoma Society
- **Mark Reasor, PhD**
  - Professor of Physiology & Pharmacology,
    Robert C. Byrd Health Sciences Center, West Virginia University
- **Bennie H. Jeng, MD**
  - Professor and Chair, Department of Ophthalmology & Visual Sciences,
    University of Maryland School of Medicine
- **Dale Usner, PhD**
  - Biostatistics Consultant to Aerie Pharmaceuticals, Inc.
- **Ken Ruettimann, PhD**
  - Vice President, Manufacturing, Aerie Pharmaceuticals, Inc.

Unmet Medical Needs in Glaucoma

Richard A. Lewis, MD

Chief Medical Officer
Aerie Pharmaceuticals, Inc.

Past President, American Glaucoma Society

Glaucoma Remains a Leading Cause of Irreversible Blindness Worldwide

- Global prevalence of 3.4%[1]
- Predominantly in the elderly
- Higher incidence in African Americans
- Chronic, asymptomatic disease with no cure
- Requires long-term therapy and follow-up
  - Poor compliance to both

1. Tham YC et al. Ophthalmol. 2014;121:2081-90

Most Glaucoma Patients Will Not Go Blind, but the Majority Will Be Visually Disabled

Vision loss from glaucoma decreases quality of life[1]

- **Daily Activities**: walking and falls, taking medications, doing housework, preparing meals, and reading
  - *Bilateral glaucoma patients are 5 times more likely to report severe difficulty with near activities than subjects without glaucoma*[2]
- **Driving**: greater motor vehicle collision rate
  - *1.65 times greater compared with those without glaucoma*[3]
- **Fear of blindness**: social withdrawal and depression[4]

1. Medeiros FA et al. Ophthalmol. 2015,122:293-301.
2. Freeman EE et al. Ophthalmology. 2008;115(2):233-8.
3. Kwon M et al. Ophthalmology. 2016;123:109-16
4. Skalicky I et al. J Glaucoma. 2008;17:546-551.

78% of Glaucoma Patients Have IOPs <25 mmHg at Time of POAG Diagnosis

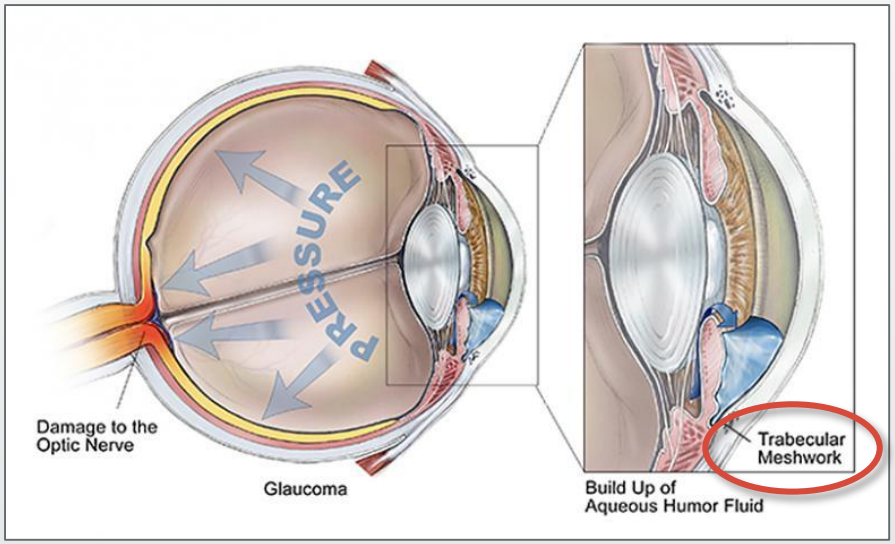
Baltimore Eye Survey, 1991

Baseline IOP	Percentage of POAG Patients Identified	Cumulative Percentage
≤15	13%	13%
16-18	24%	37%
19-21	22%	59%
22-24	19%	78%
25-29	10%	88%
30-34	9%	97%
≥35	3%	100%

5308 individuals were screened for the prevalence of Primary Open-Angle Glaucoma (POAG)
Sommer A et al. Arch Ophthalmol. 1991;109:1090-1095

Reducing Elevated IOP is the Only Effective Therapy for Treating Glaucoma

- Lowering IOP protects optic nerve, delays or prevents progressive loss[1]
- Elevated IOP is a result of structural changes in the trabecular meshwork and outflow system that increase resistance to aqueous outflow



1. Heijl A et al, Arch Ophthalmol. 2002;120:1268-79

Degeneration of TM Outflow Pathway Causes Elevated IOP and Vision Loss in Glaucoma

Cellular Stress
- Aging
- Oxidation

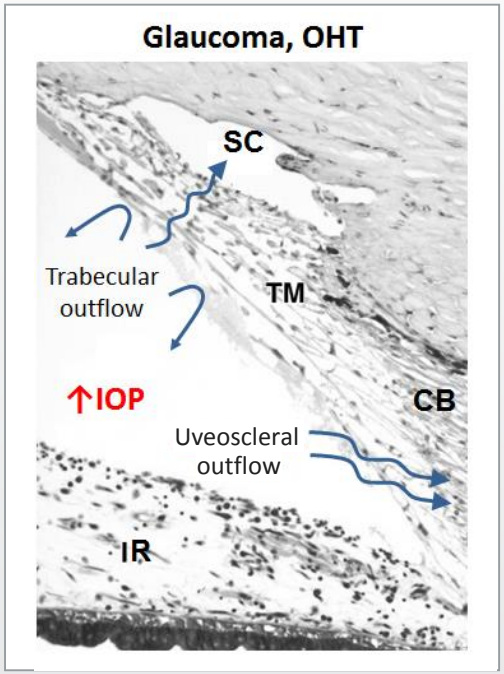
Healthy TM
Normal IOP

Fibrosis, Stiffness
Contraction

Reduced Aqueous
Perfusion Area

Less Nutrients,
Antioxidants

Cellular Stress



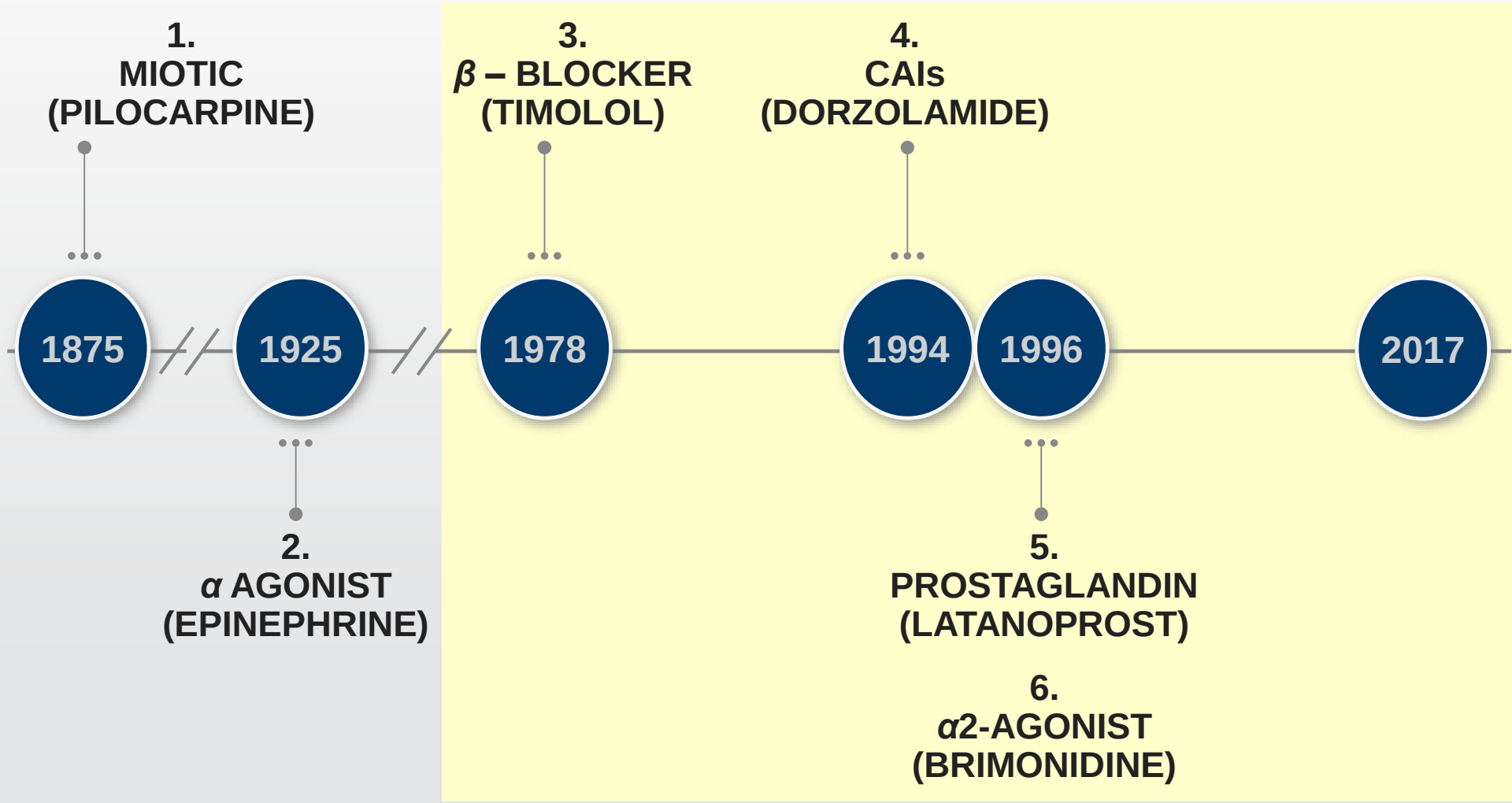
Elevated IOP → Vision Loss

Commonly Used Medications Do Not Target the Diseased TM

Wang SK, Chang RT. Clin Ophthalmol. 2014;8:883-890
Yuan He, et al. Invest Ophthalmol Vis Sci. 2008;49:1447-58

Current Glaucoma Market: 21 Years Without a New Drug Class

Timeline of currently approved glaucoma drops



Approaches to Lowering IOP

1. Medications enhancing outflow
2. Medications to reduce aqueous production
3. Surgery

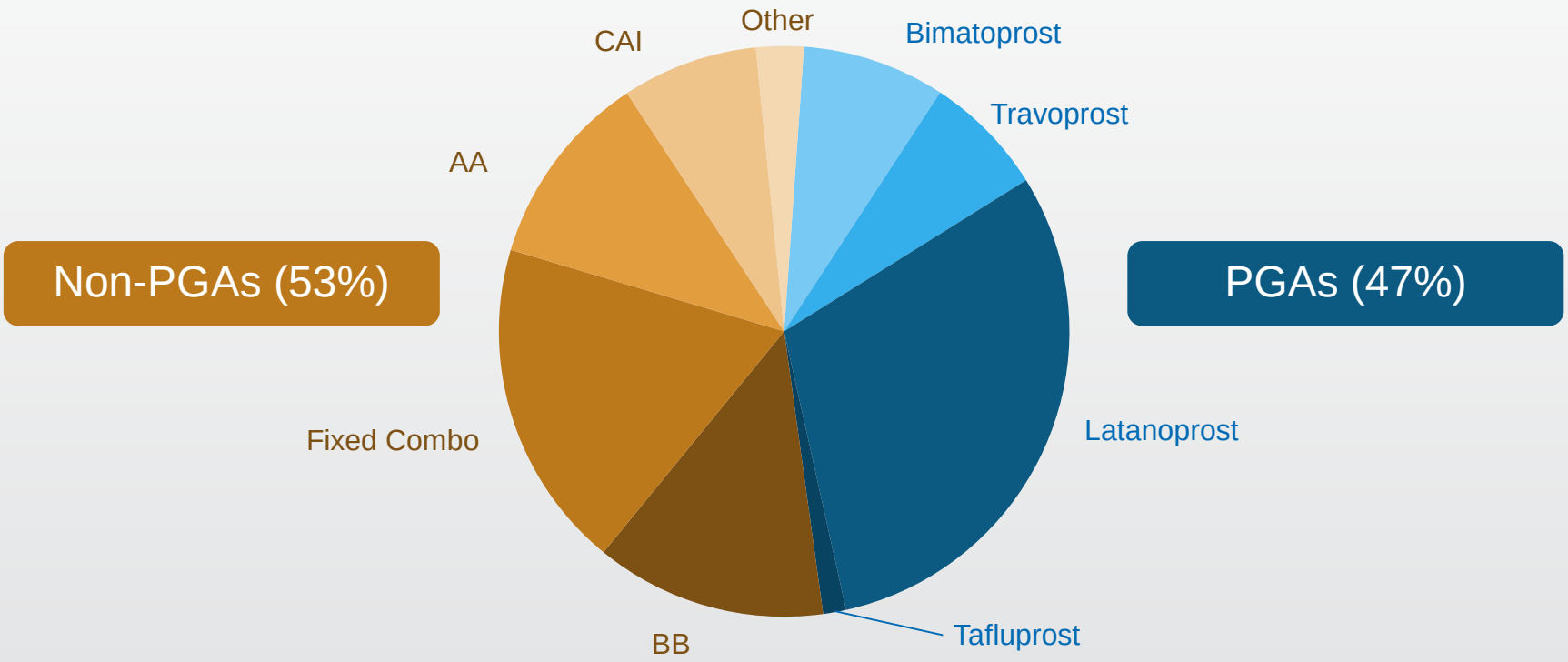
Caveats:

- Enhancing outflow is preferred over reducing inflow[1]
- Over 50% of glaucoma patients require more than one medication to control their IOP[2]

1. Kaufman, P. Invest Ophthalmol. 2012;53:2495-2500
2. Kobelt-Nguyen G. J Glaucoma. 1998;7:95-104

Half of Glaucoma Prescriptions Are for Non-PGA Drug Classes in 2016

US Glaucoma Topical Monthly Units



Non-PGA Drug Classes Are Required to Adequately Treat Glaucoma

PGA: Prostaglandin Analogue; BB: Beta Blocker; AA: Alpha Agonist; CAI: Carbonic Anhydrase Inhibitor
Sources: IMS Analytics Link at ex-manufacturer price level. Monthly Units calculated from IMS SU Data

Most Commonly Used Non-PGAs Require Multiple Doses Per Day

Places a major burden on the patients' daily activities and makes compliance challenging

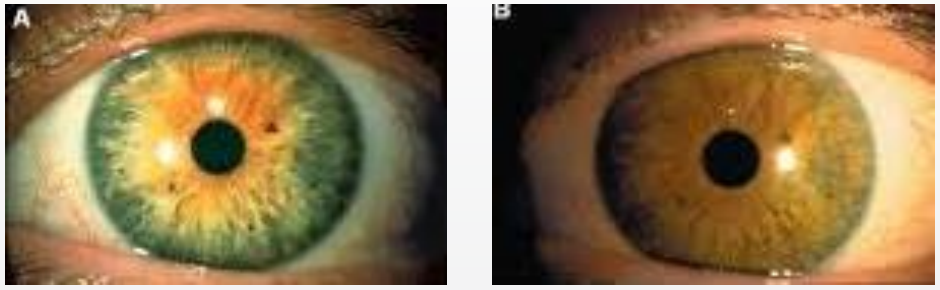
Drug	Daily Doses
1. Prostaglandins (PGAs)	One
2. Beta adrenergic antagonists	One or Two
3. Topical carbonic anhydrase inhibitors	Three
4. Nonselective α and β adrenergic agonists	Two or Three
5. Miotics	Four
6. Fixed dose combination: Timolol + Dorzolamide	Two
7. Fixed dose combination: Timolol + Brimonidine	Two

All IOP-lowering Medications Cause Multiple Ocular and Systemic Side Effects

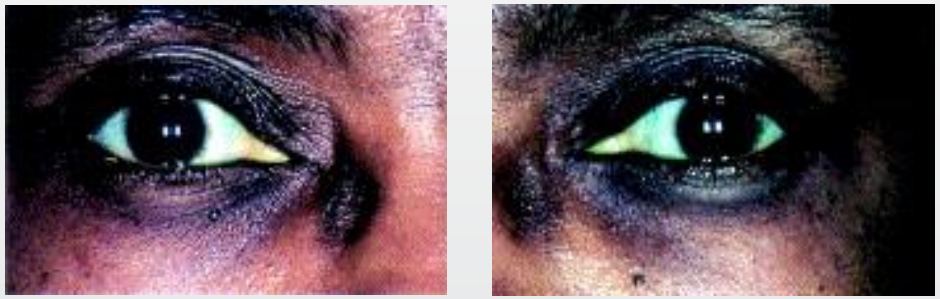
Drug	Ocular Side Effects	Systemic Side Effects
1. Prostaglandins	Hyperemia, increased iris pigmentation, eyelash growth, foreign body sensation, loss of orbital fat tissue, periocular hyperpigmentation, eye ache	Headache, flu-like symptoms
2. Beta adrenergic antagonists	Dry eyes, hyperemia	Decreased exercise tolerance, decreased pulse, bronchospasm, fatigue, depression, impotence
3. Selective alpha$_2$ adrenergic agonists	Hyperemia, allergic conjunctivitis/dermatitis, follicular conjunctivitis	Dry mouth and nose, hypotension, headache, fatigue, somnolence
4. Topical carbonic anhydrase inhibitors	Hyperemia, burning, blurred vision, allergic conjunctivitis/ dermatitis	Bitter taste, sulfa-related side effects
5. Nonselective α and β adrenergic agonists	Ocular allergy, irritation, hyperemia, tachyphylaxis	Tachycardia, arrhythmia, headache, hypertension
6. Miotics	Decreased vision, dermatitis, small pupil, increased myopia, cataract, retinal tears, eye pain	Brow ache, headache, increased salivation, abdominal cramps

