A double-masked, randomized, parallel study of Netarsudil Ophthalmic Solution, 0.02% QD compared to timolol maleate ophthalmic solution, 0.5% BID in patients with elevated intraocular pressure (ROCKET-4)

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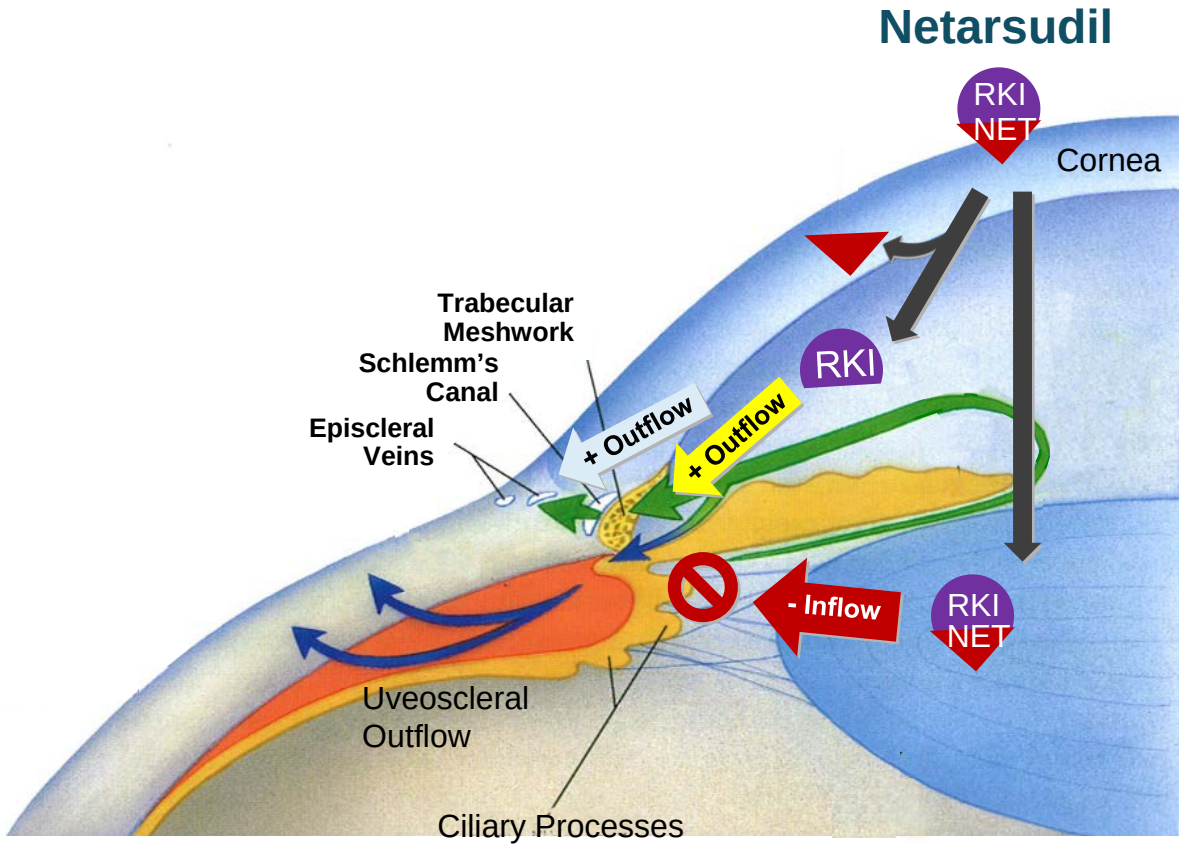
NETARSUDIL: An Investigational Drug Candidate for Glaucoma

IOP LOWERING MECHANISMS

ROCK inhibition relaxes TM[1], increases outflow[1,2]

ROCK inhibition lowers Episcleral Venous Pressure (EVP)[3]

