3-month Interim Report of a Prospective 12-month Safety and Efficacy Study of Topical PG324 (Fixed Combination of Netarsudil 0.02% and Latanoprost 0.005%) Compared to the Individual Components in Subjects with Elevated Intraocular Pressure (**MERCURY 1)**

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Netarsudil 0.02%/Latanoprost 0.005% Fixed Dose Combination (n/l FDC)

Phase 3 Trial Designs

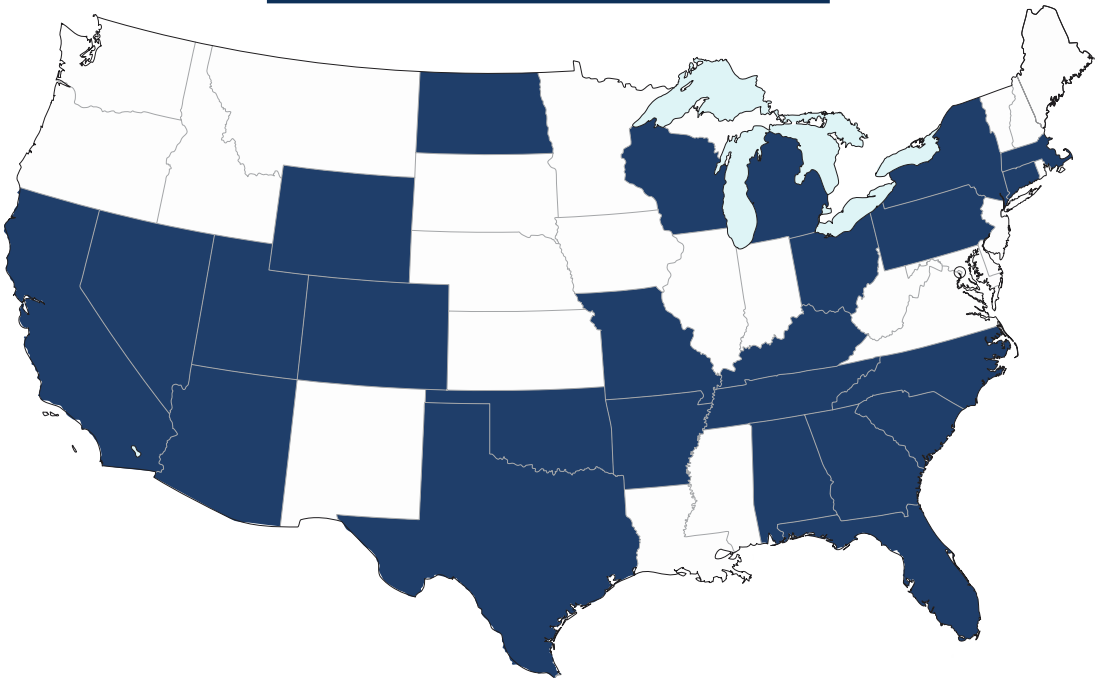
"Mercury 1" One Year Safety (3 Mo. Interim Efficacy) Registration Trial U.S.	• n/l FDC QD	~230 patients	Q3 2017-1 Year
	• netarsudil 0.02% QD	~230 patients	Topline Safety
	• latanoprost QD	~230 patients	
"Mercury 2" 90-Day Efficacy Registration Trial U.S. and Canada	• n/l FDC QD	~230 patients	Q2 2017-3 Month
	• netarsudil 0.02% QD	~230 patients	Topline Efficacy
	• latanoprost QD	~230 patients	
"Mercury 3" 6 Mo. Efficacy and Safety Registration Trial Europe	• n/l FDC QD	~230 patients	1H 2017-
	• Comparator (TBD)	~230 patients	Initiation

ClinicalTrials.gov Identifier: NCT02558400, NCT02674854 *Product Candidates/Drug Names Have Not Been Approved by the FDA*

MLR-0032

Mercury 1 Phase 3: LOCATIONS

25 States; 58 Trial Sites



Mercury 1: TRIAL DESIGN

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

IOP Inclusion criteria

>20 and <36 mmHg 8AM

>17 and <36 mmHg 10AM, 4PM

718 Patients randomized 1:1:1

netarsudil 0.02% /latanoprost 0.005% QD (PM)

netarsudil 0.02% QD (PM)

latanoprost 0.005% QD (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 12-month treatment period