Adverse Effects: Prostaglandins

- Iris darkening from latanoprost from baseline



- Peribulbar skin changes



- Enophthalmos from loss of orbital fat

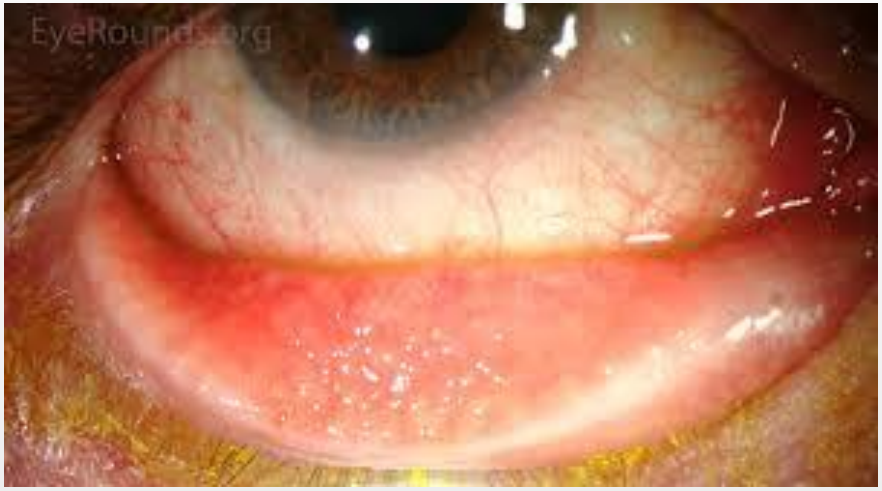
Adverse Effects: Beta Blockers

A dose of one drop of 0.5% timolol solution to each eye has a comparable peak plasma concentration to a 10 mg oral dose[1,2]

- Bradycardia and AV block
- Systemic hypotension
- Symptoms of heart failure
- Drowsiness, depression, loss of libido

1. Affrime MB et al. Clin Pharmacol Ther. 1980;27:471-7
2. Alvan G et al. Clin Pharmacokinet. 1980;5:95-100

Adverse Effects: Alpha Agonists and CAIs



- Follicular conjunctivitis

- Ocular redness and blepharitis

Limitations of Current Medical Therapy

1. Does **not** treat the trabecular outflow system
2. All **have** systemic side effects
3. First-line therapy often does **not** optimize IOP reduction
4. Adjunctive medications **all** increase complexity of dosing regimen to 2 – 3x per day

- **Given the limitations of current treatment, additional therapeutic options are necessary to manage glaucoma**

Limitations of Current Glaucoma Surgery Therapy

- Laser trabeculoplasty success rate 50% at 2 years[1,2,3]
  - Laser trabeculoplasty repeat duration 6-28 months[3,4,5]
- Incisional surgery success rate 50-60% at 5 years[6,7]
  - >50% patients require eye drops after glaucoma surgery[8]
  - Complications of surgery: 10-30%[8]

1. Bovell AM et al. Can J Ophthalmol. 2011;46:408-13. 2. Liu Y et al. J of Glaucoma. 2012; 21:112-115.
3. Polat J et al. Brit J Ophthalmol. 2016;100:1437-41. 4. Khouri AS et al. J Ophthalmic Vis Res. 2014;9:444-8.
5. Avery N et al. Int Ophthalmol. 2013;33:501-6. 6. Christakis PG et al. Am J Ophthalmol. 2017;176:118-26.
7. Minckler DS et al. Ophthalmology. 2008;115:1089-98. 8. Gedde SJ et al. Am J Ophthalmol. 2012;153:789-803

The Glaucoma Medication Wish List

1. Targeted therapy for the diseased trabecular outflow
   - Restore conventional outflow pathways
   - New adjunctive use with existing glaucoma medications
2. Effective IOP lowering
   - Longer term stable efficacy at all baseline IOPs
3. Safety
   - No drug-related systemic side effects
   - Tolerable and reversible ocular side effects
4. Convenience
   - Once a day dosing to enhance compliance and quality of life

Program Design and Efficacy

Casey Kopczynski, PhD

Chief Scientific Officer
Aerie Pharmaceuticals, Inc.

Development of a New Drug Class for Glaucoma

- Program Design

  Different mechanism of action vs. other drugs

  ⬇

  Different influence of baseline IOP on efficacy profile

  ⬇

  Different range of baseline IOPs studied in Phase 3

- Phase 3 Efficacy Results
  - Netarsudil QD non-inferior to timolol BID in 3 adequate and well-controlled Phase 3 studies

Development of a New Drug Class for Glaucoma

- Program Design

Different mechanism of action vs. other drugs

↓

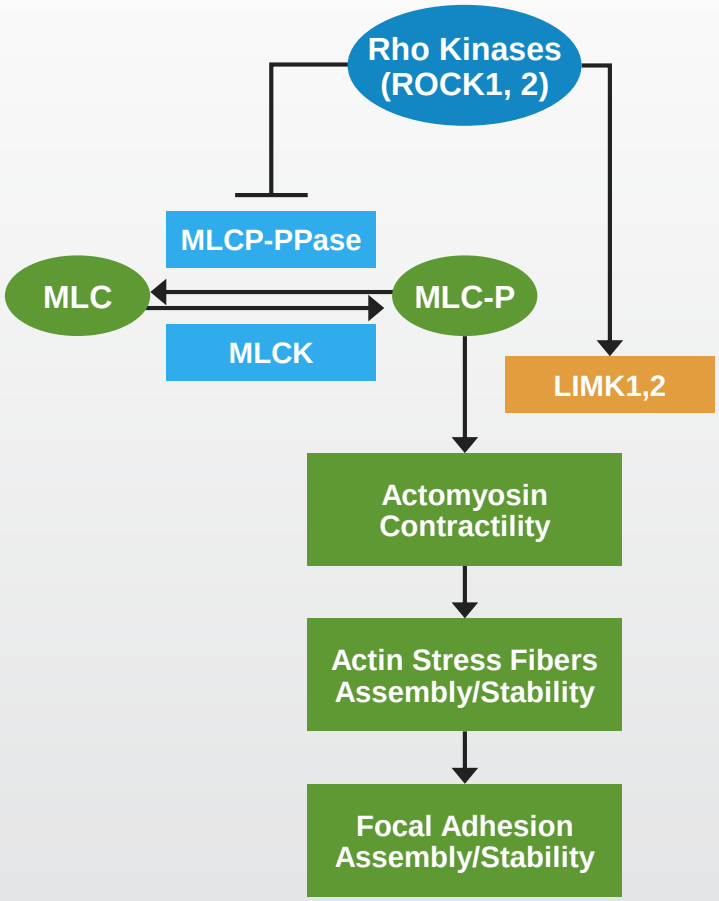
Different influence of baseline IOP on efficacy profile

↓

Different range of baseline IOPs studied in Phase 3

Netarsudil: A New Drug Class for Lowering IOP

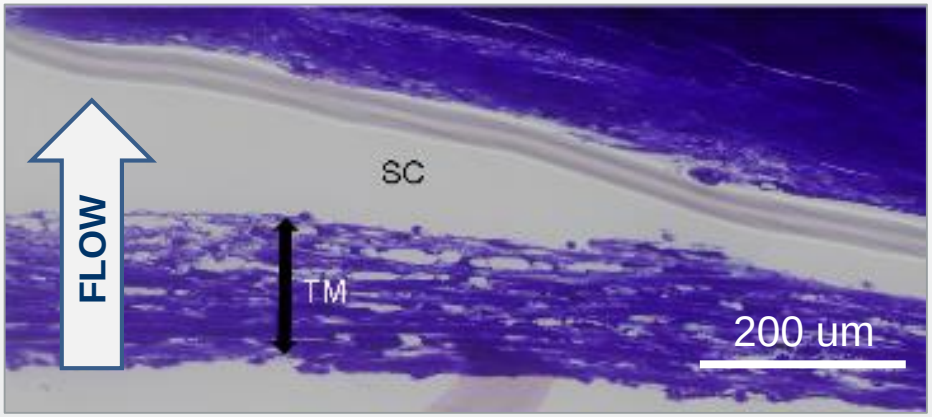
- Netarsudil is an inhibitor of Rho Kinase (ROCK)[1]
- ROCK:Ser/Thr kinase that increases cell contraction, extracellular matrix production in the trabecular outflow pathway[2]
- Netarsudil lowers IOP by 3 mechanisms
  - **Relaxes TM[3], increases outflow**[3-6]
  - Lowers Episcleral Venous Pressure[6,7]
  - Reduces fluid production[4]



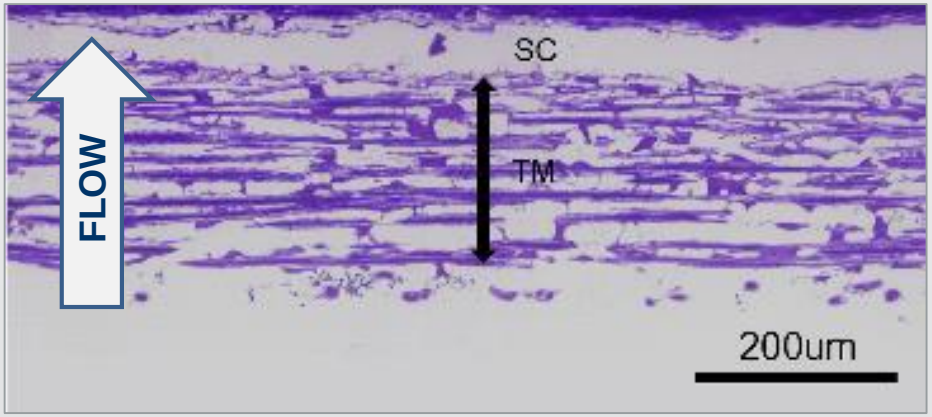
1. Sturdivant et al. Bioorg Med Chem Lett. 2016;26(10):2475-80. 2. Wang SK, Chang RT. Clin Ophthal. 2014;8:883-890.
3. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 4. Wang RF et al. J Glaucoma. 2015;24(1):51-54.
5. Li G et al. Eur J Pharmacol. 2016;787:20-31. 6. Sit AJ et al. Presented at AGS 2017.
7. Kiel JW, Kopczynski C. J Ocul Pharmacol Ther. 2015;31:146-151.

Netarsudil Causes Expansion of TM in Donor Eyes, Increases TM Outflow Facility in Clinic

Trabecular Meshwork (Donor Eyes)[1]

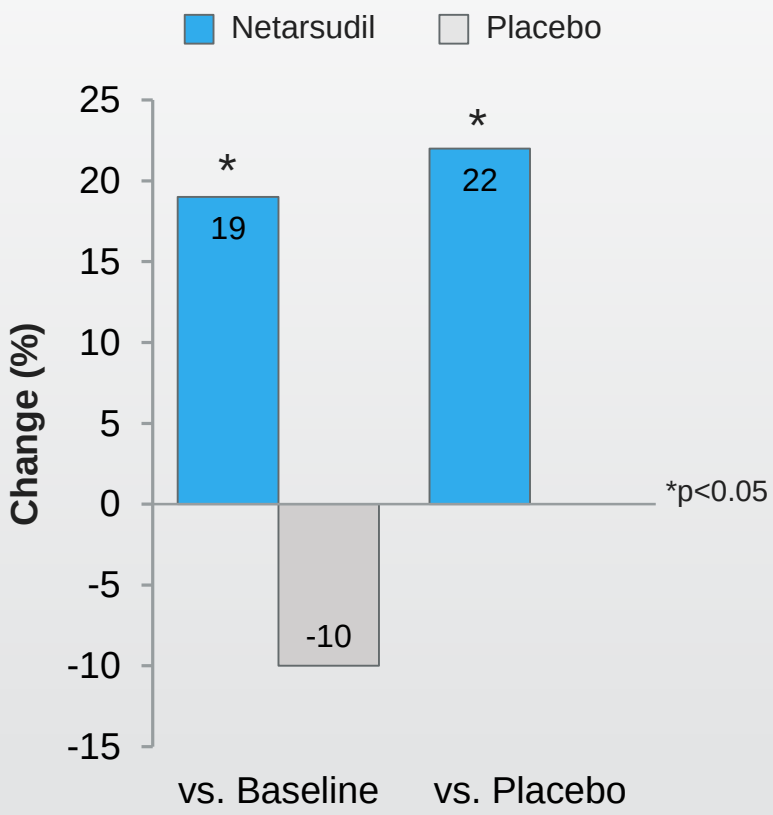


Control



+ Netarsudil

TM Outflow Facility
(Healthy Volunteers)[2]



TM: Trabecular Meshwork; SC: Schlemm's Canal; Control: buffered saline solution; ESV: Episcleral Vein

1. Ren R et al. Invest Ophthalmol Vis Sci. 2016;57(14):6197-6209. 2. Sit AJ et al. Presented at AGS 2017.

Netarsudil MOA: Clinical Relevance from Supportive Studies

- Provides additional IOP lowering to PGA therapy
  - PG324-CS201, PG324-CS301
- Provides 24-hour control of IOP
  - AR-13324-CS204

Development of a New Drug Class for Glaucoma

- Program Design

  Different mechanism of action vs. other drugs

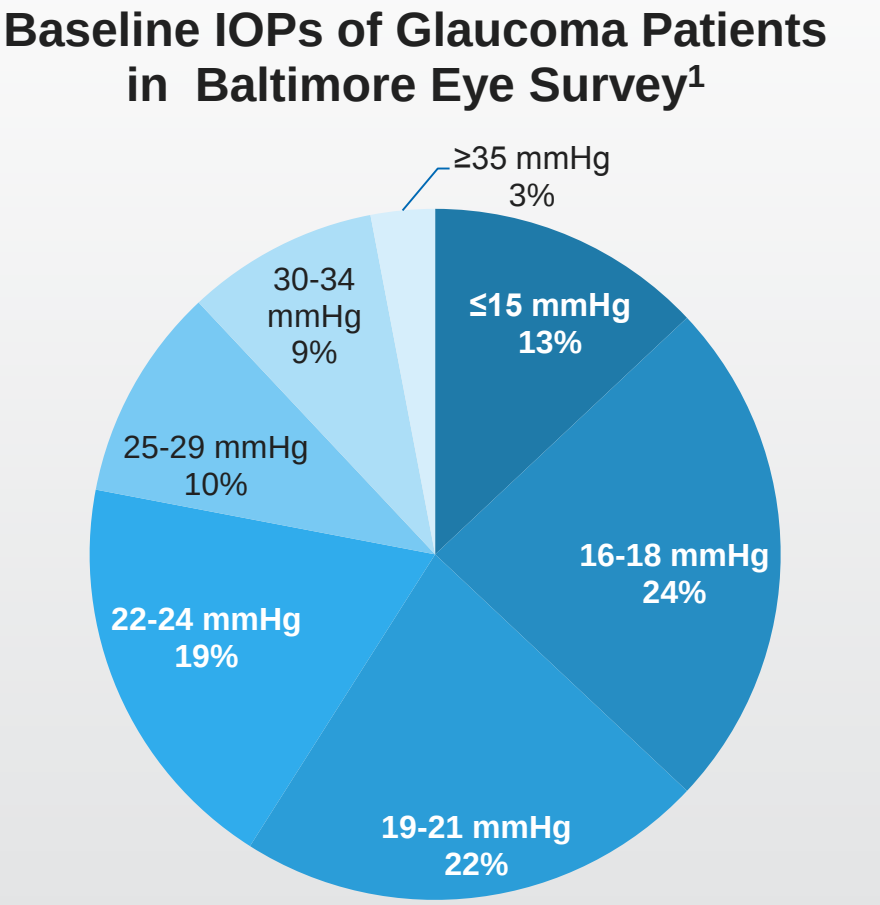
  ↓

  Different influence of baseline IOP on efficacy profile

  ↓

  Different range of baseline IOPs studied in Phase 3

Baseline IOPs of Real World Patient Population



78% of Patients Had Baseline IOPs <25 mmHg at Time of Diagnosis

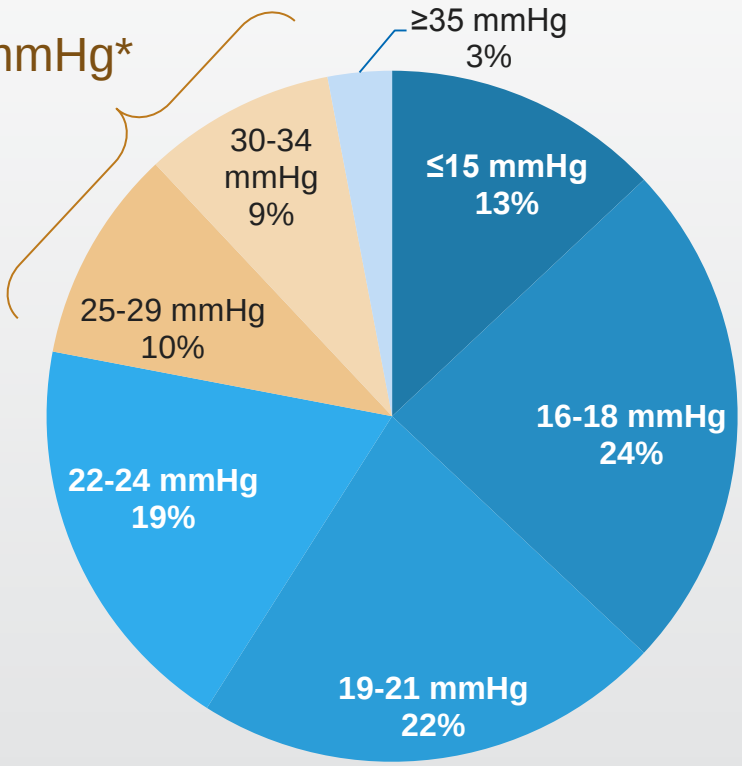
1. Sommer et al. Arch Ophthalmol. 1991;109(8):1090-5

Real World Patient Population vs. Recent Phase 3 Registration Studies

Baseline IOPs of Glaucoma Patients in Baltimore Eye Survey[1]

BL IOP 24 to 36 mmHg*

- Simbrinza™[2]
- Travoprost[3]