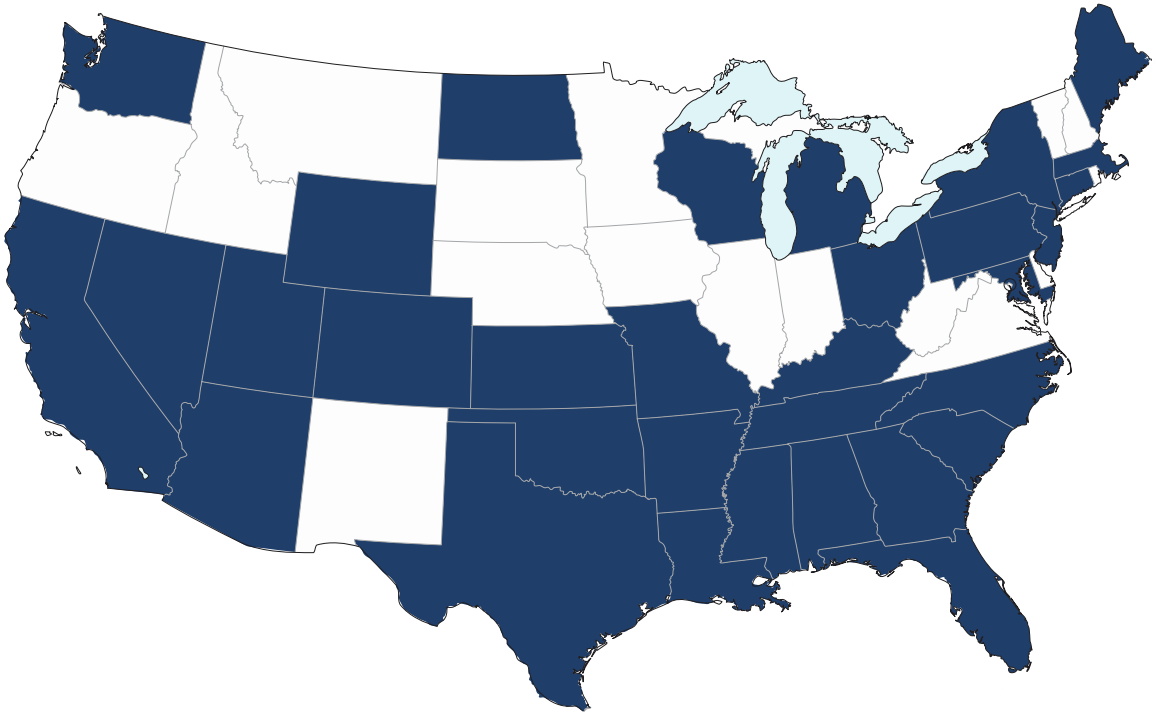
NET inhibition reduces fluid production[2]



1. Wang SK, Chang RT. *Clin Ophthal* 2014;8:883-890.
2. Wang RF, Williamson JE, Kopczynski C, Serle JB. *J Glaucoma* 2015. 24(1):51-54.
3. Kiel JW, Kopczynski C. *J Ocul Pharmacol Ther* 2015; 31:146–151.

Rocket-4 Phase 3: LOCATIONS

26 States; 58 Trial Sites



Rocket 4: TRIAL DESIGN

Patients with open angle glaucoma (OAG) or ocular hypertension (OHT)

with **IOP > 20 mmHg and < 30 mmHg at 8 AM**,

N = 708 subjects

Patients randomized 1:1

Netarsudil 0.02%
(AR-13324)
0.02%
QD (PM)

Timolol 0.5%
BID (AM and PM)

PRIMARY ENDPOINTS:

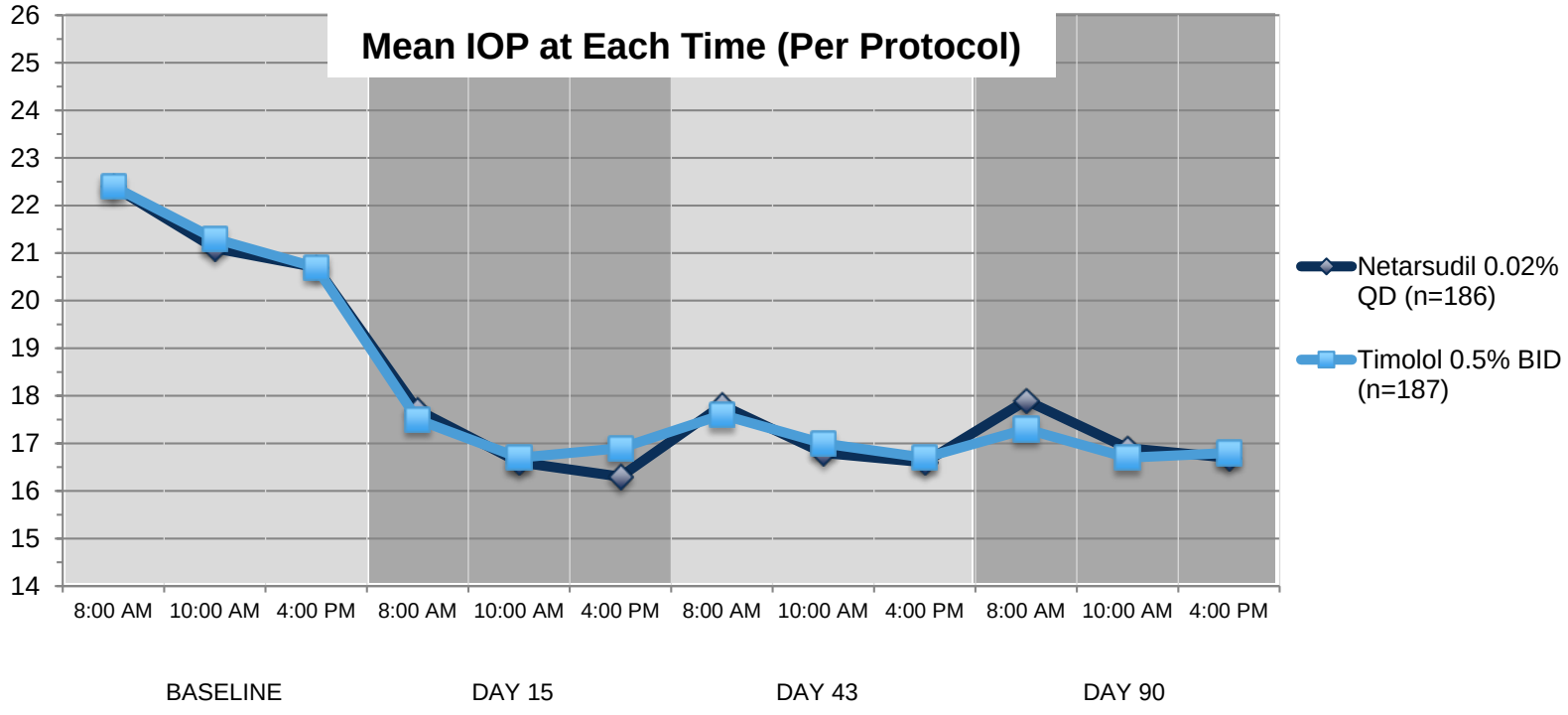
Efficacy
Mean IOP at nine time points (08:00, 10:00, and 16:00 at **Week 2, Week 6, and Month 3)** Interim analysis