Mercury 1 Phase 3: REGISTRATION TRIAL DESIGN

Trial design follows FDA requirement for fixed dose combination

Superiority of combination over each individual component

Statistically significant difference at each measured time point

Higher combo efficacy vs. components at ~1–3 mmHg, similar to FDA for product approval *(i.e., Simbrinza®)**

Data on File, Based on n/l 0.02%/0.005% EOP2 meeting

*Alcon Simbrinza® accessed on 29th Sept 2016 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204251Orig1s000MedR.pdf

Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032

Mercury 1: BASELINE DEMOGRAPHICS

	netarsudil/latanoprost FDC n=238	netarsudil n=244	latanoprost n=236
Gender			
Male	104 (43.7%)	108 (44.4%)	100 (42.4%)
Female	134 (56.3%)	136 (55.7%)	136 (57.6%)
Race, n (%)			
White	162 (68.1%)	167 (68.4%)	157 (66.5%)
Black/African American	69 (29.0%)	70 (28.7%)	67 (28.4%)
Asian	7 (2.9%)	6 (2.5%)	10 (4.2%)
Multiple	0 (0%)	1 (0.4%)	2 (0.8%)
Age (yrs)			
< 65	109 (45.8%)	107 (43.9%)	95 (40.3%)
> 65	129 (54.2%)	137 (56.1%)	141 (59.7%)
Iris Color, n (%)			
Brown/Black	141 (59.2%)	137 (56.1%)	154 (65.3%)
Blue/Grey/Green	68 (28.6%)	73 (29.9%)	62 (26.3%)
Hazel	29 (12.2%)	34 (13.9%)	20 (8.5%)

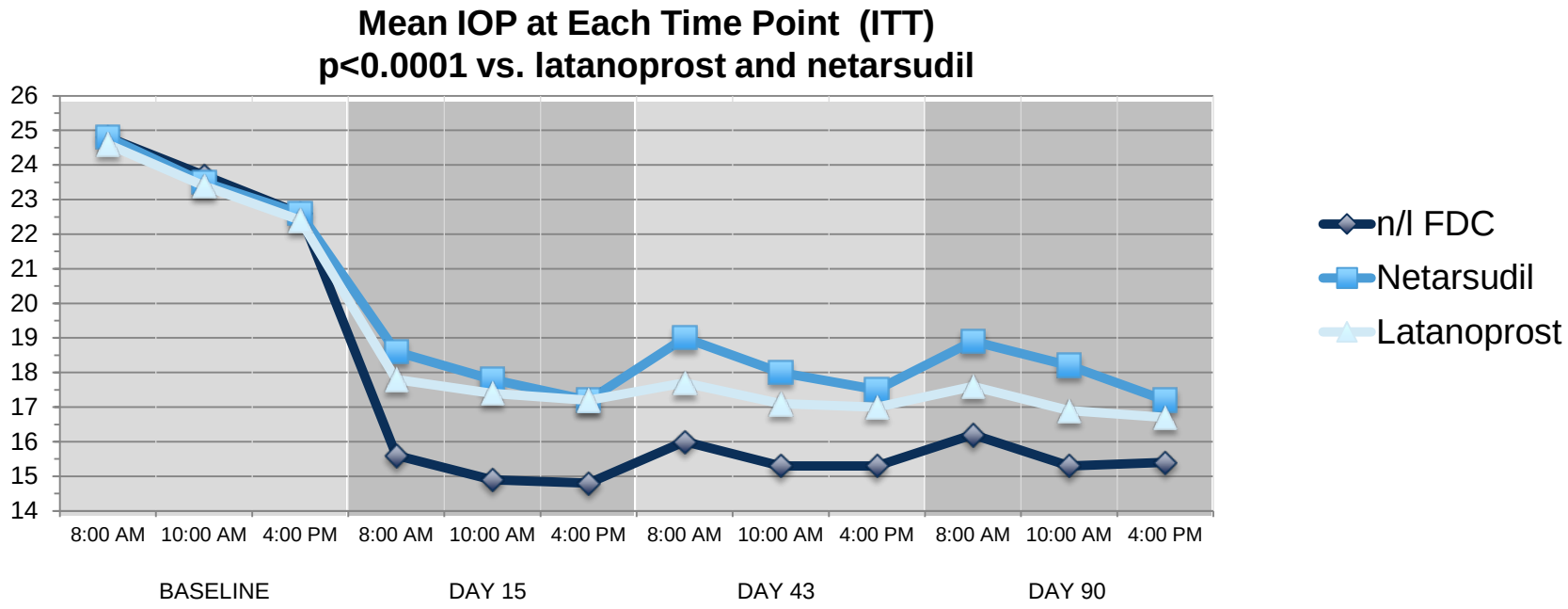
Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032 Data on File, Based on Mercury 1 3-month Interim Analysis