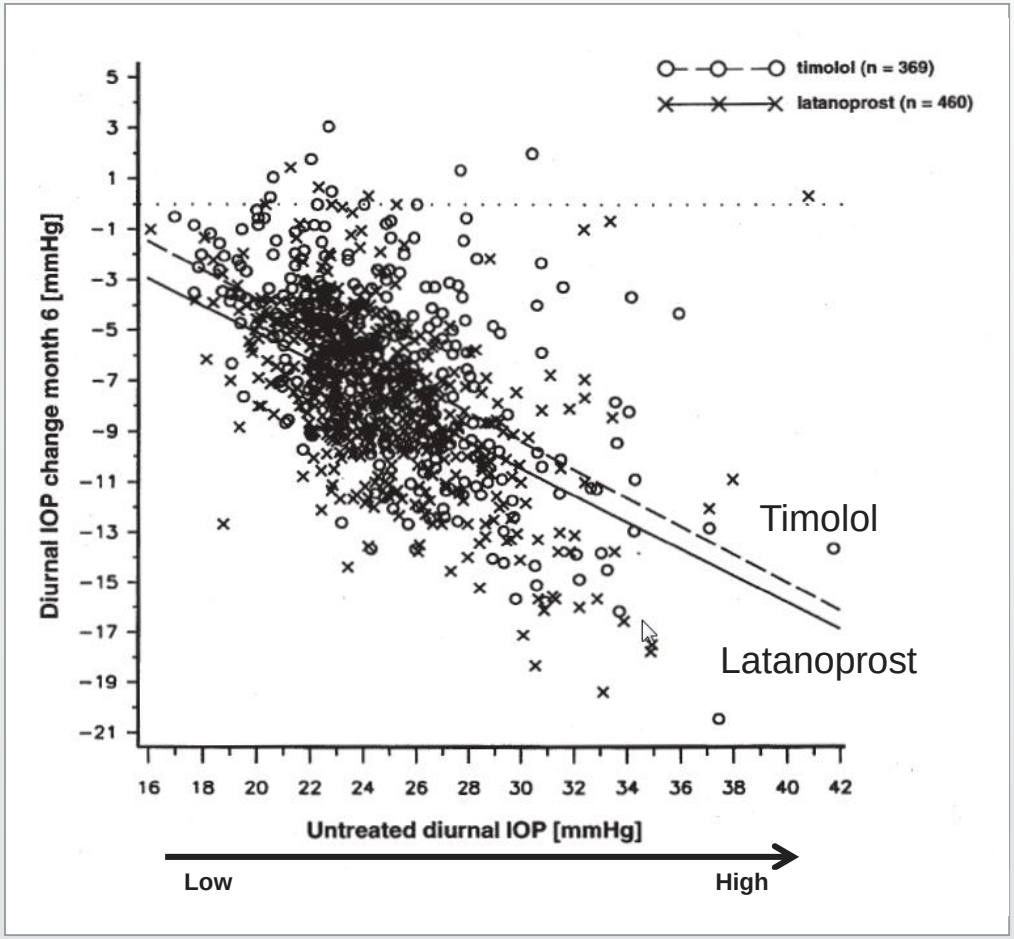


* 8 AM IOPs

Simbrinza™, Travoprost Studies Selected Only Highest Baseline IOP Patients Representing ~20% of POAG Population

1. Sommer et al. Arch Ophthalmol. 1991 Aug;109(8):1090-5. 2. Whitson et al. Clin Ophthalmol. 2013;7:1053-60.
3. Dubiner et al. Clin Ophthalmol. 2012;6:525-31. Simbrinza™ = brimonidine/brinzolamide FDC

Current Glaucoma Medications Achieve Larger IOP Reductions at Higher Baseline IOPs



- Historical data from 3 latanoprost registration studies (n=829)[1]
- Latanoprost and timolol gain 0.5 mmHg efficacy for every 1 mmHg increase in baseline IOP
  - Similar results reported for combinations of PGA+timolol[2]

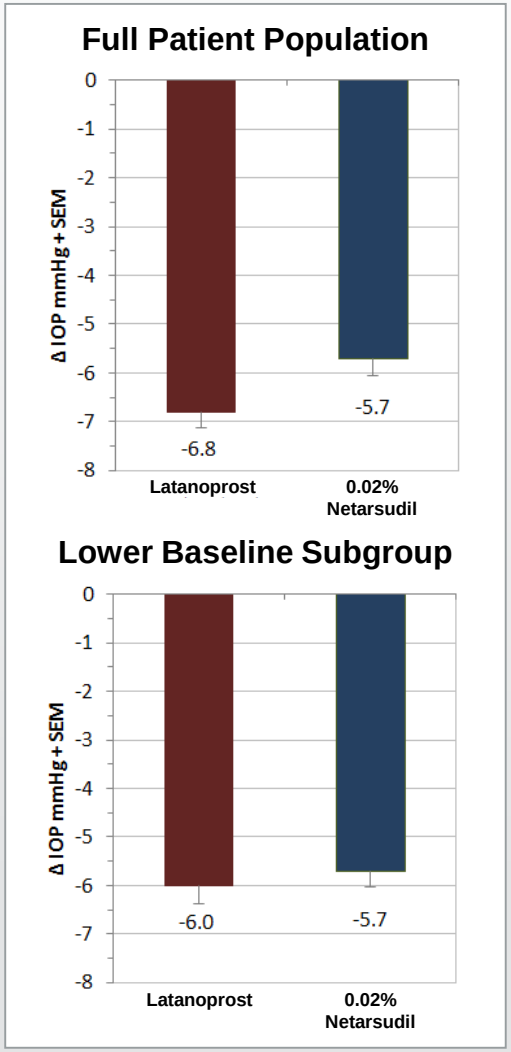
1. Hedman and Alm, Eur J Ophthalmol. 2000;10(2):95-104. 2. Hollo et al. Adv. Ther. 2014;31(9):932-44.

Phase 2b: Netarsudil Achieves Same IOP Reduction at Lower and Higher Baseline IOPs

Study CS202

Baseline IOP: 24-36 mmHg

- Netarsudil was compared to latanoprost in full patient population and lower baseline IOP subgroup
- Latanoprost produced ~1 mmHg larger IOP reduction in higher baseline group vs. lower baseline subgroup
- Netarsudil produced same IOP reduction regardless of patient baseline IOP



Baseline 24-36 mmHg (n=221)

Baseline 24-26 mmHg (n=99)

Phase 2b minimum baseline IOP: 24, 22, 22 mmHg (8am, 10am, 4pm)

Baseline IOP Summary: Netarsudil IOP Reductions Are Less Dependent on Baseline IOP

- Netarsudil differs from current glaucoma drugs with respect to the influence of baseline IOP on efficacy
- Current drug classes most effective at higher baseline IOPs, less effective at lower baseline IOPs
- Netarsudil maintains similar IOP-lowering effect across lower and higher baseline IOPs up to 36 mmHg

Development of a New Drug Class for Glaucoma

- Program Design

  Different mechanism of action vs. other drugs

  ⬇

  Different effect of baseline IOP on efficacy profile

  ⬇

  Different range of baseline IOPs studied in Phase 3

Netarsudil Phase 3 Study Design: Baseline IOP of Study Populations

CS301, CS302

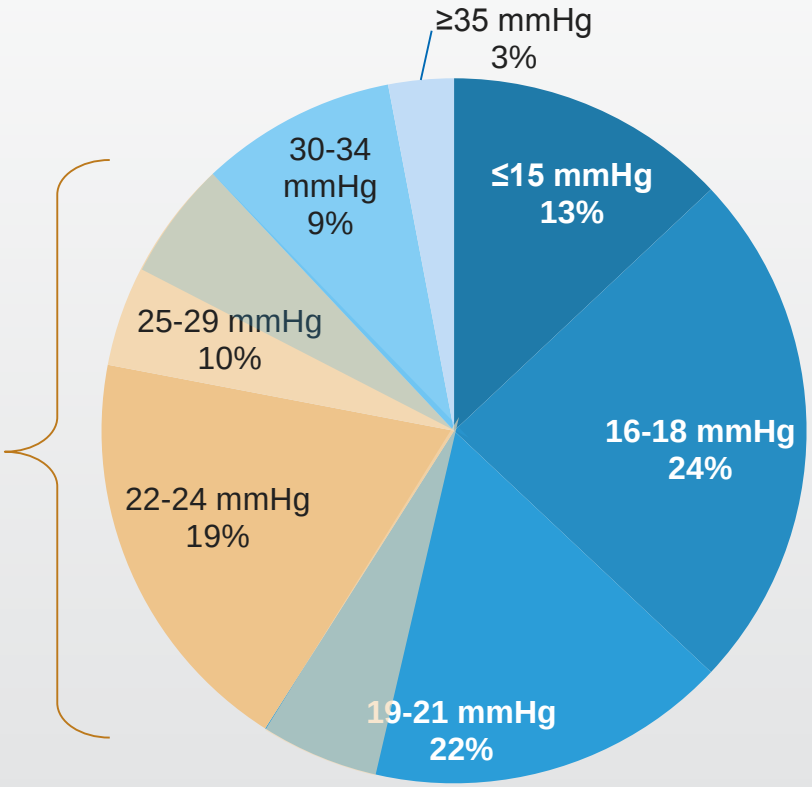
BL IOP >20 to <27 mmHg*

CS304

BL IOP >20 to <30 mmHg*

* 8 AM IOPs

Baseline IOPs of Glaucoma Patients in Baltimore Eye Survey[1]



~30% of POAG Population Represented in CS301, CS302 Studies

~35% of POAG Population Represented in CS304 Study

1. Sommer et al. Arch Ophthalmol. 1991 Aug;109(8):1090-5

Netarsudil 0.02% Phase 3 Study Design

	Treatment	8 AM 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

Studies Powered to Show Non-inferiority of Netarsudil QD to Timolol BID

Products Approved Using Timolol As Active Comparator in Phase 3 Studies

Drug Class	Product	Year Approved
Beta blocker	Betaxolol	1985
Carbonic anhydrase inhibitor	Dorzolamide	1994
Alpha agonist	Brimonidine	1996
Prostaglandin	Latanoprost	1996
	Bimatoprost	2001
	Travoprost	2001
	Tafluprost	2012

Timolol Has Been "Gold Standard" Comparator for Over 30 Years

Non-inferiority Analysis

- Primary outcome: Mean IOP at each of 9 time points measured over 3 months
  - PP population, historically considered conservative population for non-inferiority
  - Sensitivity analysis: ITT population
- Primary analysis: Difference netarsudil vs. timolol
  - Two-sided 95% CI, observed data only
  - Sensitivity analysis: adjusting for baseline and missing data imputed using LOCF, Multiple Imputation, and BOCF
- Non-inferiority definition: Upper limit of the 2-sided 95% CI must be:
  - Within 1.5 mmHg at each of 9 time points over 3 months
  - Within 1.0 mmHg at a majority of time points over 3 months

Key Inclusion, Exclusion Criteria (Other than IOP)

- Inclusion Criteria
  - 18 years of age or greater (also 0-2 yrs in CS301/CS302)
  - Diagnosis of OAG or OHT
  - Corrected visual acuity in each eye +1.0 logMAR or better
- Exclusion
  - Glaucoma: pseudoexfoliation or pigment dispersion component, history of angle closure, or narrow angles
  - Previous glaucoma intraocular surgery or glaucoma laser procedures in either eye
  - Refractive surgery in either eye

Study Design Summary: Non-inferiority vs. Timolol, More Common Range of Baseline IOPs

- Baseline IOP is an important variable when comparing efficacy of drugs with different mechanisms of action
- Netarsudil provides opportunity to evaluate efficacy in patients with more typical, moderately elevated IOPs
  - Represents larger proportion of the patient population
  - Often excluded from glaucoma Phase 3 studies

Development of a New Drug Class for Glaucoma

- Program Design

  Different mechanism of action vs. other drugs

  ⬇

  Different influence of baseline IOP on efficacy profile

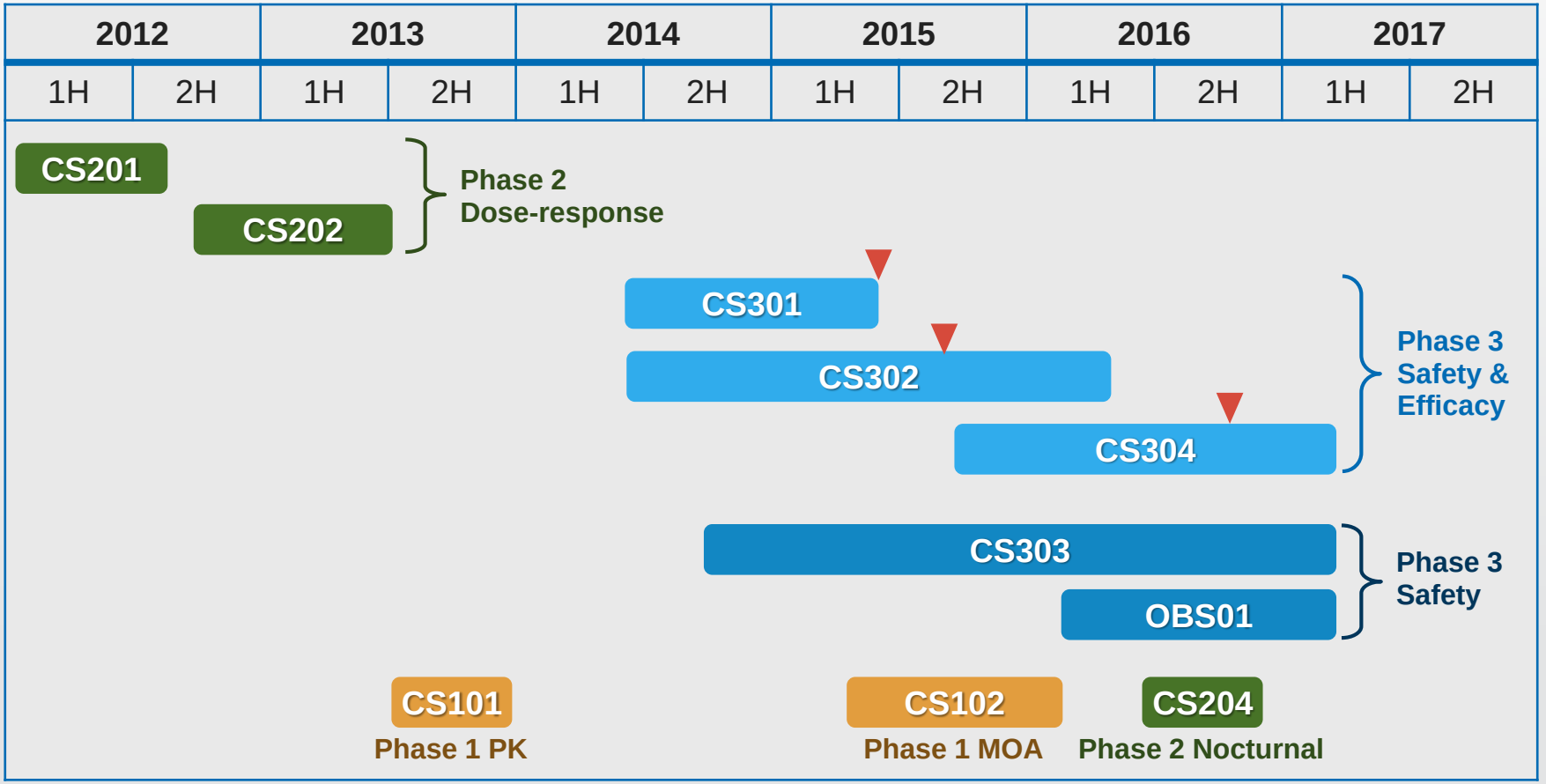
  ⬇

  Different range of baseline IOPs studied in Phase 3

- **Phase 3 Efficacy Results**
  - Netarsudil QD non-inferior to timolol BID in 3 adequate and well-controlled Phase 3 studies

Netarsudil Clinical Trials

- 10 clinical trials
- 5 Phase 3 trials



Phase 3 Efficacy Results: Netarsudil 0.02% QD Is Effective at Lowering IOP

- Non-inferior to timolol in 3 large, randomized and well-controlled Phase 3 studies
  - At baseline IOP up to <25 mmHg in CS301, CS302, CS304
  - At baseline IOP up to <30 mmHg in CS304
- Efficacy stable over 12 months

Demographics and Baseline Characteristics Similar across All Studies and Study Arms

- Sex: Majority female (~60%)
- Mean age: ~65 years
- Race: White ~70%, Black/African American ~25%
- Diagnosis: OAG ~66%, OHT ~34%
- Prior Therapy: On prior therapy ~65%,
  Treatment naïve ~35%

Disposition at Month 3 (Primary Efficacy Endpoint)

	CS301		CS302			CS304	
Analysis Populations	Netarsudil QD (N=202)	Timolol BID (N=209)	Netarsudil QD (N=251)	Netarsudil BID (N=254)	Timolol BID (N=251)	Netarsudil QD (N=351)	Timolol BID (N=357)
Safety	203 (100.5)	208 (99.5)	251 (100.0)	253 (99.6)	251 (100.0)	351 (100.0)	357 (100.0)
Intent to Treat	202 (100.0)	209 (100.0)	251 (100.0)	253 (99.6)	251 (100.0)	351 (100.0)	357 (100.0)
Per Protocol	182 (90.1)	188 (90.0)	206 (82.1)	209 (82.3)	217 (86.5)	306 (87.2)	317 (88.8)
Completed Month 3	**171 (84.7)**	**196 (93.8)**	**205 (81.7)**	**153 (60.2)**	**237 (94.4)**	**290 (82.6)**	**335 (93.8)**

- Timolol BID: 94% completed Month 3
- Netarsudil QD: 82%-85% completed Month 3
- Netarsudil BID: 60% completed Month 3

Seeking Marketing Approval for Netarsudil QD

Netarsudil 0.02% QD Phase 3 Efficacy Summary

		Non-inferiority to Timolol (No. of Time Points Met)		
	Max. Baseline IOP Enrolled	Max. Baseline IOP <25 mmHg	Max. Baseline IOP <27 mmHg	Max. Baseline IOP <30 mmHg
CS301	<27	*Yes (9/9)**	**No (6/9)**	–
CS302	<27	**Yes (9/9)**	No (7/9) #	–
CS304	<30	**Yes (9/9)**	Yes (9/9) #	Yes (9/9) #