Safety
Ocular and systemic safety during a 6-month treatment period

Rocket 4: BASELINE DEMOGRAPHICS

	Netarsudil QD n=351	Timolol BID n=357
Gender		
Male	143 (40.7%)	120 (33.6%)
Female	208 (59.3%)	237 (66.4%)
Race, n (%)		
White	259 (73.8%)	274 (76.8%)
Black/African American	84 (23.9%)	75 (21.0%)
Asian	7 (2.9%)	6 (1.7%)
Multiple	0 (0.0%)	1 (0.3%)
Other	1 (0.3%)	1 (0.3%)
Age (yrs)		
< 65	165 (47.0%)	164 (45.9%)
> 65	186 (53.0%)	193 (54.1%)
Iris Color, n (%)		
Brown/Black	241 (68.7%)	227 (63.6%)
Blue/Grey/Green	73 (20.8%)	90 (25.2%)
Hazel	36 (10.3%)	40 (11.2%)
Other	1 (0.3%)	0 (0.0%)

Rocket 4: Netarsudil Achieved Non-Inferiority in the Primary Efficacy Analysis (Baseline IOPs <25 mmHg)



Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0033 Data on File, Based on Rocket 4 Topline Interim 3-month

Rocket 4: PER PROTOCOL

	Mean IOP mmHg		Difference from Netarsudil 0.02% QD (95% CI)
	Netarsudil 0.02% QD N=186	Timolol 0.5% BID N=187	
BASELINE			
8:00 AM	22.4	22.4	
10:00 AM	21.1	21.3	
4:00 PM	20.7	20.7	
Mean Diurnal	**21.4**	**21.5**	
DAY 15			
8:00 AM	17.7	17.5	0.2 (-0.4, 0.8)
10:00 AM	16.6	16.7	-0.2 (-0.7, 0.4)
4:00 PM	16.3	16.9	-0.6 (-1.2, 0.0)
Mean Diurnal	**16.8**	**17.0**	**-0.2 (-0.7, 0.3)**
DAY 43			
8:00 AM	17.8	17.6	0.3 (-0.3, 0.8)
10:00 AM	16.8	17.0	-0.2 (-0.8, 0.4)
4:00 PM	16.6	16.7	-0.1 (-0.7, 0.5)
Mean Diurnal	**17.0**	**17.1**	**0.0 (-0.6, 0.5)**
DAY 90			
8:00 AM	17.9	17.3	0.6 (-0.0, 1.2)
10:00 AM	16.9	16.7	0.2 (-0.4, 0.8)
4:00 PM	16.7	16.8	-0.1 (-0.7, 0.6)
Mean Diurnal	**17.2**	**16.9**	**0.2 (-0.3, 0.8)**

SUMMARY

Primary Endpoint (PP Subjects with Baseline IOP < 25 mmHg)