Mercury 1: PATIENT DISPOSITION

	netarsudil/latanoprost FDC n=238	netarsudil n=244	latanoprost n=236
Completed Month 3	**201 (84.5%)**	**201 (82.4%)**	**223 (94.5%)**
Discontinued Prior to Month 3	**37 (15.5%)**	**43 (17.6%)**	**13 (5.5%)**
Reasons for Discontinuation			
Adverse Event	25 (10.5%)	23 (9.4%)	0
Withdrawal of Consent	4 (1.7%)	4 (1.6%)	4 (1.7%)
Non-Compliant	0	1 (0.4%)	1 (0.4%)
Lost to Follow-up	1 (0.4%)	3 (1.2%)	1 (0.4%)
Lack of Efficacy	0	5 (2.0%)	1 (0.4%)
Disallowed Concurrent Medication	1 (0.4%)	4 (1.6%)	1 (0.4%)
Investigator Decision	2 (0.8%)	0	0
Protocol Violation	4 (1.7%)	1 (0.4%)	5 (2.1%)
Other	0	2 (0.8%)	0

Mercury 1: Netarsudil 0.02%/Latanoprost 0.005%

FDC achieved **statistical superiority** over individual components at all time points



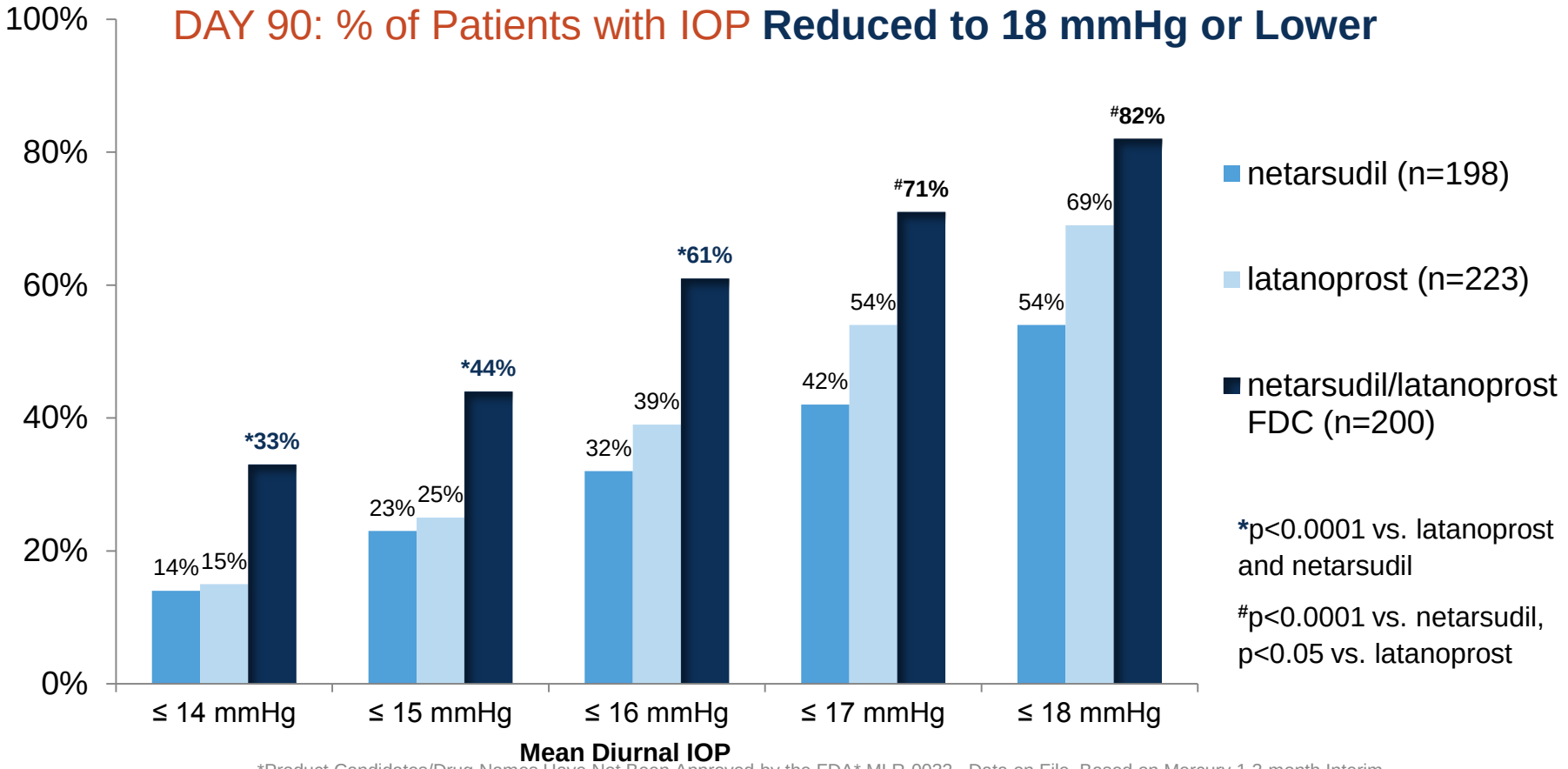
Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032. Data on File, Based on Mercury 1 3-month Interim Analysis