Bold = Primary analysis
# Secondary analysis
* Post-hoc analysis

Efficacy Results Confirmed Through Multiple Analyses of Robustness

Baseline IOP <25 mmHg

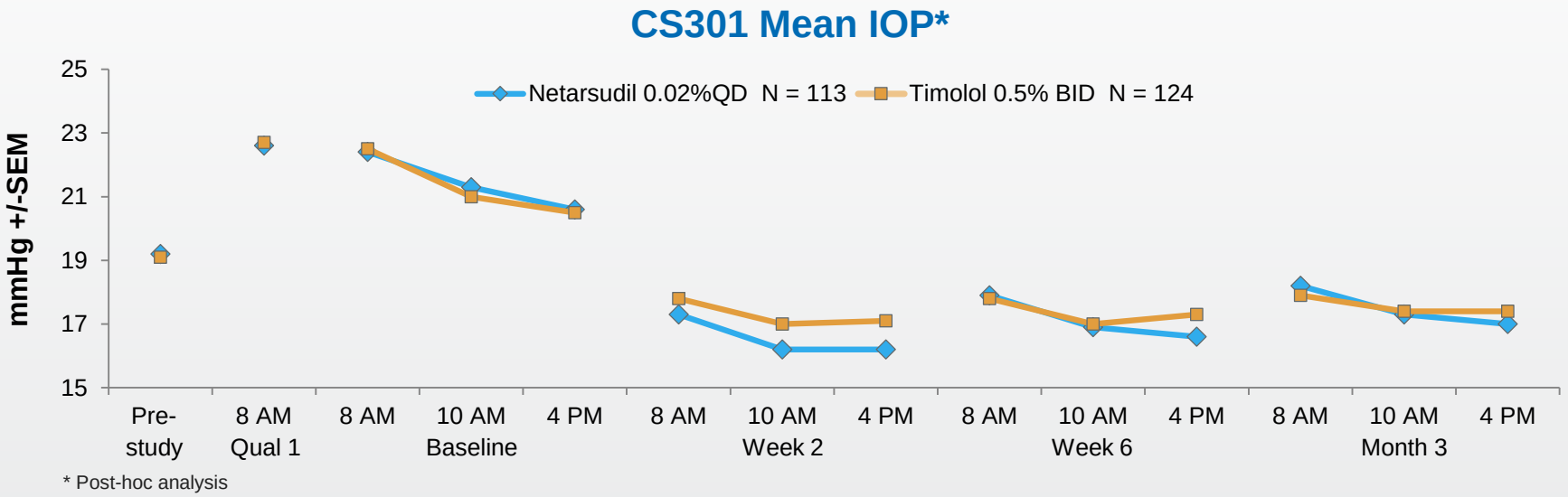
		Non-inferiority of Netarsudil 0.02% to Timolol			
		CS301*	CS302		CS304
Population	Imputation	QD	QD	BID	QD
PP	None	Yes	Yes	Yes	Yes
PP	MCMC	Yes	Yes	Yes	Yes
PP	LOCF	Yes	Yes	Yes	Yes
PP	BOCF	Yes	No	No	Yes
ITT	None	Yes	Yes	Yes	Yes
ITT	MCMC	Yes	Yes	Yes	Yes
ITT	LOCF	Yes	Yes	Yes	Yes
ITT	BOCF	Yes	No	No	Yes

* Post hoc analysis

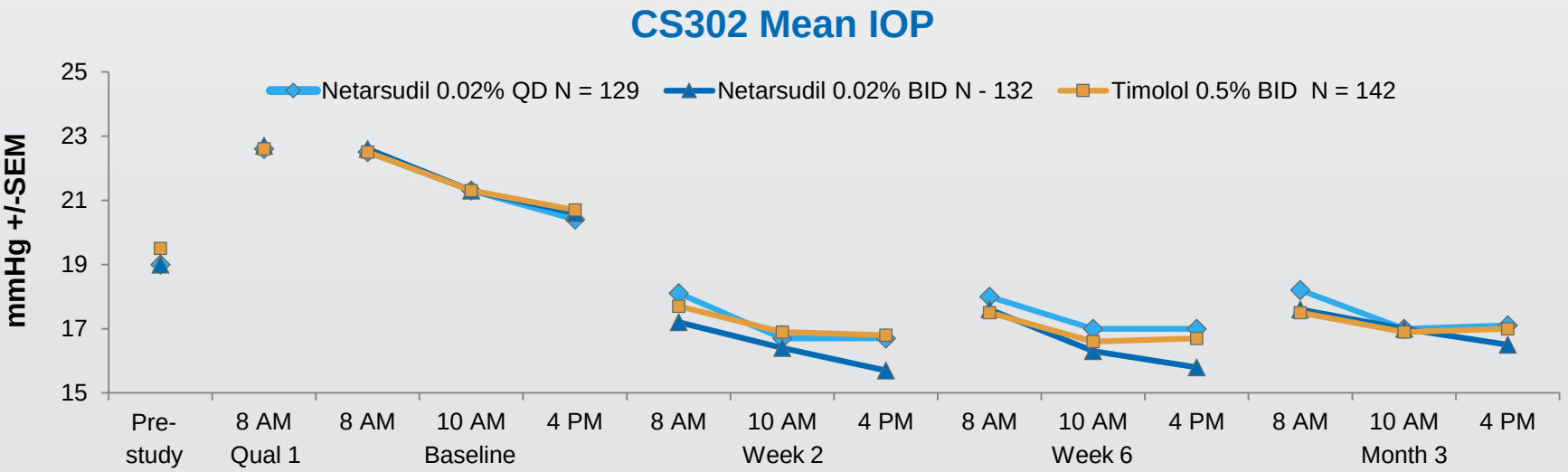
MCMC: Markov Chain Monte Carlo; LOCF: Last Observation Carried Forward; BOCF: Baseline Observation Carried Forward

CS301, CS302 Efficacy Results

Baseline IOP <25 mmHg

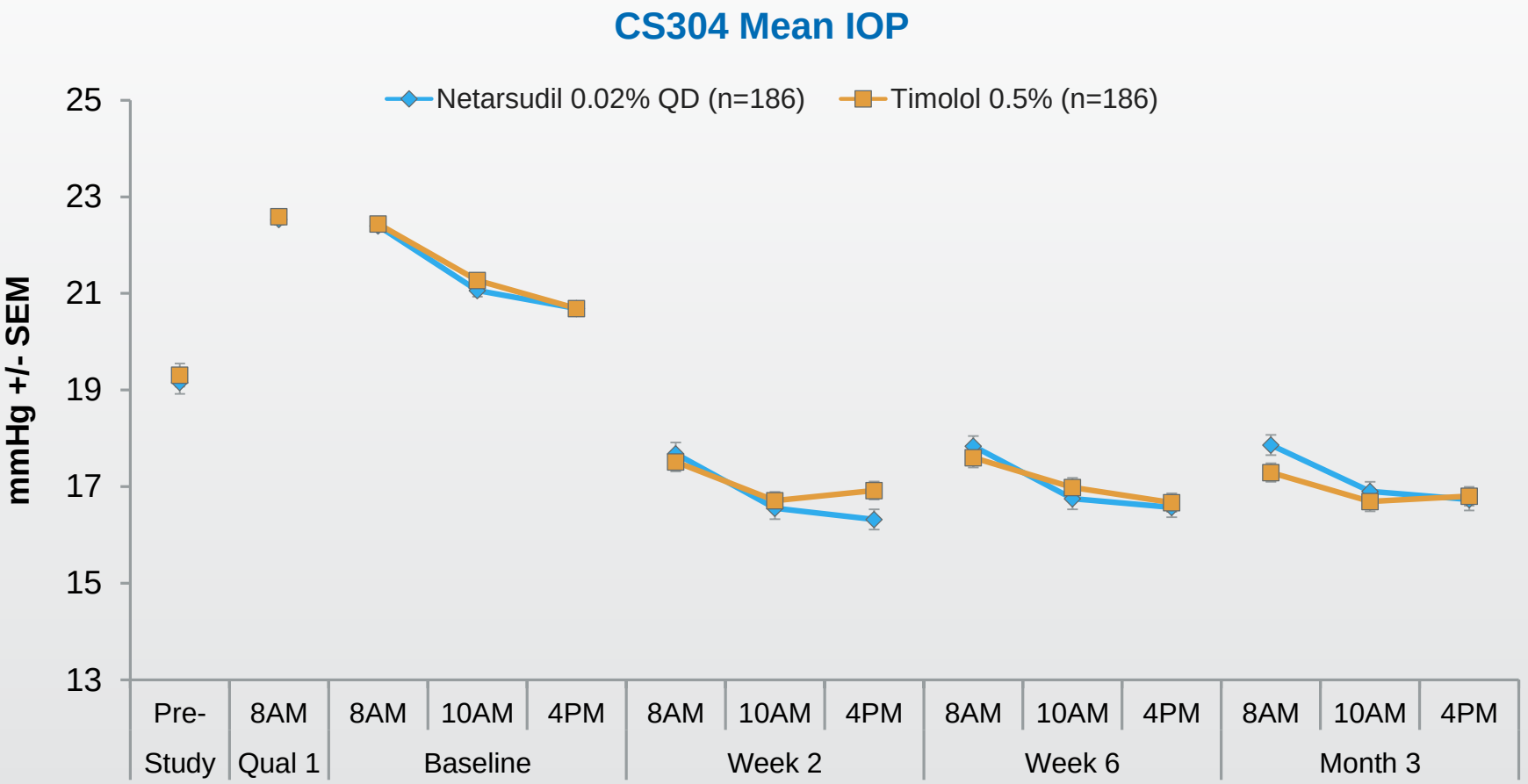


* Post-hoc analysis



CS304 Efficacy Results

Baseline IOP <25 mmHg



Netarsudil QD Non-inferior to Timolol BID at All Time Points

CS301: Netarsudil QD Non-inferior to Timolol BID

Baseline IOP <25 mmHg, Post Hoc Analysis

		Netarsudil 0.02% QD (N=113)		
		N	Mean IOP (mmHg)	Difference (95% CI)
Day 15	08:00	108	17.34	-0.44 (-1.10, 0.22)
	10:00	107	16.18	-0.81 (-1.44, -0.17)
	16:00	107	16.22	-0.92 (-1.58, -0.26)
Day 43	08:00	105	17.85	0.05 (-0.68, 0.77)
	10:00	105	16.88	-0.08 (-0.74, 0.58)
	16:00	105	16.57	-0.69 (-1.40, 0.02)
Day 90	08:00	99	18.22	0.31 (-0.40, 1.02)
	10:00	99	17.34	-0.09 (-0.82, 0.63)
	16:00	99	17.02	-0.35 (-1.03, 0.34)

Difference = netarsudil – timolol; 2-sided 95% CIs based on 2-sample t-tests

Netarsudil QD Difference from Timolol: -0.92 to +0.31 mmHg

CS302: Netarsudil QD and BID Non-inferior to Timolol BID

Baseline IOP <25 mmHg, Primary Analysis

		Netarsudil 0.02% QD (N=129)			Netarsudil 0.02% BID (N=132)		
		N	Mean	Difference (95% CI)	N	Mean	Difference (95% CI)
Day 15	08:00	127	18.07	0.37 (-0.25, 0.99)	122	17.21	-0.48 (-1.19, 0.22)
	10:00	126	16.72	-0.21 (-0.82, 0.41)	120	16.35	-0.57 (-1.24, 0.09)
	16:00	126	16.68	-0.15 (-0.75, 0.46)	118	15.65	-1.18 (-1.82, -0.54)
Day 43	08:00	122	17.95	0.49 (-0.13, 1.12)	111	17.64	0.17 (-0.51, 0.86)
	10:00	120	16.95	0.32 (-0.31, 0.95)	106	16.28	-0.34 (-1.02, 0.33)
	16:00	120	17.00	0.40 (-0.22, 1.02)	106	15.75	-0.85 (-1.53, -0.17)
Day 90	08:00	116	18.24	0.77 (0.03, 1.50)	91	17.58	0.11 (-0.64, 0.86)
	10:00	114	17.03	0.10 (-0.59, 0.80)	88	16.94	0.02 (-0.72, 0.77)
	16:00	114	17.13	0.18 (-0.55, 0.91)	88	16.51	-0.44 (-1.16, 0.27)

Difference = netarsudil – timolol; 2-sided 95% CIs based on 2-sample t-tests

Netarsudil QD Difference from Timolol: -0.21 to +0.77 mmHg

CS304: Netarsudil QD Non-inferior to Timolol BID

Baseline IOP <25 mmHg, Primary Analysis

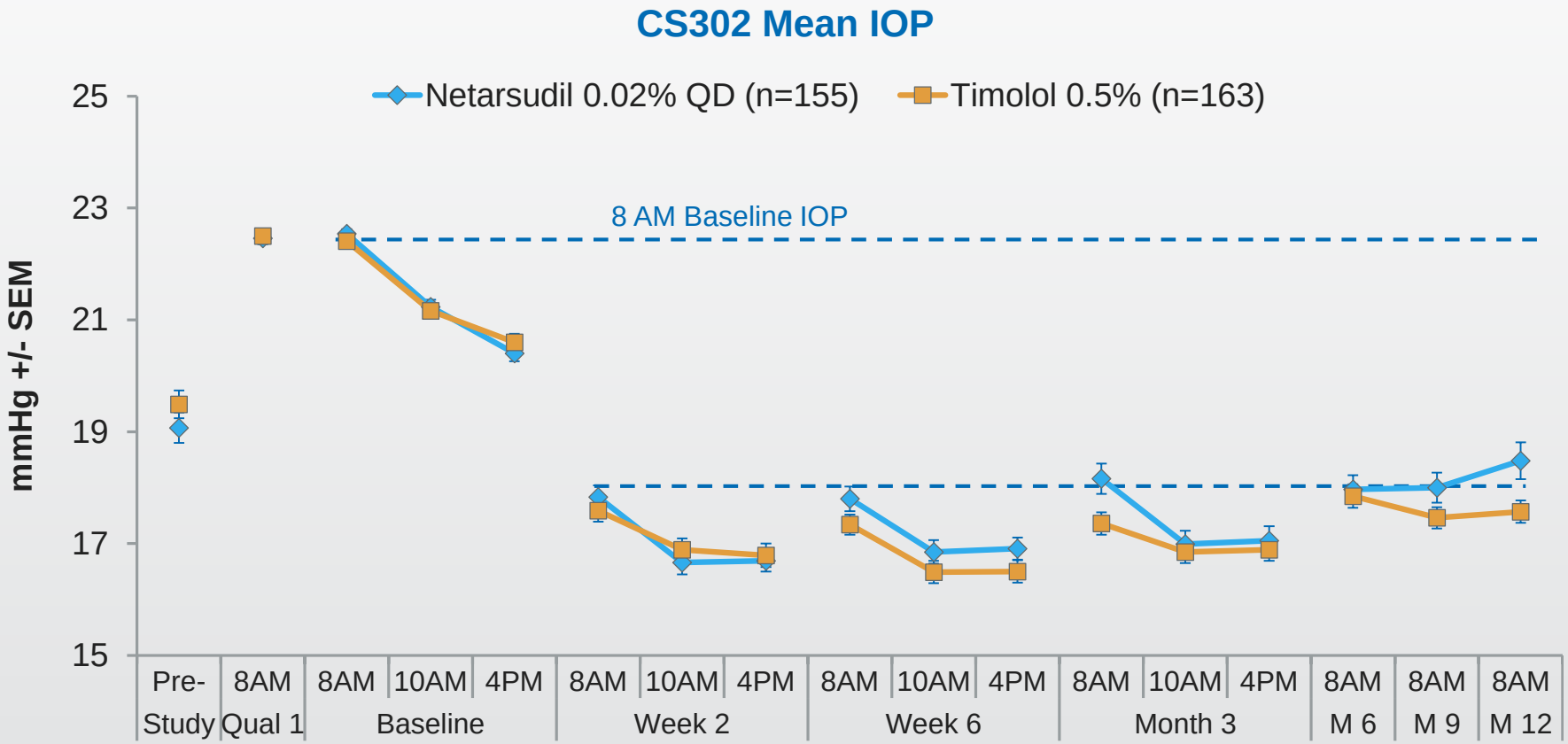
		Netarsudil 0.02% QD (N=186)		
		N	Mean IOP (mmHg)	Difference (95% CI)
Day 15	08:00	184	17.68	0.17 (-0.43, 0.77)
	10:00	181	16.55	-0.16 (-0.73, 0.41)
	16:00	181	16.32	-0.60 (-1.16, -0.04)
Day 43	08:00	177	17.84	0.25 (-0.34, 0.83)
	10:00	177	16.75	-0.22 (-0.82, 0.37)
	16:00	176	16.57	-0.10 (-0.66, 0.46)
Day 90	08:00	167	17.86	0.56 (-0.02, 1.15)
	10:00	166	16.90	0.21 (-0.37, 0.79)
	16:00	165	16.73	-0.07 (-0.68, 0.55)

Difference = netarsudil – timolol; 2-sided 95% CIs based on 2-sample t-tests

Netarsudil QD Difference from Timolol: -0.60 to +0.56 mmHg

CS302: Netarsudil QD Maintains Efficacy Through 12 Months

Baseline IOP <25 mmHg



8 AM IOP Collected as Safety Measure at Months 6, 9 and 12

Efficacy at Higher Baseline IOPs

Pooled Efficacy Analysis

Non-inferiority Results vs. Maximum Baseline IOP

		Non-inferiority to Timolol (No. of Time Points Met)		
	Max. Baseline IOP Enrolled	Max. Baseline IOP <25 mmHg	Max. Baseline IOP <27 mmHg	Max. Baseline IOP <30 mmHg
CS301	<27	*Yes (9/9)**	**No (6/9)**	–
CS302	<27	**Yes (9/9)**	No (7/9) #	–
CS304	<30	**Yes (9/9)**	Yes (9/9) #	Yes (9/9) #

Bold = Primary analysis
# Secondary analysis
* Post-hoc analysis

Netarsudil Non-inferior to Timolol across Wide Range of Baseline IOPs in Pooled Analysis