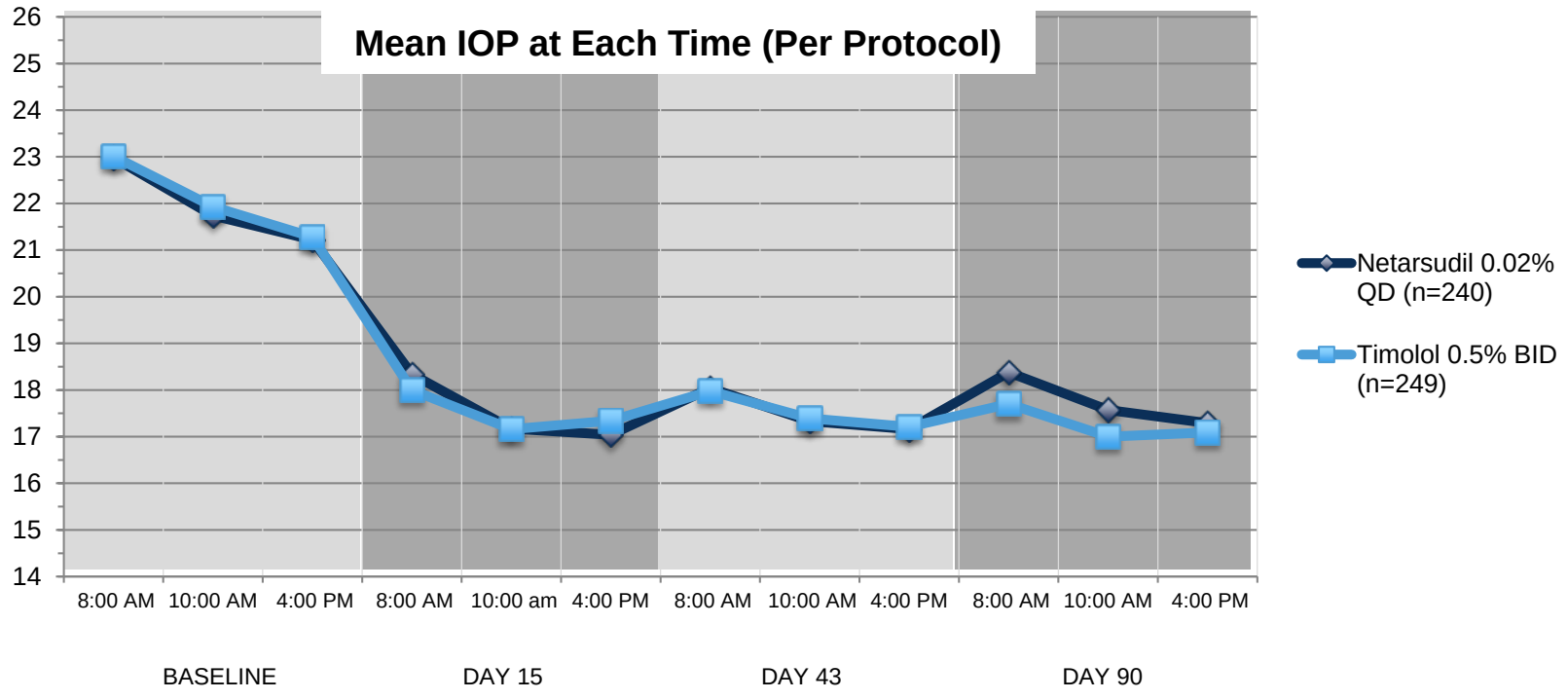
Upper 95% CI ≤ 1.5 mmHg at all time points, ≤ 1.0 mmHg at majority (8/9) time points

Met the criteria for demonstrating non-inferiority

- Rocket 1: ≤ 1.0 mmHg at majority (7/9) time points
- Rocket 2: ≤ 1.0 mmHg at majority (6/9) time points

Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0033 Data on File, Based on Rocket 4 Topline Interim 3-month

Rocket 4: Netarsudil Achieved Non-Inferiority in a Secondary Efficacy Analysis of Subjects with Baseline IOPs <27 mmHg



Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0033 Data on File, Based on Rocket 4 Topline Interim 3-month