Mercury 1 Phase 3: ITT

	Mean IOP mmHg			Difference from n/l FDC 0.02%/0.005% (95% CI)	
	n/l FDC 0.02%/0.005% N=238	netarsudil 0.02% N=244	latanoprost 0.005% N= 236	netarsudil 0.02%	latanoprost 0.0005%
BASELINE					
8:00 AM	24.8	24.8	24.6		
10:00 AM	23.7	23.5	23.4		
4:00 PM	22.6	22.6	22.4		
Mean Diurnal	**23.7**	**23.6**	**23.5**		
DAY 15					
8:00 AM	15.6	18.6	17.8	-3.0 (-3.6, -2.5)	-2.2 (-2.8, -1.7)
10:00 AM	14.9	17.8	17.4	-2.9 (-3.5, -2.3)	-2.5 (-3.1, -1.9)
4:00 PM	14.8	17.2	17.2	-2.4 (-2.9, -1.9)	-2.3 (-2.9, -1.8)
Mean Diurnal	**15.1**	**17.9**	**17.5**	**-2.8 (-3.3, -2.3)**	**-2.4 (-2.9, -1.9)**
DAY 43					
8:00 AM	16.0	19.0	17.7	-3.0 (-3.6, -2.4)	-1.7 (-2.3, -1.1)
10:00 AM	15.3	18.0	17.1	-2.7 (-3.3, -2.2)	-1.9 (-2.5, -1.3)
4:00 PM	15.3	17.5	17.0	-2.2 (-2.7, -1.6)	-1.7 (-2.2, -1.1)
Mean Diurnal	**15.5**	**18.2**	**17.3**	**-2.7 (-3.1, -2.2)**	**-1.8 (-2.3, -1.3)**
DAY 90					
8:00 AM	16.2	18.9	17.6	-2.7 (-3.4, -2.1)	-1.5 (-2.1, -0.9)
10:00 AM	15.3	18.2	16.9	-2.9 (-3.5, -2.3)	-1.6 (-2.2, -1.0)
4:00 PM	15.4	17.2	16.7	-1.8 (-2.4, -1.2)	-1.3 (-2.0, -0.7)
Mean Diurnal	**15.6**	**18.1**	**17.1**	**-2.5 (-3.0, -2.0)**	**-1.5 (-2.0, -1.0)**

Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032 Data on File, Based on Mercury 1 3-month Interim Analysis.