Pooled CS301/CS302/CS304

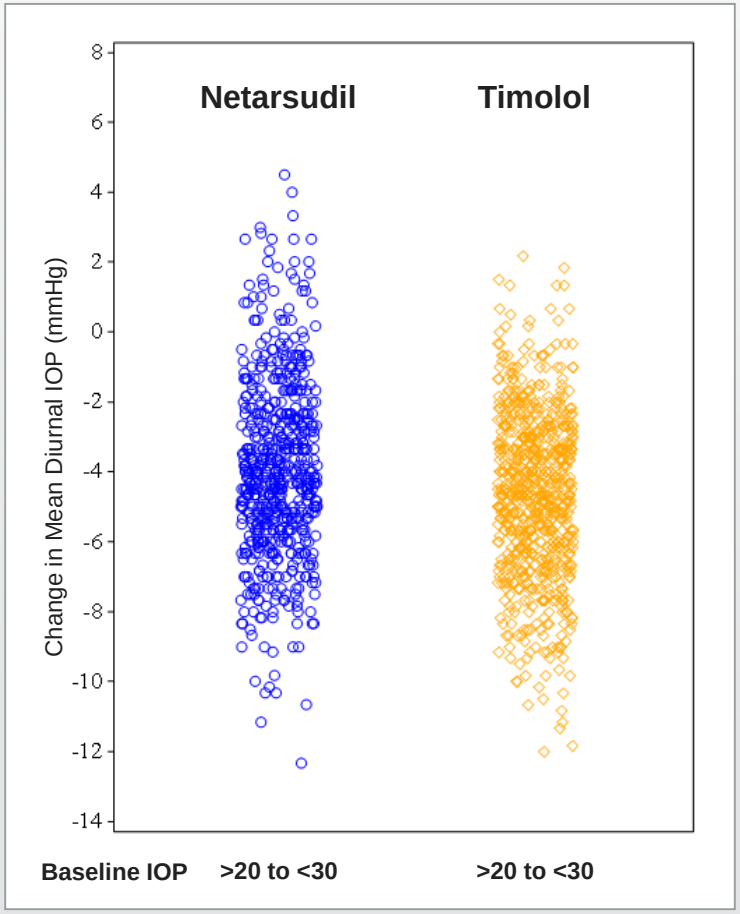
Baseline IOP (mmHg)	Met Non-inferiority*
<30	Yes
<27	Yes
<26	Yes
<25	Yes
<24	Yes
<23	Yes
<22	Yes

* Upper limit of the 2-sided 95% CI:
  Within 1.5 mmHg at each of 9 time points over 3 months
  Within 1.0 mmHg at a majority of time points over 3 months

Distribution of Patient IOP Reductions Highly Similar at Baseline IOPs <30 mmHg

Pooled Analysis CS301/CS302/CS304

Day 90: Change from Baseline IOP (Pooled)



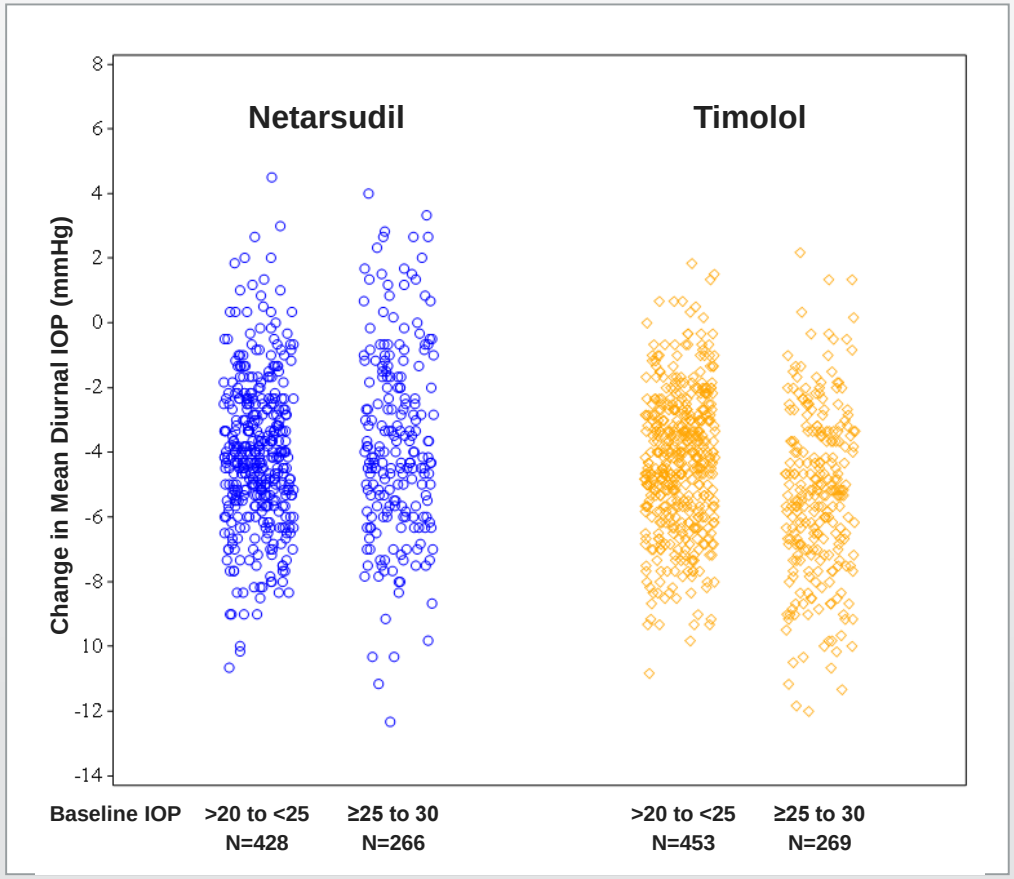
Baseline IOP <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.7
Mean	-3.9	-4.7
Max	-12.3	-12.0

Netarsudil Is Similarly Effective at Baseline IOPs <25 mmHg and ≥25 mmHg

Pooled Analysis CS301/CS302/CS304

Day 90: Change from Baseline IOP by Baseline Subgroup (Pooled)



Baseline IOP >20 to <25 mmHg

	Netarsudil QD	Timolol BID
Median	-4.2	-4.3
Mean	-4.1	-4.3
Max	-10.7	-10.8

Baseline IOP ≥25 to <30 mmHg

	Netarsudil QD	Timolol BID
Median	-4.0	-5.3
Mean	-3.7	-5.3
Max	-12.3	-12.0

Efficacy Summary: Netarsudil 0.02% QD Is Effective at Lowering IOP

Phase 3 Studies

- Non-inferior to timolol in 3 large, randomized and well-controlled Phase 3 studies
  - At baseline IOP up to <25 mmHg in CS301, CS302, CS304
  - At baseline IOP up to <30 mmHg in CS304
- Efficacy stable over 12 months

Supportive Studies (Phase 2, Phase 3)

- Effective at lowering IOP in subjects with baseline IOPs up to 36 mmHg
- Equal IOP-lowering during nocturnal and diurnal periods
- Efficacy benefit when combined with prostaglandin

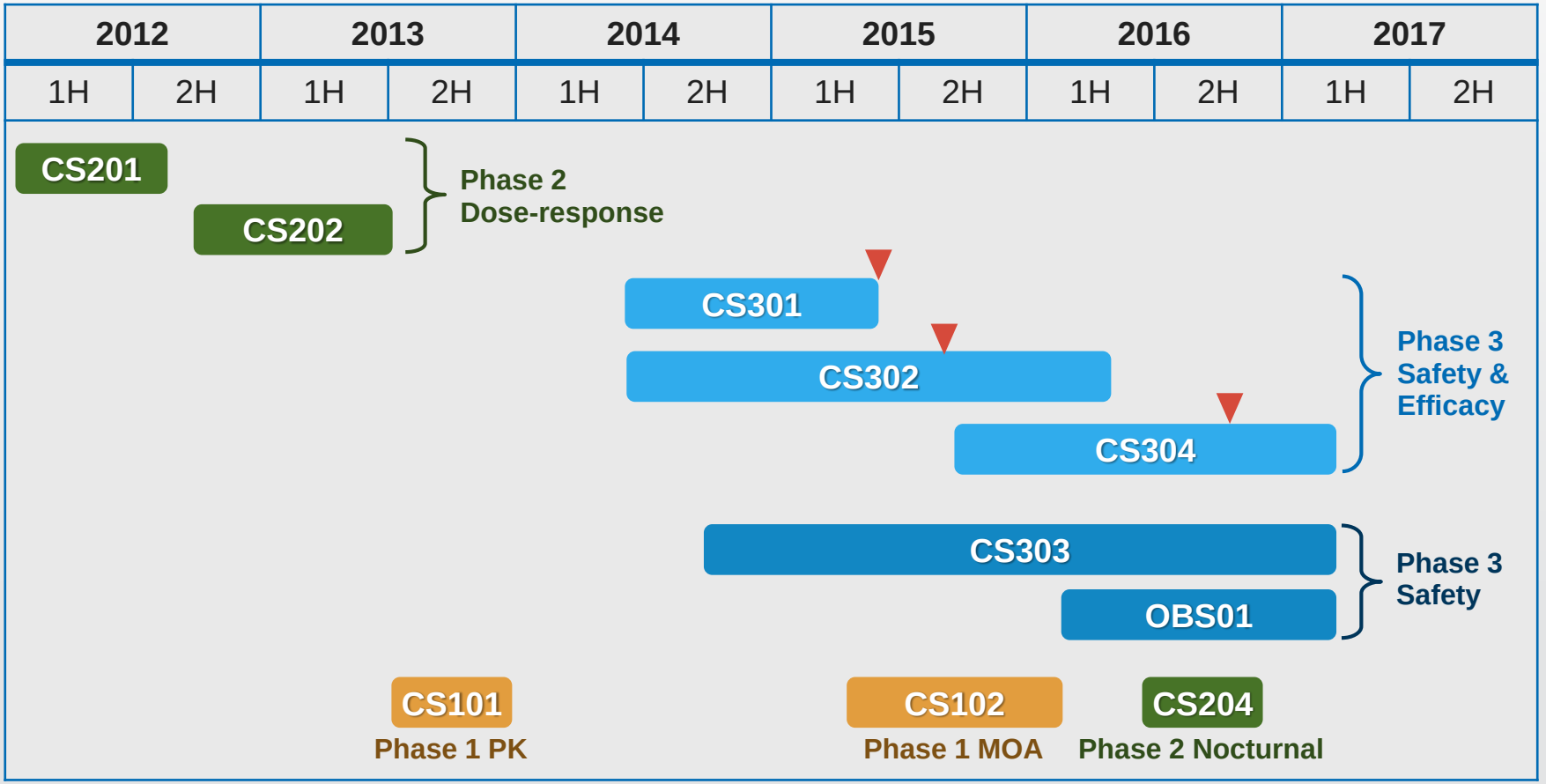
Safety

Theresa Heah, MD, MBA

VP Clinical Research and Medical Affairs
Aerie Pharmaceuticals, Inc.

Overview of Netarsudil 0.02% Safety

- Over 1,000 clinical patients in 10 clinical trials
- Minimal treatment-related systemic events
- Ocular side effects were generally mild and well tolerated



Total Exposure in Four Phase 3 Studies

Protocol Number	Safety N	Netarsudil 0.02% QD (N=839)	Netarsudil 0.02% BID (N=289)	Timolol 0.5% BID (N=839)
Phase 3 Studies				
AR-13324-CS301	411	203		208
AR-13324-CS302 (12-month)	755	251	253	251
AR-13324-CS303 (12-month)	93	34	36	23
AR-13324-CS304	708	351		357
Total	1967	**839**	**289**	839
		Total netarsudil subjects 1128		

- A total of 1128 subjects received netarsudil 0.02% (839 subjects QD and 289 subjects BID)
- Long-term safety data were provided in the 12-month Phase 3 studies (AR-13324-CS302 and CS303) with netarsudil 0.02% (285 subjects QD and 289 subjects BID)

Comprehensive Safety Evaluation of Netarsudil

- Evaluation on all randomized OAG or OHT subjects who received at least 1 dose of study drug

List of Safety Parameters

• Extent of exposure	• Slit-lamp biomicroscopy
• Systemic vital signs	• Ophthalmoscopy parameters
• Clinical laboratory testing	• Ocular comfort assessment
• Adverse events	• Specular microscopy parameters
• Visual acuity	• Visual fields
• Intraocular pressure	• Pupil size

Overall Summary Treatment-emergent AEs

Pooled Phase 3 Studies

- Adverse events (AEs) were reported as treatment-emergent AEs (TEAEs) for any change (expected or unexpected) in a subject's ocular and/or systemic health that occurred after initiation of study treatment
- Any changes in any safety parameters (such as visual acuity/field, biomicroscopy and ophthalmoscopy, vital signs) were reported as TEAEs based upon assessment by the investigator

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with ≥1 TEAE	699 (83.3)	261 (90.3)	506 (60.3)
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 with ≥1 Serious TEAE	28 (3.3)	8 (2.8)	27 (3.2)

Overall Systemic Safety Profile

Pooled Phase 3 Studies

- Adverse events (AEs) were reported as non-ocular treatment-emergent AEs (TEAEs) for any change (expected or unexpected) in a subject's systemic health that occurred after initiation of study treatment

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with ≥1 Systemic (non-ocular) TEAE	221 (26.3)	77 (26.6)	223 (26.6)

Subjects With Known Contraindications or Hypersensitivity to β-adrenoceptor Antagonists Were Excluded

Most Frequently Reported Systemic TEAEs

Pooled Phase 3 Studies

- Systemic (non-ocular) adverse events reported in ≥2.0% of subjects by treatment group (Safety Population)

	Netarsudil		Timolol
Standard Organ Classes Preferred Terms	**0.02% QD (N=839) n (%)**	**0.02% BID (N=289) n (%)**	**0.5% BID (N=839) n (%)**
Infections and Infestations	92 (11.0)	39 (13.5)	84 (10.0)
Upper respiratory tract infection	15 (1.8)	9 (3.1)	23 (2.7)
Nervous System Disorders	34 (4.1)	22 (7.6)	43 (5.1)
Headache	13 (1.5)	13 (4.5)	16 (1.9)
Skin and Subcutaneous Tissue Disorders	23 (2.7)	19 (6.6)	16 (1.9)
Dermatitis Allergic	4 (0.5)	8 (2.8)	0

Treatment-related Systemic SAE

Pooled Phase 3 Studies

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with ≥1 Treatment-related Systemic Serious TEAE	1 (0.1)	0	0

SAE	Subject	Relevant Medical History	Relevant Concomitant Medications
Exacerbation of Coronary Artery Disease	69-year old, White female	Type 2 diabetes, hypertension, coronary artery disease, cardiac bypass surgery, hypercholesterolemia	metformin, atenolol, rosuvastatin calcium, aspirin, levothyroxine, fenofibrat

*Sponsor's Medical Monitor assessed the event as not related to study drug

- Study CS301: 1 SAE was reported by investigator as possibly treatment-related to investigational drug and recovered/resolved (subject completed study)

SAEs Leading to Death Were Non-Treatment-related

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with TEAEs Resulting in Death	3 (0.4)	0	0

Subject	Cause of Death	Relevant Medical History	Relevant Concomitant Medications
75-year old, Caucasian male	Myocardial infarction	hypertension, Type 2 diabetes, coronary artery disease, hyperlipidemia, and osteoarthritis.	isosorbide, metoprolol, acetylsalicylic acid (Aspirin), ibuprofen, metformin, lisinopril, multivitamin and atorvastatin.
82-year old, Caucasian male	Myocardial infarction	coronary artery disease, mitral valve replacement, pacemaker insertion, hypercholesterolemia, gastroesophageal reflux disease, drug allergies (sulfa and penicillin).	rabeprazole sodium (Aciphex), metoprolol tartrate, diltiazem CD, simvastatin, and warfarin.
77-year old, Caucasian male	Cardiac arrest	hypertension, hypercholesterolemia, intermittent vertigo	lisinopril, simvastatin (Zocor), nicotinic acid (Niacin), fenofibrate and meclizine hydrochloride (Antivert)

No Clinically Relevant Clinical Laboratory and Vital Sign Findings for Netarsudil

- Clinical laboratory testing (chemistry and hematology) within the reference ranges with minimal changes from baseline for both netarsudil and timolol treatment groups
- Mean blood pressure:
  - The mean changes from baseline in systolic blood pressure and diastolic blood pressure were generally small and not clinically relevant in all treatment groups
- Mean heart rate:
  - Timolol reduced mean heart rate by 2.0-3.0 beats per minute ($p < 0.001$) despite all measures to exclude patients with possible negative sensitivity to beta-blockers
  - Netarsudil groups did not demonstrate significant reductions in mean heart rate

Summary of Netarsudil Systemic Safety Profile

Minimal treatment-related systemic events

SAEs leading to death were non-treatment-related

Overall Ocular Safety Profile

Pooled Phase 3 Studies

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with ≥1 Ocular TEAE	665 (79.3)	258 (89.3)	414 (49.3)
Number with TEAEs Resulting in IP Discontinuation	185 (22.1)	167 (57.8)	34 (4.1)

Seeking Marketing Approval for Netarsudil QD

Treatment-related Ocular SAE

Pooled Phase 3 Studies

	Netarsudil		Timolol
	0.02% QD (N=839) n (%)	0.02% BID (N=289) n (%)	0.5% BID (N=839) n (%)
Number with ≥1 Treatment-related Serious TEAE	0	1 (0.3)	0

SAE	Subject	Relevant Medical History	Relevant Con Meds
Iridocyclitis OS (Left Eye only)	65-year old, Caucasian female	high blood pressure, anxiety and cataracts (OU)	hydrochlorothiazide, fluoxetine, aspirin

- Subject treated with netarsudil BID in both eyes

Netarsudil Once Daily Demonstrated Consistent Ocular Safety Profile with Two Phase 3 (CS301 and CS302) Studies

Preferred Term (with Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (N=454) n (%)	Timolol 0.5% BID (N=459) n (%)
Eye Disorders		
Conjunctival Hyperemia	260 (57.3)	52 (11.3)
Cornea Verticillata (corneal deposits/corneal opacity)	76 (16.7)	2 (0.4)
Conjunctival Hemorrhage	81 (17.8)	4 (0.9)
Vision Blurred	38 (8.4)	8 (1.7)
Lacrimation Increased	27 (5.9)	0
Erythema of Eyelid	26 (5.7)	2 (0.4)
Visual Acuity Reduced	30 (6.6)	9 (2.0)
General Disorders and Administration Site Conditions		
Instillation Site Pain	75 (16.5)	83 (18.1)
Instillation Site Erythema	38 (8.4)	9 (2.0)
Investigations		
Vital Dye Staining Cornea Present	31 (6.8)	33 (7.2)