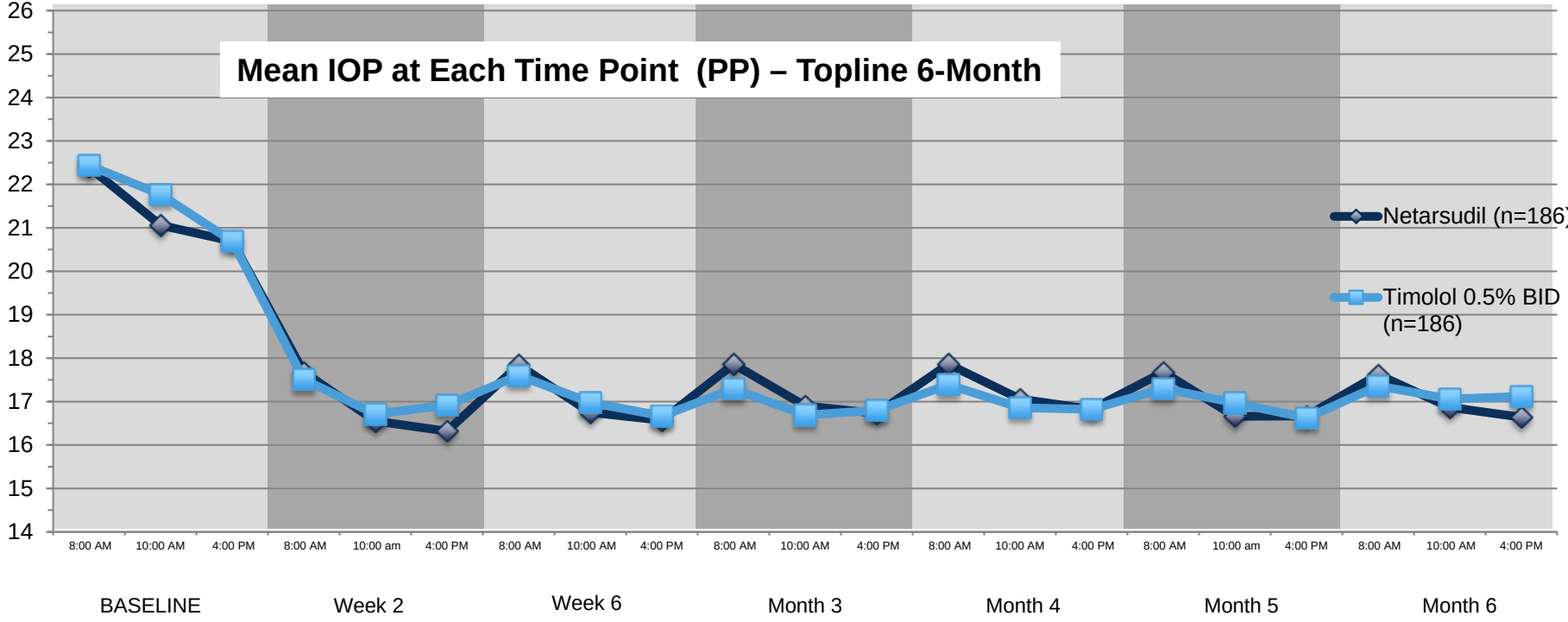
Rocket 4: Efficacy in Subgroups with Different Baseline IOPs

Baseline IOP (mmHg)	Non-inferiority
<30	Met
<29*	Met
<28	Met
<27	Met
<26	Met
<25 (primary)	Met
<24	Met
<22	Insufficient power

***Post-hoc analysis**

Netarsudil Achieved Non-Inferiority in the Primary Efficacy Analysis for Baseline IOP < 25 mmHg and Maintained Stable Efficacy

Netarsudil performance remained within the non-inferiority range



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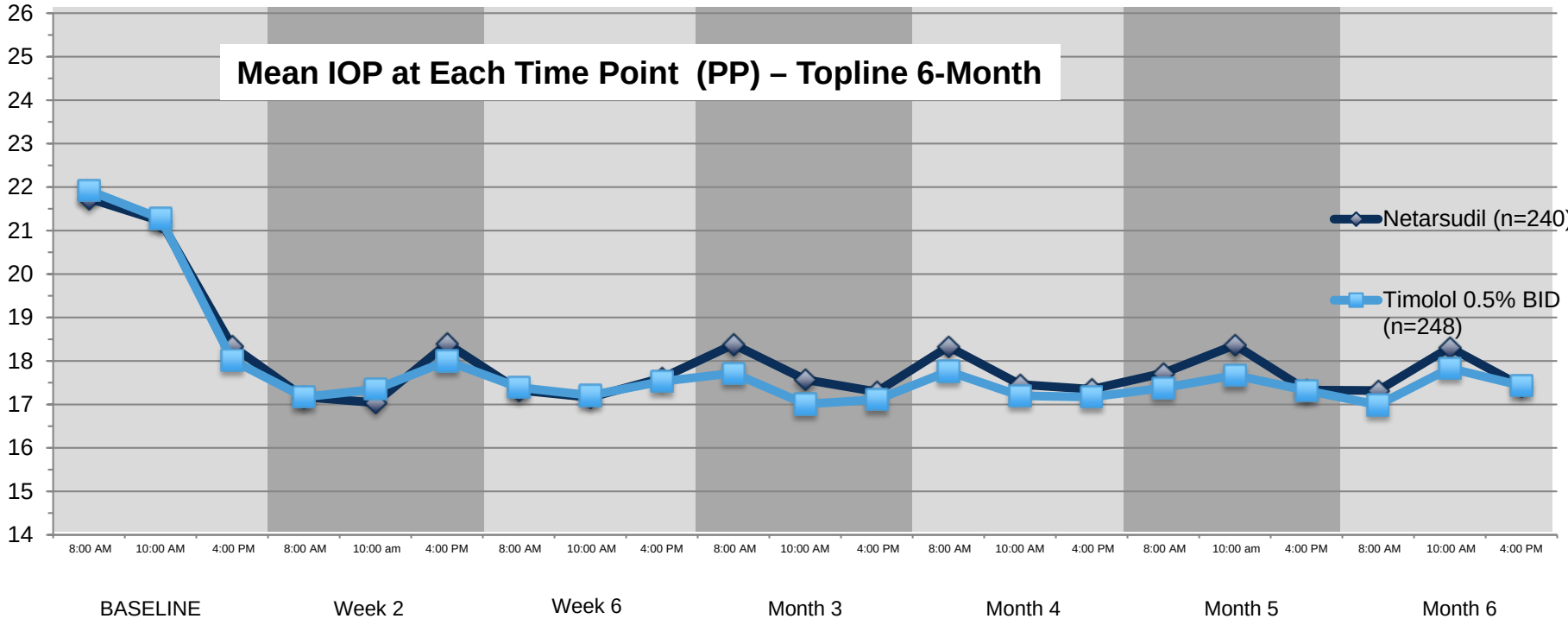
Data on File, Based on Rocket 4 Topline Interim 6-month