Mercury 1: RESPONDER ANALYSIS



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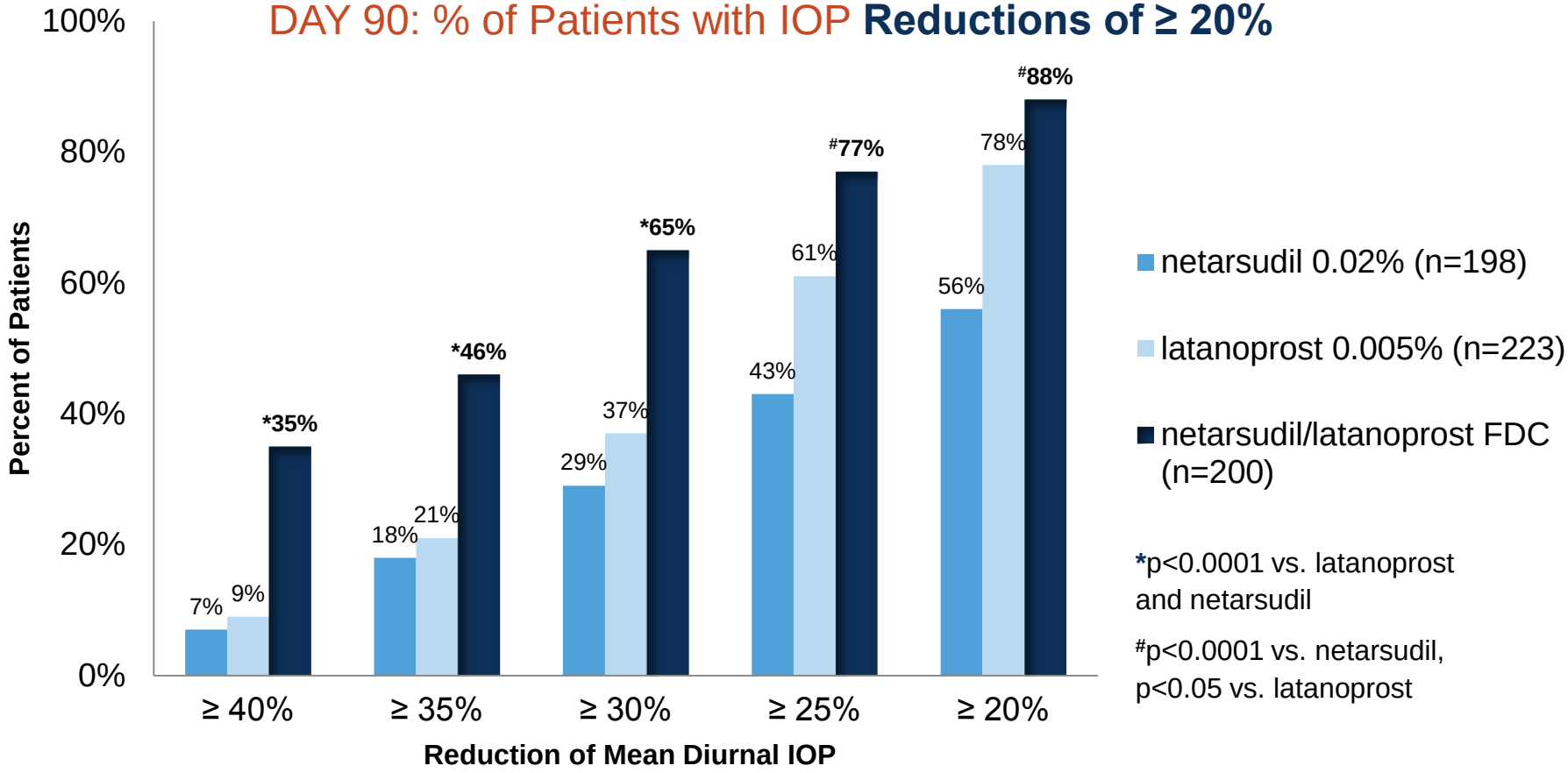

Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032 Data on File, Based on Mercury 1 3-month Interim Analysis

Netarsudil/Latanoprost FDC 0.02%/0.005%

SAFETY PROFILE TO DATE

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 ~50% incidence, ~80% mild on biomicroscopy

Other ocular AEs occurring in ~5-11% of subjects receiving netarsudil/latanoprost FDC included: **conjunctival hemorrhage, eye pruritus, lacrimation increased and cornea verticillata**

Mercury 1: Interim Safety Results

Adverse Events (≥5% in any group)	netarsudil/latanoprost n=238	netarsudil n=244	latanoprost n=236
Eye Disorders			
Conjunctival Hyperemia	127 (53.4%)	100 (41.0%)	33 (14.0%)
Conjunctival Hemorrhage	25 (10.5%)	34 (13.9%)	1 (0.4%)
Eye Pruritus	18 (7.6%)	17 (7.0%)	3 (1.3%)
Lacrimation Increased	14 (5.9%)	15 (6.1%)	1 (0.4%)
Cornea Verticillata	12 (5.0%)	10 (4.1%)	0 (0.0%)
Administration Site Conditions			
Instillation site pain	46 (19.3%)	51 (20.9%)	15 (6.4%)

Patients with known contraindications or hypersensitivity to latanoprost were excluded