Netarsudil Once Daily Demonstrated Consistent Ocular Safety Profile with Four Phase 3 Studies

Preferred Term (with Incidence ≥5% (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Eye Disorders		
Conjunctival Hyperemia	456 (54.4)	87 (10.4)
Cornea Verticillata (corneal deposits/corneal opacity)	175 (20.9)	2 (0.2)
Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
Vision Blurred	62 (7.4)	12 (1.4)
Lacrimation Increased	60 (7.2)	5 (0.6)
Erythema of Eyelid	57 (6.8)	6 (0.7)
Visual Acuity Reduced	44 (5.2)	13 (1.5)
General Disorders and Administration Site Conditions		
Instillation Site Pain	167 (19.9)	181 (21.6)
Instillation Site Erythema	76 (9.1)	13 (1.5)
Investigations		
Vital Dye Staining Cornea Present	79 (9.4)	64 (7.6)

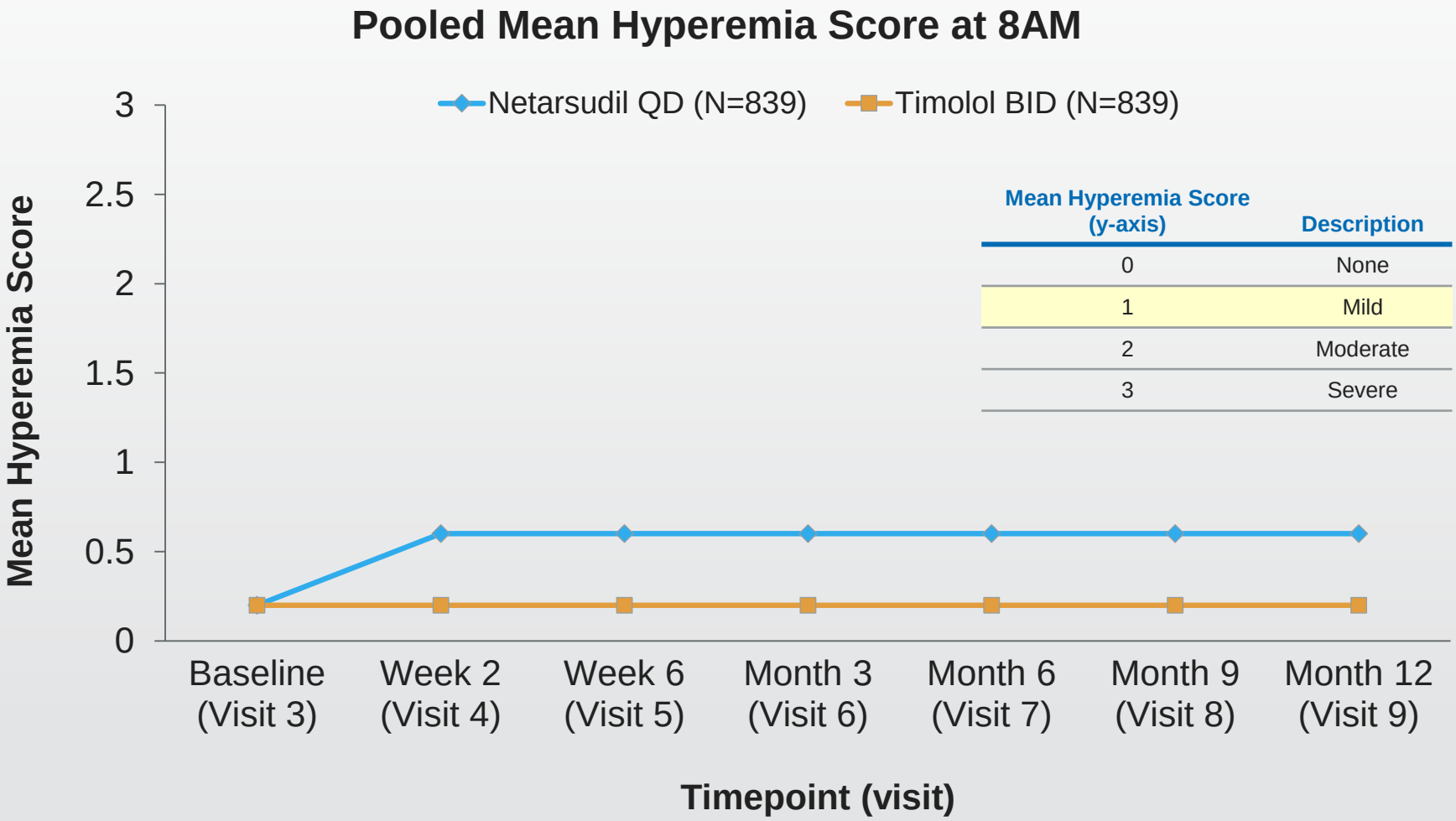
Ocular AEs Leading to Discontinuations

Pooled Phase 3 Studies

Most Common Ocular Adverse Events Associated with Discontinuation of Subjects Overall	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Any TEAEs Resulting in TA Discontinuation	185 (22.1)	34 (4.1)
Eye Disorders	145 (17.3)	6 (0.7)
Conjunctival Hyperemia	50 (6.0)	0
Cornea Verticillata	31 (3.7)	0
Conjunctival Hemorrhage	8 (1.0)	0
Vision Blurred	13 (1.5)	2 (0.2)
Lacrimation Increased	13 (1.5)	0
Erythema of Eyelid	11 (1.3)	0
Visual Acuity Reduced	10 (1.2)	0
Eyelid Edema	16 (1.9)	1 (0.1)

Discontinuations < 1.5% due to other ocular AEs including eye irritation, conjunctivitis allergic, eye pruritus, conjunctival edema and eye pain

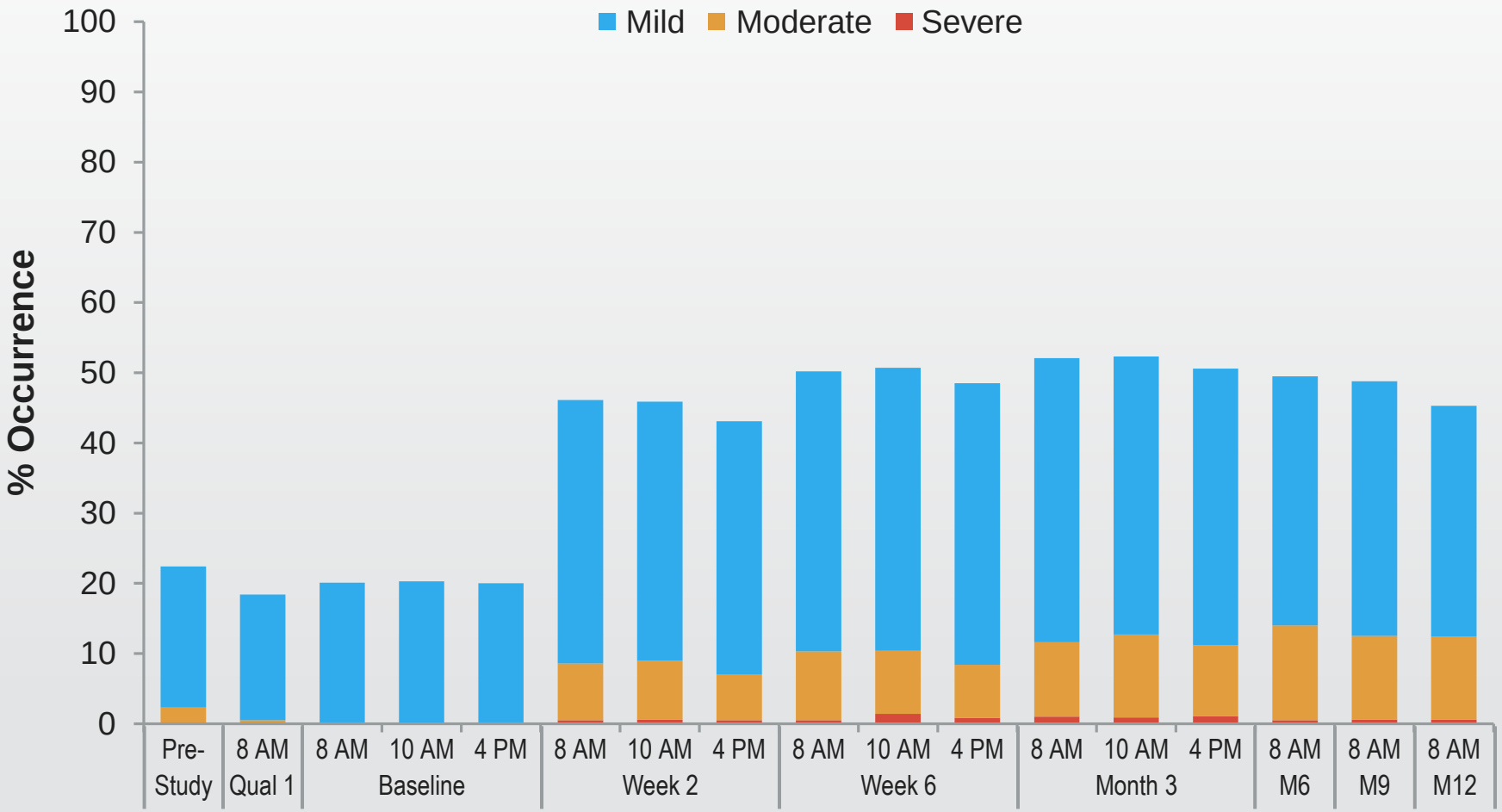
Conjunctival Hyperemia Was Sporadic and Severity Did Not Increase with Continued Dosing



Mean Hyperemia Score (y-axis)	Description
0	None
1	Mild
2	Moderate
3	Severe

Netarsudil Once-Daily Dosing Biomicroscopy Hyperemia Severity Did Not Increase Over Time

Netarsudil QD (N=839)



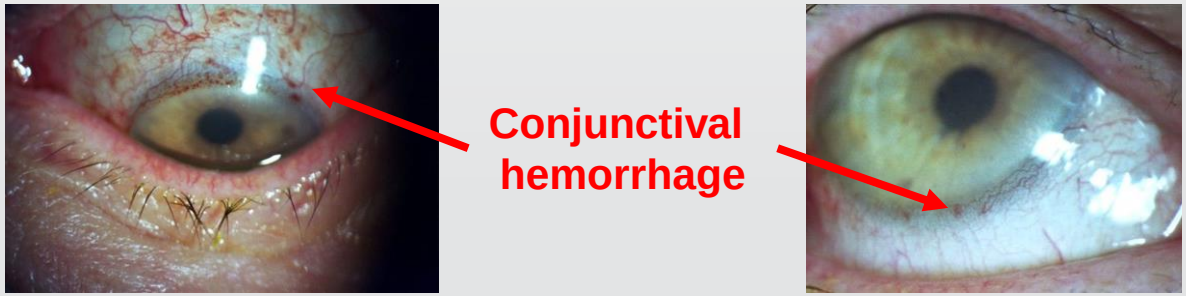
Awareness of Conjunctival Hyperemia by Study Subjects Was Low

	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Treatment-emergent Conjunctival Hyperemia	456 (54.4%)	87 (10.4%)
Subject-Reported Conjunctival Hyperemia	83 (9.9%)	17 (2.0%)
Investigator-Reported Conjunctival Hyperemia	388 (46.2%)	60 (7.2%)

Conjunctival Hemorrhage Was Sporadic and Severity Did Not Increase with Continued Dosing

Adverse Events	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
TEAE Conjunctival Hemorrhage	144 (17.2)	15 (1.8)
AE Resulting in Discontinuation	8 (1.0)	0

- Majority 92.4% (133/144) of the conjunctival hemorrhage in netarsudil QD group was mild, 6.3% (9/144) was moderate and 1.4% (2/144) was severe
- Self-resolving with continued dosing

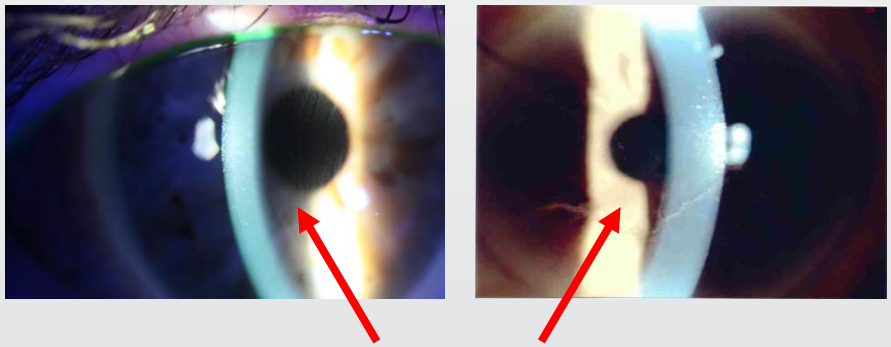


Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS301, -CS302

Cornea Verticillata Observed in Phase 3 Studies

- Cornea verticillata refers to a whorl-like pattern of deposits typically localized to the basal corneal epithelium
- Subjects are asymptomatic
- The onset was ~6 to 13 weeks (netarsudil QD)

AR-13324-CS302
netarsudil QD subject



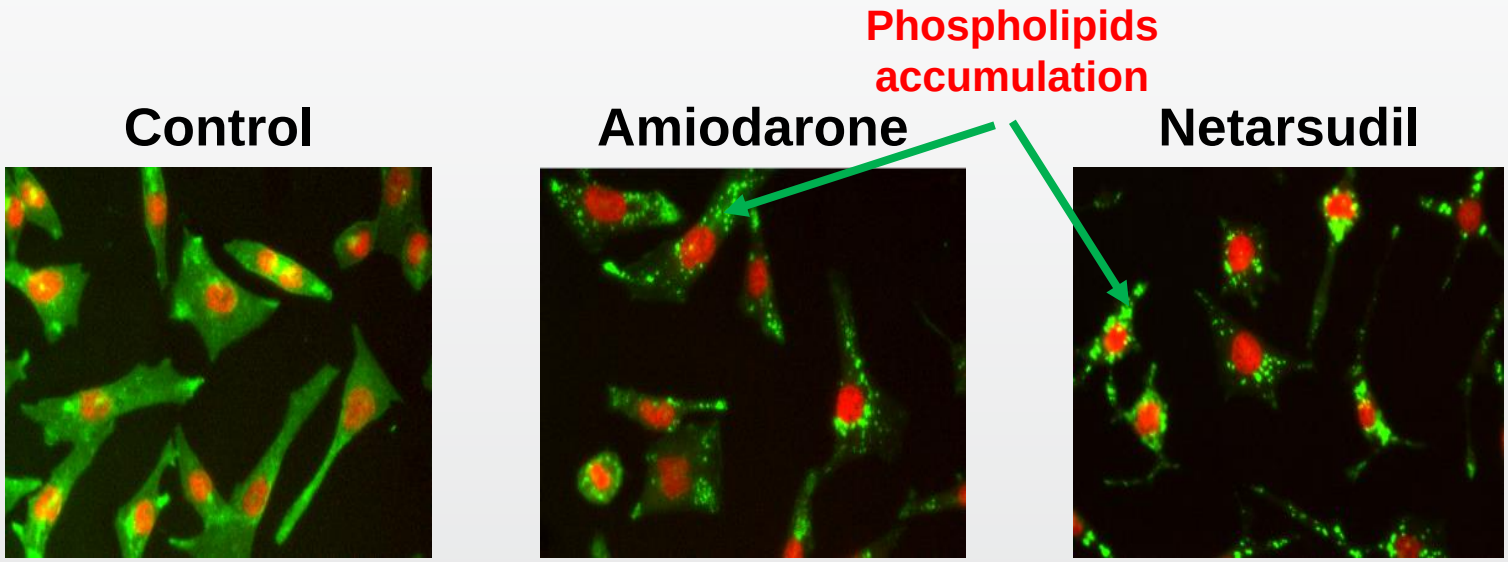
AR-13324-CS302
netarsudil BID subject

Cornea verticillata

Images were taken from netarsudil subjects
Source: Courtesy of study investigators AR-13324-CS302

Cornea Verticillata Due to Phospholipidosis

- Medications known to cause verticillata: amiodarone, chloroquine, naproxen, phenothiazine, ocular gentamicin and tobramycin*



- Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes
- Literature review suggested it is an adaptive response by the body rather than an adverse pathology*

Data on File Based on AR-13324-IPH07

* Raizman MB et al. Surv. Ophthalmol. 2017;62:286-301

Cornea Verticillata Followed Up in an Observational Study Did Not Impact Visual Function

- Long-term Observational Study (AR-13324-OBS01) conducted to follow up cornea verticillata subjects following completion of Phase 3 study (without study drug dosing)
- 47 subjects were enrolled in the study
- Did not affect visual function (visual acuity, contrast sensitivity and visual function -14 questionnaire)
- All subjects have resolved/improved to stabilization

Summary of the Most Common Netarsudil Ocular TEAEs

Conjunctival Hyperemia	Cornea Verticillata	Conjunctival Hemorrhage
• 54.4% TEAE • Severity did not increased with continued dosing • Sporadic	• 20.9% TEAE • Asymptomatic • Did not impact visual function	• 17.2% TEAE • Mild in severity and transient • Self-resolving with continued dosing

Corneal Endothelial Cell Evaluation Did Not Demonstrate Clinically Relevant Changes

- Specular microscopy conducted at Baseline and at Month 3 (AR-13324-CS302)
- No cell loss in netarsudil-treated subjects (confirmed by central reading center)
- Changes from baseline were small and not clinically relevant between treatment groups

Parameter	Netarsudil 0.02% QD (N=137)	Timolol 0.5% BID (N=157)
Endothelial cell density (cells/mm^2)		
Baseline	2480	2455
Day 90	2489	2451
Co-efficient of variation (%)	-1.6	-1.4
Hexagonality (%)	-0.5	+0.7

Vision Blurred Events Reported by Subjects Were Sporadic

	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Subjects with treatment-emergent vision blurred	62 (7.4)	12 (1.4)
Vision blurred reported by number of consecutive visits		
1	35 (56.4)	6 (50.0)
2	17 (27.4)	1 (8.3)
3	4 (6.5)	3 (25.0)
4	4 (6.5)	2 (16.7)
5	1 (1.6)	0
6	1 (1.6)	0
7	0	0