Netarsudil Achieved Non-Inferiority for Baseline IOP < 27 mmHg and Maintained Stable Efficacy

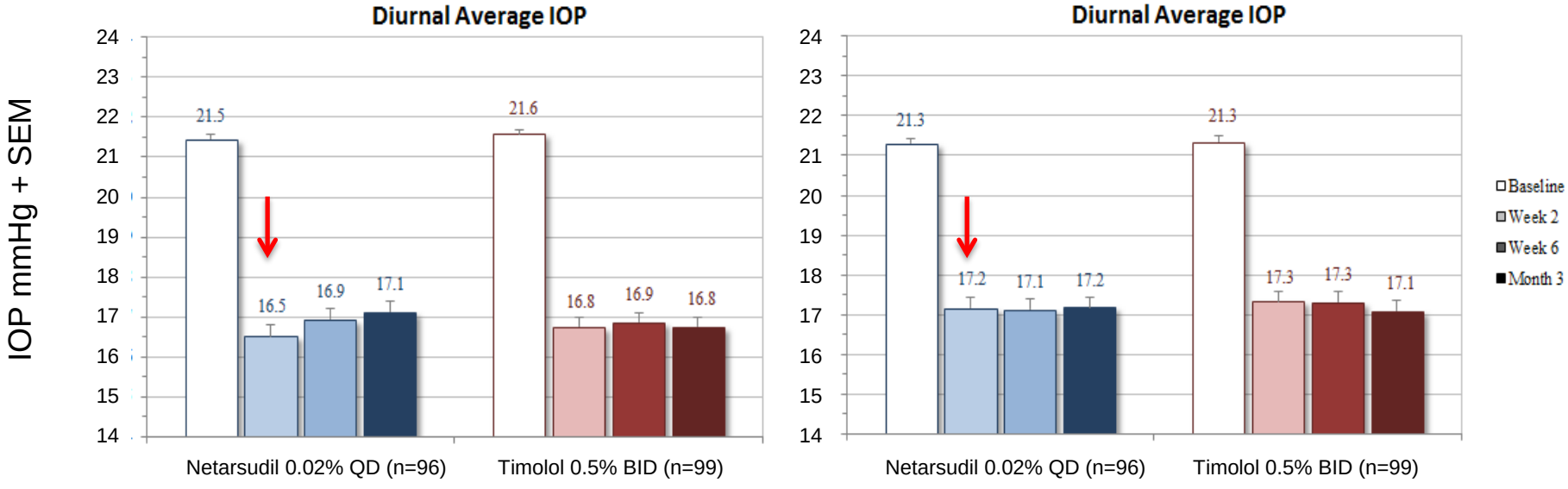
Netarsudil performance remained within the non-inferiority range



 Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0033

Data on File, Based on Rocket 4 Topline Interim 6-month

Rocket 4: Prior PGA Use Enhanced Netarsudil Efficacy



Netarsudil synergy with prior PGA use evident at Week 2

No synergy observed for timolol

Similar results reported for Rocket 1 trial

Data on File, Based on Rocket 4 Topline Interim 3-month

Netarsudil

3 Month SAFETY/TOLERABILITY OVERVIEW

There were no drug-related serious adverse events (SAEs)

There was no evidence of treatment-related systemic effects (e.g., clinical laboratory or haematology values, heart rate or blood pressure)

The most common adverse event was conjunctival hyperemia with ~40% incidence, and was scored as mild for ~85% of the patients

Other ocular AEs occurring in ~5-12% of subjects receiving netarsudil included: **conjunctival hemorrhage, cornea verticillata, lacrimation increased and vision blurred**

Data on File, Based on Rocket 4 Topline Interim 3-month

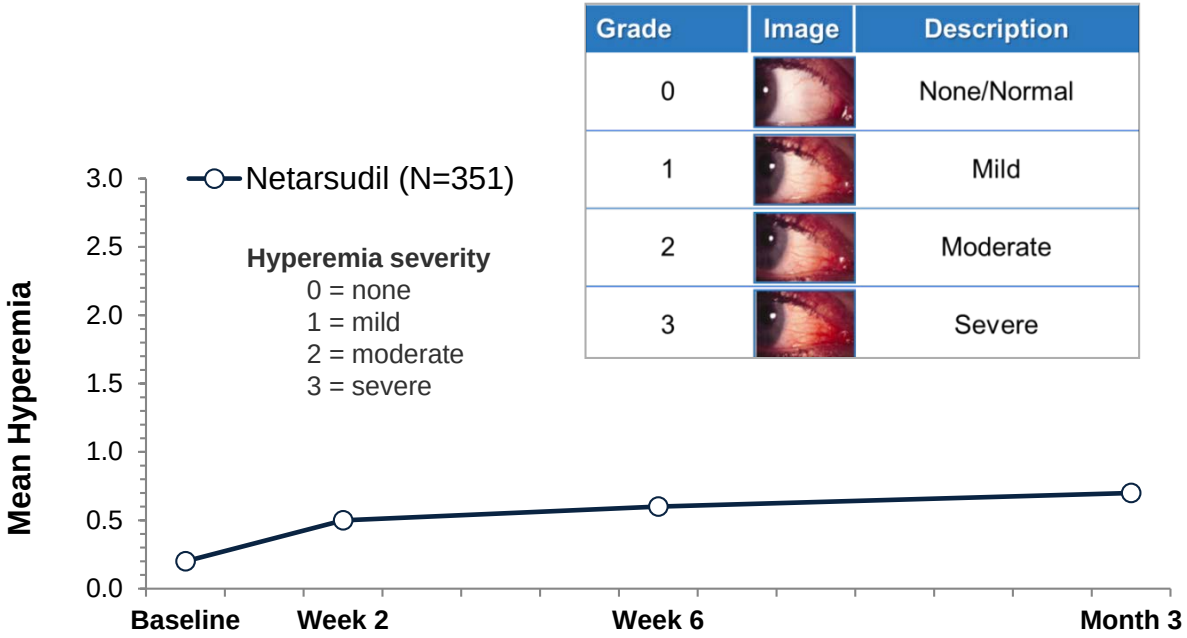
Rocket 4: INTERIM SAFETY RESULTS

Adverse Events (≥5% in any group)	Netarsudil QD n=351	Timolol BID n=357
Eye Disorders		
Conjunctival Hyperemia	148 (42.2%)	24 (6.7%)
Conjunctival Hemorrhage	41 (11.7%)	7 (2.0%)
Corna Verticillata	41 (11.7%)	0 (0.0%)
Lacrimation Increased	21 (6.0%)	4 (1.1%)
Vision Blurred	20 (5.7%)	2 (0.6%)
Administration Site Conditions		
Instillation site pain	82 (23.4%)	89 (24.9%)
Instillation Site Erythema	36 (10.3%)	3 (0.8%)

Patients with known contraindications or hypersensitivity to timolol were excluded

OCULAR TOLERABILITY: Conjunctival Hyperemia

No Change in Mean Hyperemia Score Over Time (Interim Month 3)



Grade	Image	Description
0		None/Normal
1		Mild
2		Moderate
3		Severe

Hyperemia severity did not increase with continued dosing

Hyperemia was sporadic

- Only ~16% of patients had hyperemia on each study visit day from week 2 to month 3 (similar to the rates seen for Rocket 1, Rocket 2 and Mercury 1)
- In Rocket 2, only ~10% of patients had hyperemia on each study visit day from week 2 to month 12

OCULAR TOLERABILITY: Cornea Verticillata

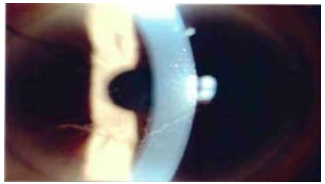
Corneal deposits (lipid micro-deposits in the corneal epithelial level)

Benign corneal lipid deposits are a familiar outcome with amiodarone* and other FDA-approved drugs

Due to phospholipidosis where the parent drug is complexed with phospholipids in the lysosomes

Physicochemical trait, not metabolic

Asymptomatic. Did not affect visual acuity



Rocket 2 Patient

Approximately 75% resolved by interim 12-month results from Rocket 2 (February 2016)