Vision Blurred Did Not Demonstrate Direct Association with Ocular Surface Adverse Events

Preferred Term (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Subjects with Treatment-emergent Vision Blurred	62 (7.4)	12 (1.4)
Concurrent with ocular surface AE terms		
Vision Blurred + Foreign Body Sensation	0	0
Vision Blurred + Superficial Punctate Keratitis	5 (0.6)	0
Vision Blurred + Eye Pruritus	2 (0.2)	1 (0.1)
Vision Blurred + Eye Irritation	6 (0.7)	0
Vision Blurred + Meibomian Gland Dysfunction	1 (0.1)	1 (0.1)
Vision Blurred + Eye Pain	0	1 (0.1)
Vision Blurred + Eyelid Edema	3 (0.4)	1 (0.1)
Vision Blurred + Photophobia	1 (0.1)	0
Vision Blurred + Eye Discharge	1 (0.1)	1 (0.1)
Vision Blurred + Lacrimation Increased	7 (0.8)	0

Visual Acuity Reduced Events Were Intermittent

	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Subjects with Treatment-emergent Visual Acuity Reduced	44 (5.2)	13 (1.5)
By Number of Consecutive Visits		
1	30 (68.2)	8 (61.5)
2	8 (18.2)	2 (15.4)
3	4 (9.1)	3 (23.1)
4	1 (2.3)	0
5	1 (2.3)	0
6	0	0
7	0	0

Visual Acuity Reduced Did Not Demonstrate Direct Association with Ocular Surface Adverse Events

Preferred Term (Pooled Safety Population)	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Subjects with Treatment-emergent Visual Acuity Reduced	44 (5.2)	13 (1.5)
Concurrent with ocular surface AE terms		
Visual Acuity Reduced + Foreign Body Sensation	0	0
Visual Acuity Reduced + Superficial Punctate Keratitis	5 (0.6)	0
Visual Acuity Reduced + Eye Pruritus	3 (0.4)	0
Visual Acuity Reduced + Eye Irritation	1 (0.1)	0
Visual Acuity Reduced + Meibomian Gland Dysfunction	0	0
Visual Acuity Reduced + Eye Pain	1 (0.1)	0
Visual Acuity Reduced + Eyelid Edema	0	0
Visual Acuity Reduced + Photophobia	1 (0.1)	0
Visual Acuity Reduced + Eye Discharge	2 (0.2)	0
Visual Acuity Reduced + Lacrimation Increased	5 (0.6)	0

No Clinically Relevant Differences in Visual Field and Cup to Disc Ratio Assessments Between Treatment Groups

Assessment	Parameter	Netarsudil 0.02% QD (N=839)	Timolol 0.5% BID (N=839)
Visual Field (dB)	Change in mean deviation from screening		
	• Month 3	-0.035	-0.243
	• Month 12	-0.591	-0.281
	Adverse Events		
	• Visual field defect	8 (1.0%)	3 (0.4%)
Cup-to-Disc Ratio	Adverse Events		
	• Optic nerve cupping	0	2 (0.2%)

No Clinically Relevant Differences in Ophthalmoscopy Safety Assessments Between Treatment Groups

Assessment	Parameter	Netarsudil 0.02% QD (N=839)	Timolol 0.5% BID (N=839)
Ophthalmoscopy (Retina, macula, choroid, optic nerve, and vitreous humor) Adverse Events	• Vitreous detachment	7 (0.8%)	4 (0.5%)
	• Vitreous floaters	2 (0.2%)	5 (0.6%)
	• Optic disc hemorrhage	0	1 (0.1%)
	• Macular edema	1 (0.1%)	1 (0.1%)
	• Retinal aneurysm	1 (0.1%)	1 (0.1%)
	• Retinal exudates	1 (0.1%)	0

Netarsudil Generally Well Tolerated in Ocular Comfort Test

- Ocular comfort was assessed at each 8AM visit by querying subjects: "Did you experience any discomfort when placing the drops in your eyes?"
- Subjects' responses were recorded using a standardized scale (none, mild, moderate, severe)

		Netarsudil QD (N=839)	Timolol BID (N=839)
Ocular Comfort Test[1]	No Ocular Discomfort	86.3%	85.2%
	Mild Discomfort	12.4%	12.6%
	Moderate Discomfort	1.2%	2.2%
	Severe Discomfort	0	0
Adverse Events (reflective of ocular tolerability with drop instillation)[2]	Instillation Site Pain	167 (19.9%)	181 (21.6%)
	Instillation Site Discomfort	29 (3.5%)	22 (2.6%)

1. Percentages calculated based on number of respondents at each visit.
2. Percentages calculated based on number of subjects in the safety population.

Netarsudil 0.02% Once Daily Safety Summary

~ 1,000 patients from Phase 1 to 3 by ~200 ophthalmologists and optometrists

Minimal drug-related systemic events

Most common ocular side effects were conjunctival hyperemia (54.4%), cornea verticillata (20.9%) and conjunctival hemorrhage (17.2%)

- **Generally mild, sporadic and severity did not increase with continued dosing**
- **Subjects with cornea verticillata are asymptomatic with generally no impact on visual function**

Clinical Perspective: Netarsudil Benefits and Risks for the Glaucoma Patient

Janet B. Serle, MD

Professor of Ophthalmology
Glaucoma Fellowship Director

Icahn School of Medicine at Mount Sinai

Glaucoma: Patient Questions and Discussion

1. Will I go blind from glaucoma?
2. When will there be new treatments for my glaucoma?

- My response to Question 1
  - Chronic disease; inadequately treated leads to blindness
  - Work together to slow down your loss of vision and to prevent blindness
  - Emphasize compliance with medications and visits
- Discuss treatment options
  - Each drug class has different dosing, side effects, efficacy
- Assess tolerability and efficacy at every visit
  - There is a wide range of individual responses to treatment[1]
- Must individualize care for each patient

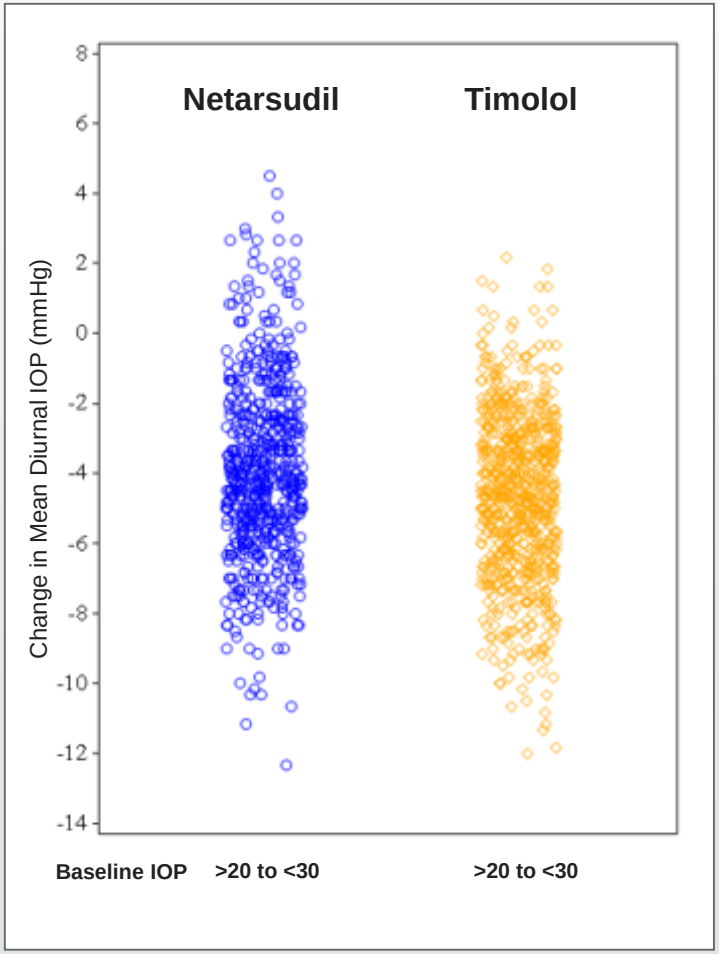
1. Moroi SE et al. Expert Rev Ophthalmol. 2009;4:145-61

Netarsudil Benefits: Efficacy

- Statistically and clinically significant IOP lowering at all tested baseline levels – up to 36 mmHg[1]
- Non-inferior to timolol BID at baseline IOPs <25 mmHg (3 studies), <30 mmHg (1 study)
  - Only non-PGA drug to meet non-inferiority criteria vs. timolol
  - Similar efficacy without the systemic side effects of timolol
- Stable IOP reductions over 12 months of dosing
- Wide range of IOP responses, including reductions up to 12 mmHg

Baseline IOPs <30 mmHg

Day 90: Change from Baseline IOP

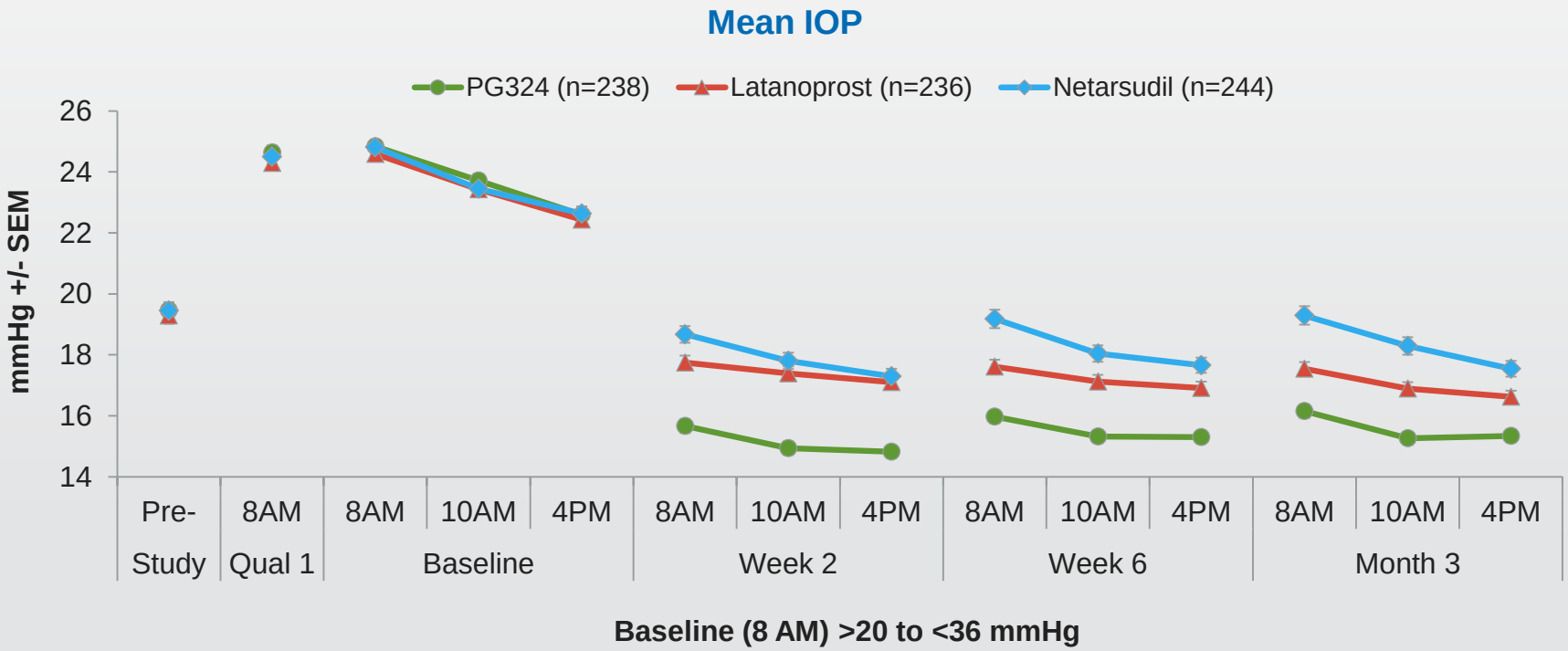


Pooled Analysis CS301/CS302/CS304

1. Clinical studies PG324-CS201, PG324-CS301

Netarsudil Benefits: New Drug Class

- Primary mechanism of IOP reduction is enhanced trabecular outflow
- Anticipate additive to drug classes that lower IOP primarily by reducing aqueous formation
- Demonstrated additive efficacy when added to prostaglandins[1]



1. Clinical studies PG324-CS201, PG324-CS301.

Netarsudil Benefits: Dosing

- Netarsudil dosed once daily (PM)
  - Addresses patient compliance[1]
    - Ease of dosing regimen helpful
      - For patients (elderly– forgetful, complex dosing regimens challenging)
      - For caregivers (only available for limited hours)
  - QD PM dosing regimen is same as the most widely used drug class, the prostaglandins
    - Same dosing schedule if netarsudil added as adjunct
- Beta-blockers may be prescribed once daily or BID, but dosed in the AM if used once daily (since do not lower IOP at night)
  - Netarsudil QD PM demonstrated non-inferiority to timolol BID

1. Tsai JC. Ophthalmology 2009;116:S30-6

Dosing of Currently Approved IOP Lowering Medications

Drug	Daily dosing
1. Prostaglandins	Once daily (pm)
2. Beta adrenergic antagonists	Once (AM) or twice daily
3. Selective alpha$_2$ adrenergic agonists	Three times daily
4. Topical carbonic anhydrase inhibitors	Three times daily
5. Nonselective α and β adrenergic agonists*	Twice daily
6. Miotics *	Three or four times daily

* Infrequently used

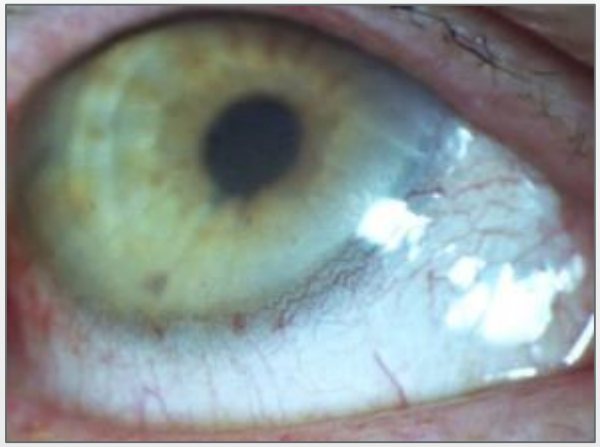
Preferred Practice Pattern, POAG Suspect, AAO, 2016

Netarsudil: Side Effects

- Tolerable safety profile
  - Minimal treatment-related systemic side effects
  - Ocular side effects mostly mild, sporadic and reversible
- Three most common ocular side effects with netarsudil in the clinical studies were:
  - Hyperemia
  - Conjunctival hemorrhage
  - Cornea verticillata

Netarsudil Side Effects: Conjunctival Hemorrhage

- Conjunctival hemorrhage (17.2%)
  - Small
  - Transient
  - Visualized by examiner with slit lamp magnification
- Do not appear to be associated with or cause ocular pathology



Netarsudil Side Effects: Cornea Verticillata

- Cornea verticillata observed (20.9%)
  - Resolved in 95.6% of patients after treatment ended (OBS01); 2 patients still being followed
  - Not associated with changes in visual function
- Cornea verticillata well-studied in patients on amiodarone therapy[1,2]
  - Approved 1984 USA, observed for decades
  - Present in >98% of patients taking standard oral dosages of amiodarone
  - Rarely interferes with vision
  - Typically reversible within 3-20 months of cessation of treatment

1. Mantyjarvi M et al. Surv Ophthalmol. 1998;42(4):360-6
2. Raizman M et al. Surv Ophthalmol. 2017;62:286-301

How I Currently Discuss Side Effects with My Patients

- Prostaglandin analogues
  - Hyperemia
  - Lash growth
  - Skin discoloration
  - Iris color change

Unilateral prostaglandin treatment

- Beta blockers
  - Associated systemic side effects
    - Exercise intolerance, impotence, depression, bronchospasm contraindicated in patients with pulmonary disease; asthma, COPD
    - Less efficacious in patients already on systemic beta-blocker
  - Possible effect on nighttime vasculature, no nocturnal IOP effect[1-6]
- Alpha agonists - Dry mouth, headache, fatigue
- Carbonic anhydrase inhibitors - Bitter taste, stinging, blurred vision

1. Liu JH et al. Am J Ophthalmol. 2004;138:389-395. 2. Gulati V et al. Arch Ophthalmol. 2012;130:677-684.
3. Liu JH et al. Ophthalmology. 2009;116:449-454. 4. Liu JH et al. Ophthalmology. 2010;117:2075-9.
5. Fan S et al. J Glaucoma. 2014;23:276-81. 6. Liu JH et al. Am J Ophthalmol. 2016;169:249-257.

Benefits and Risks: How I Will Discuss Netarsudil with My Patients

- Netarsudil is an effective medication to lower IOP
- Instilled once a day in the evening
- It has minimal systemic side effects
- Hyperemia may occur and is typically tolerated
- Cornea verticillata may occur, visible to the doctor on high magnification exam but does not affect vision or the health of the eye
- Small transient hemorrhage may occur, visible to the doctor on high magnification exam but does not affect vision or the health of the eye
- Side effects are mostly tolerable, transient, and reversible

How Will I and Other Ophthalmologists Use Netarsudil to Treat Glaucoma?

- **As a monotherapy in patients who:**
  - Have concerns about the ocular side effects of PGs
  - Are intolerant to or have inadequate efficacy with PGs
  - Need or prefer alternative to beta blockers, alpha agonists, CAIs
- **As an adjunct agent:**
  - Add to a prostaglandin
  - Add to or alternative to other adjunctive agents
- **To improve patient compliance -** fewest number of daily doses is beneficial
- **After glaucoma surgery** when desired IOP is not achieved
- **As another medical option to help delay or defer glaucoma surgery**

Netarsudil: Summary

- Netarsudil is an exciting new investigational drug for lowering IOP
- The benefits of netarsudil outweigh the risks for clinical use
  - Effective clinically and statistically
  - Tolerable side effects
  - Convenient dosing
- Netarsudil is an effective, convenient, safe, and important new glaucoma medication that will help physicians meet the needs of their patients

Closing

Marvin Garrett

Vice President, Regulatory Affairs and Quality Assurance

Aerie Pharmaceuticals, Inc.

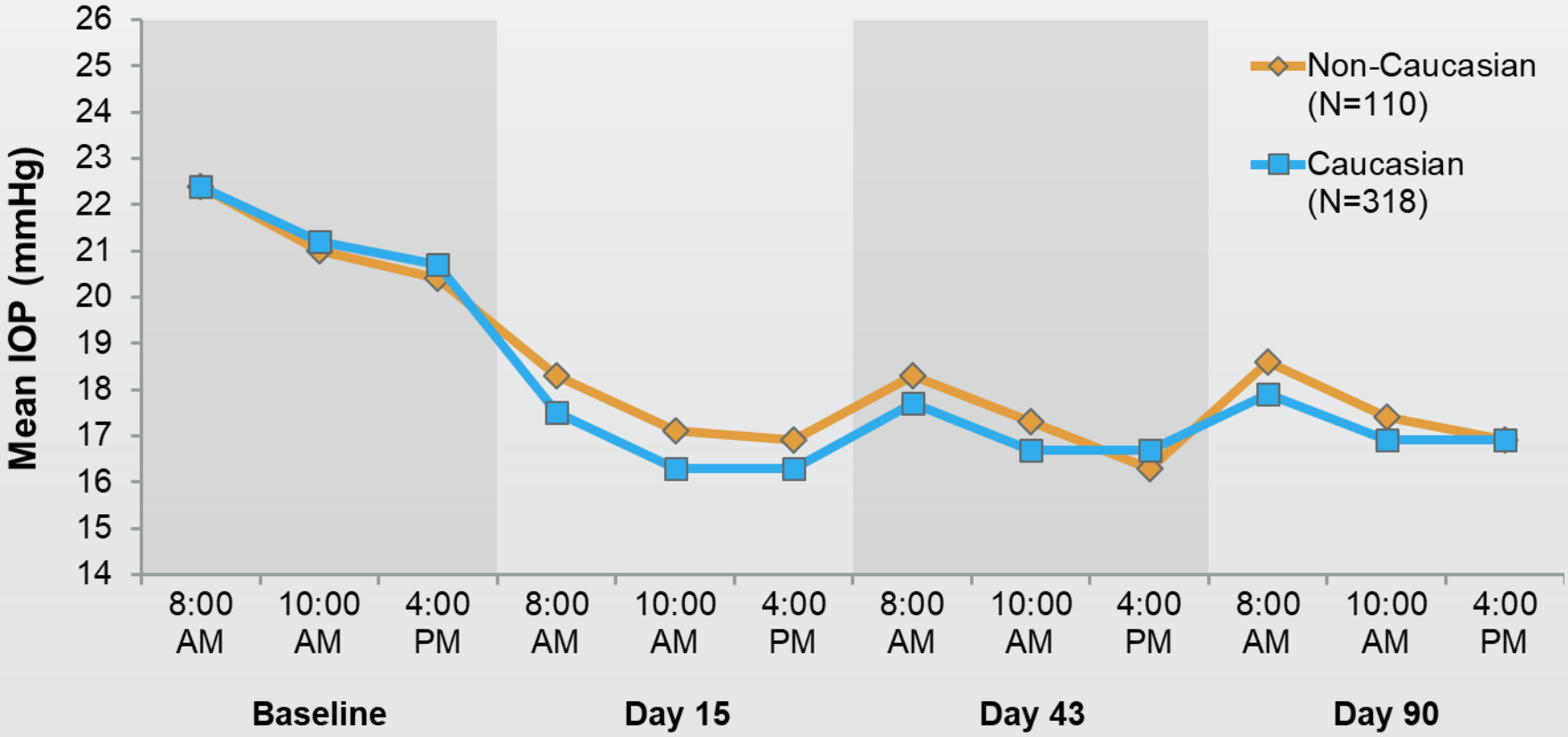
Netarsudil: A New Drug Class for Lowering IOP

We are requesting a recommendation for approval of netarsudil ophthalmic solution 0.02% for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension given one drop QD

Supportive Slides

Similar Efficacy of Netarsudil 0.02% QD in Caucasian vs Non-Caucasian Subjects

Pooled Analysis



PP Population with BL IOP <25 mmHg, ODO
Source: ISE Table 14.2.1.1.10.1 and 14.2.1.1.10.2

Pediatric Subject Profile

Subject	Treatment	Ocular AEs	Relevant Medical History	Relevant Con Meds
14-year old, Black (Hispanic/Latino) male	Netarsudil 0.02% QD	None	Seasonal allergies	Travatan (glaucoma), Loratadine (allergeries)
11-year old, White (Hispanic/Latino) female	Timolol 0.5% BID	None	Seasonal allergies, Attention Deficit Disorder (ADD)	Loratadine (allergies), Concerta (ADD)

Source: CS302 Listing 16.2.4.1, 16.4.1.1, 16.4.1.3.1

Conjunctival Hyperemia – AEs in Approved PGAs

	Bimatoprost	Latanoprost	Travoprost
Treatment Related Conjunctival Hyperemia	15%-45%	5-15%	35%-50%
Discontinuation Due to Conjunctival Hyperemia	3%	<1%	3%

Source: Ophthalmic Drug Facts 21 Edition

Overall Discontinuation Rates During Clinical Registration Studies for First-In-Class Glaucoma Drugs

- Xalatan*:
  - 6-Month Phase 3 Trial Discontinuations:
    - *25% for Xalatan 0.005% QD*
    - *21% for timolol 0.5% BID comparator*
- Alphagan#:
  - 12-Month Phase 3 Trial Discontinuations:
    - 46% for Alphagan 0.2%
    - 25% for timolol 0.5% BID comparator

* SBA for original Xalatan NDA 020597 (6-month Phase 3 US study 9400369)
# SBA for original Alphagan NDA 020163 (12-month Phase 3 study A342-103-7831)

Cornea Verticillata, Cornea Deposits, or Cornea Opacity Study Day of Discontinuation QD

Study Day Discontinuation	Netarsudil 0.02% QD (N=34) n (%)	Timolol 0.5% BID (N=0) n (%)
1-12	0	0
13-24	0	0
25-36	1 (2.9)	0
37-48	1 (2.9)	0
49-60	1 (2.9)	0
61-72	4 (11.8)	0
73-84	0	0
85-96	4 (11.8)	0
97-108	1 (2.9)	0
109-120	2 (5.9)	0
121-132	1 (2.9)	0
133-144	2 (5.9)	0
145-156	2 (5.9)	0
157-187	6 (17.6)	0
188-277	9 (26.5)	0
278-372	0	0

Source: ISS Table 14.3.99.3.2.2

TEAE Conjunctival Hyperemia Study Day of Discontinuation QD

Study Day Discontinuation	Netarsudil 0.02% QD (N=50) n (%)	Timolol 0.5% BID (N=0) n (%)
1-12	2 (4.0)	0
13-24	6 (12.0)	0
25-36	5 (10.0)	0
37-48	4 (8.0)	0
49-60	3 (6.0)	0
61-72	2 (4.0)	0
73-84	0	0
85-96	7 (14.0)	0
97-108	5 (10.0)	0
103-120	1 (2.0)	0
121-132	4 (8.0)	0
133-144	2 (4.0)	0
145-156	1 (2.0)	0
157-187	2 (4.0)	0
188-277	4 (8.0)	0
278-372	2 (4.0)	0

Source: ISS Table 14.3.99.3.1.2

TEAE Conjunctival Hemorrhage Study Day of Discontinuation QD

Study Day Discontinuation	Netarsudil 0.02% QD (N=8) n (%)	Timolol 0.5% BID (N=0) n (%)
1-12	0	0
13-24	0	0
25-36	2 (25.0)	0
37-48	1 (12.5)	0
49-60	0	0
61-72	0	0
73-84	0	0
85-96	3 (37.5)	0
97-108	0	0
109-120	0	0
121-132	0	0
133-144	0	0
145-156	1 (12.5)	0
157-187	0	0
188-277	1 (12.5)	0
278-372	0	0

Source: ISS Table 14.3.99.3.3.2

Cornea Verticillata AE Resolution Netarsudil QD Pooled

Study Eye

	Action Taken with Study Treatment		
Outcome of Adverse Event	**Drug Withdraw**	**No Drug Withdraw**	**Total**
Not Recovered/Not Resolved	68	0	68
Recovered/Resolved	90	2	93
Recovered/Resolved with Sequelae	2	0	2
Recovering/Resolving	21	0	21
Total	181	2	183

Fellow Eye

	Action Taken with Study Treatment		
Outcome of Adverse Event	**Drug Withdraw**	**No Drug Withdraw**	**Total**
Not Recovered/Not Resolved	68	0	68
Recovered/Resolved	91	3	94
Recovered/Resolved with Sequelae	2	0	2
Recovering/Resolving	19	0	19
Total	180	3	183

Source: Ad hoc table CornealVert Outcome

Conjunctival Hyperemia QD

	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Treatment-Emergent Conjunctival Hyperemia	456 (54.4)	87 (10.4)
Treatment Related Conjunctival Hyperemia	420 (50.1)	72 (8.6)
Discontinuation Due to Treatment Related Conjunctival Hyperemia	49 (5.8)	0

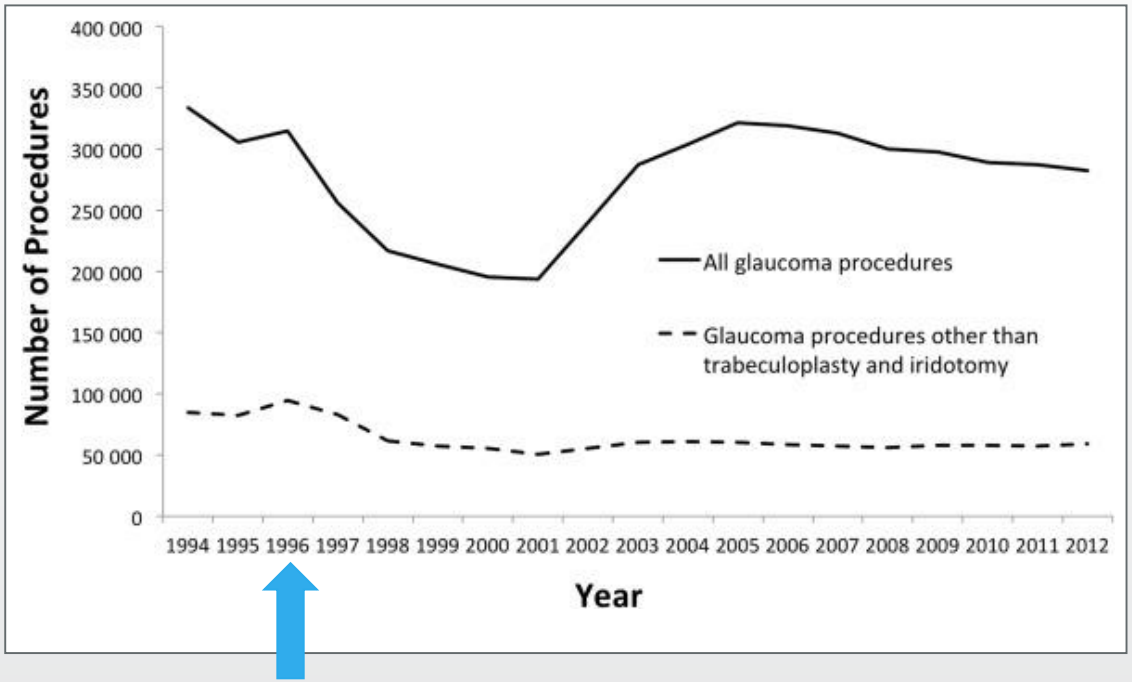
Source: ISS Table 14.3.3.1.1, Table 14.3.3.3.1, Table 14.3.3.4.9.1

Concurrent AEs with Hyperemia QD

	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Conjunctival Hyperemia and Cornea Verticillata/ Corneal Deposits/Opacity	99 (11.8)	0
Conjunctival Hyperemia and Conjunctival Hemorrhage	81 (9.7)	3 (0.4)
Conjunctival Hyperemia and Vision Blurred	40(4.8)	2 (0.2)
Conjunctival Hyperemia and Visual Acuity Reduced	16 (1.9)	3 (0.4)

Source: ISS Table 14.3.99.4

Total Number of Glaucoma Procedures Reimbursed by Medicare 1994-2012



Laser & Incisional Surgeries

Incisional Surgeries

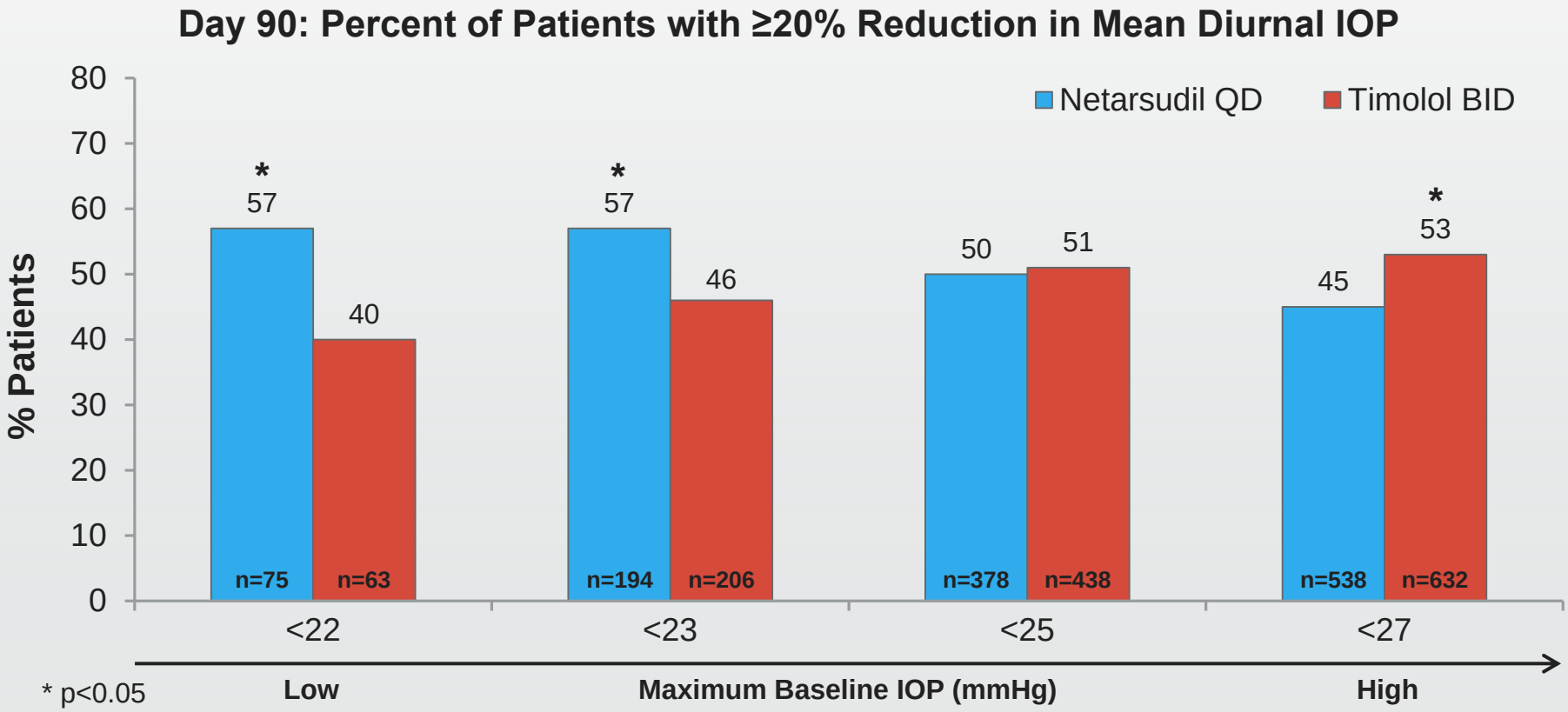
Latanoprost 1996
Brimonidine 1996
Dorzolamide 1995

1. Reduction in surgical and laser volume 1996-8; new medications
2. Incisional surgical volume constant since1998
3. Laser volume increasing since 2002, introduction of SLT laser

Karun S. Arora, Alan L. Robin, Kevin J. Corcoran, Suzanne L. Corcoran, Pradeep Y. Ramulu. Use of various glaucoma surgeries and procedures in medicare beneficiaries from 1994 to 2012. Use of Various Glaucoma Surgeries and Procedures in Medicare Beneficiaries from 1994-2012. Ophthalmology, Volume 122, Issue 8, 2015, 1615–1624

More Patients Achieve ≥20% IOP Reduction With Netarsudil vs Timolol at Lower Baseline IOPs

Pooled Analysis from 3 Phase 3 Efficacy Studies



AAO Practice Guidelines Suggest Initial Glaucoma Treatment Should Target 20%-30% Reduction in IOP[1]

1. Prum BE Jr. et al, Ophthalmol. 2015; 123 (1), P112-P151
New ISE Tables 14.2.4.1.1, 14.2.99.2.1, 14.2.99.2.4, 14.2.99.2.5

Anterior Chamber Cell QD

	Anterior Chamber Cells Grading	Netarsudil 0.02% QD (N=839) n (%)	Timolol 0.5% BID (N=839) n (%)
Screening	0	839 (100.0)	839 (100.0)
	+1	0	0
	≥+2	0	0
Day 15, 08:00 Hours	0	805 (99.9)	822 (100.0)
	+1	1 (0.1)	0
	≥+2	0	0
Day 43, 08:00 Hours	0	725 (100.0)	809 (100.0)
	+1	0	0
	≥+2	0	0
Month 3, 08:00 Hours (Month 3 Completers only)	0	679 (100.0)	783 (99.9)
	+1	0	1 (0.1)
	≥+2	0	0
Month 6, 08:00 Hours (Month 6 Completers only)	0	437 (100.0)	552 (100.0)
	+1	0	0
	≥+2	0	0
Month 9, 08:00 Hours	0	168 (100.0)	227 (100.0)
	+1	0	0
	≥+2	0	0
Month 12, 08:00 Hours (Month 12 Completers only)	0	161 (100.0)	223 (100.0)
	+1	0	0
	≥+2	0	0

Source: ISS Table 14.3.5.4.1.1