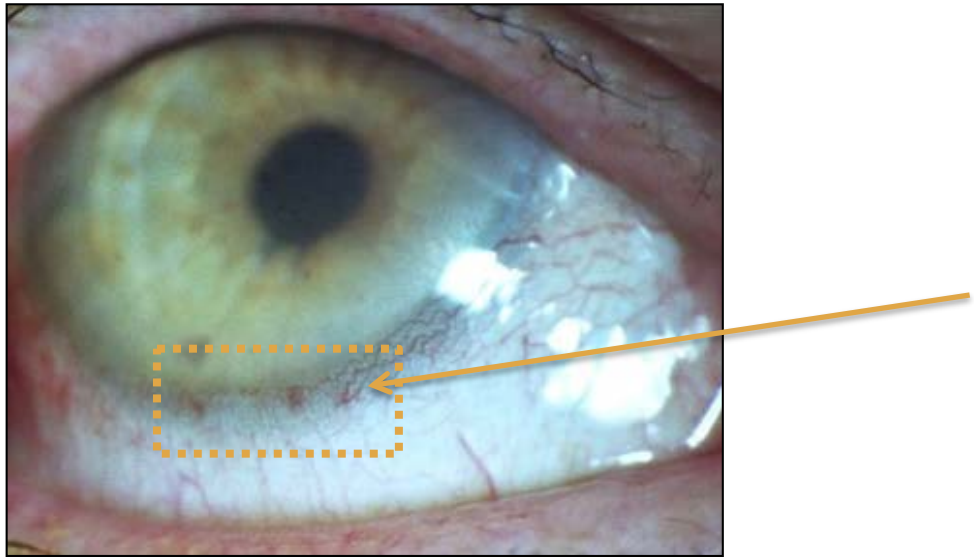
Follow-up continues in these patients

* From the amiodarone prescribing information

OCULAR TOLERABILITY: Conjunctival hemorrhage

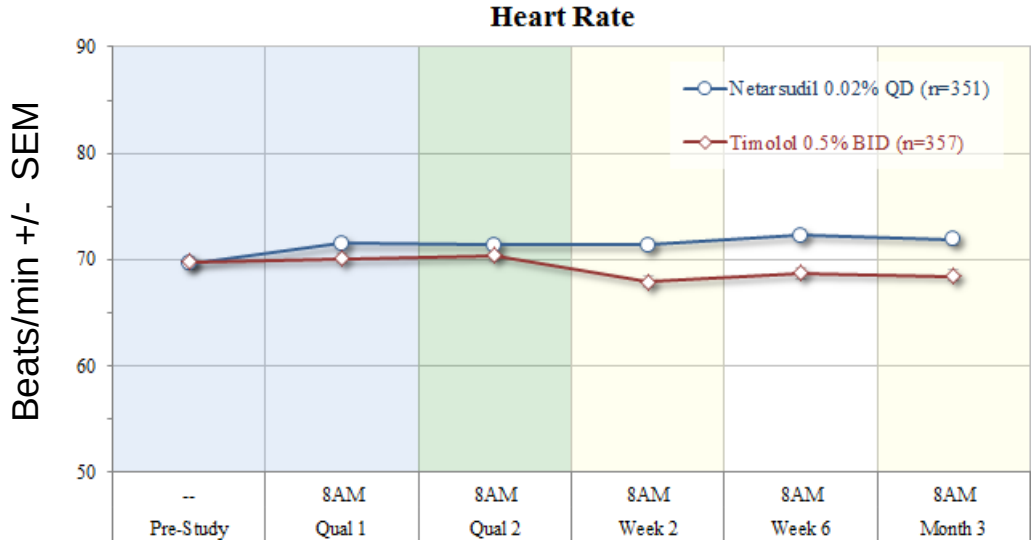
Observed sporadically in netarsudil group using biomicroscopy.

- Seen in about one of ten patients.



Rocket 4: HEART RATE

Timolol Caused Statistically Significant Reduction in Heart Rate



Timolol reduced mean heart rate by 2–3 beats per minute (average across all patients; $p < 0.001$)

Despite all measures to exclude patients with possible negative sensitivity to beta-blockers

Netarsudil

PERFORMANCE SUMMARY *to date*

Well researched with nearly 2,000 clinical patients

Once-daily efficacy demonstrated in 4 Phase 3 trials (Rocket 1, 2, 4 and Mercury 1)

Stable efficacy through 12 months (Rocket 2)

Synergistic/ additive effect with prostaglandin analogues

Well-tolerated with no evidence of treatment-related systemic effects

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Lin Christopher

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Ou Richard J.

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Tepedino Michael

Tsai Julie

Tubbs Carl

Tukel David B.

Wallace Dana

Walters Thomas R.

Wirta David