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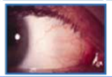
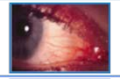
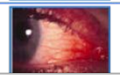
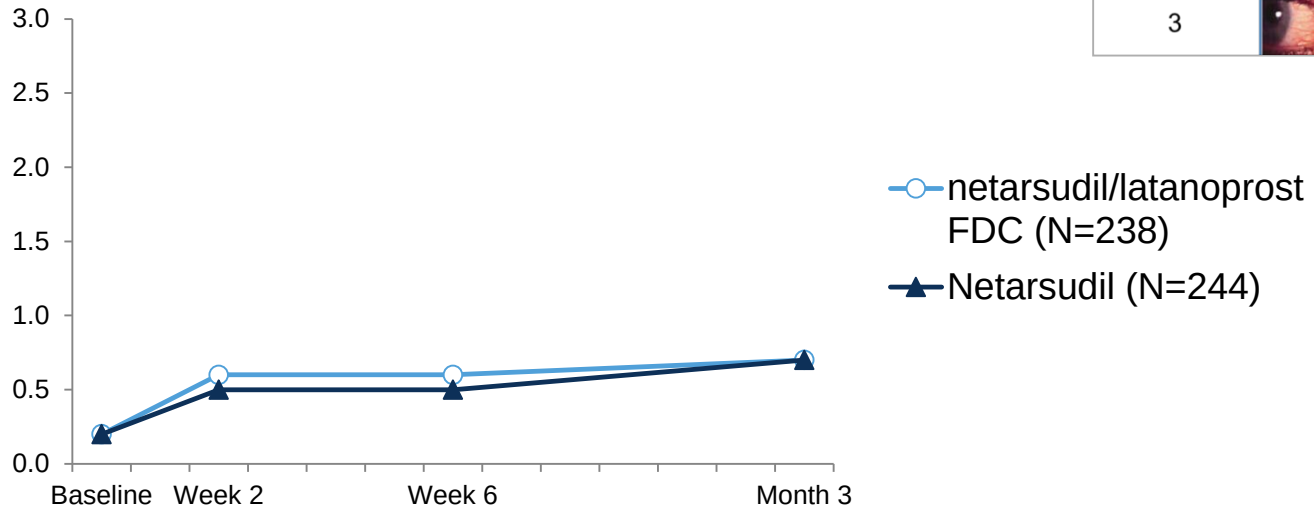
Ocular Tolerability: Conjunctival Hyperemia

- Hyperemia was sporadic ~18% of patients had hyperemia at every study visit.
- Mean hyperemia score was mild, non-inflammatory and thought to be related to the vasodilation effect of the drug

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



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OCULAR TOLERABILITY: Cornea Verticillata

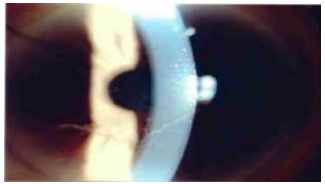
Corneal deposits (lipid micro-deposits in the corneal epithelial level):

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)

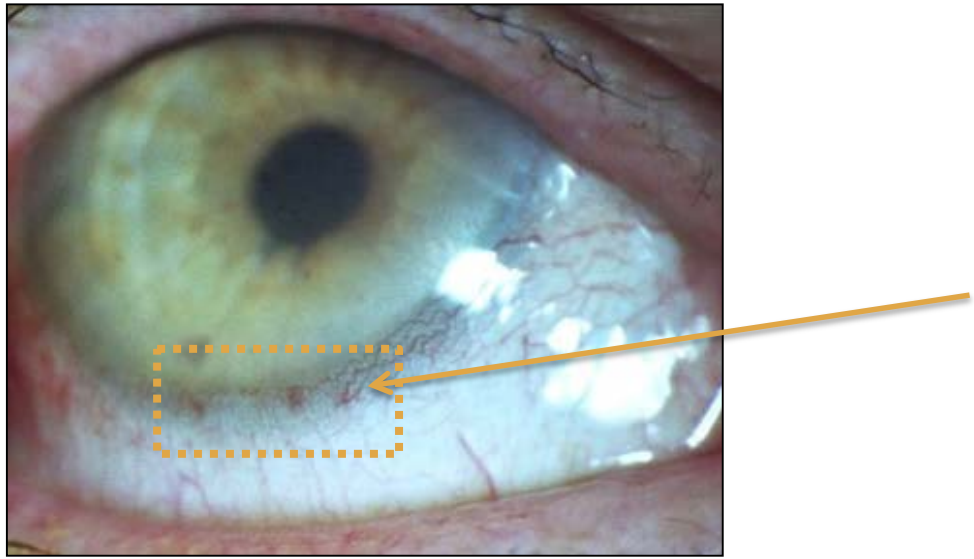
Follow-up continues in these patients

* From the amiodarone prescribing information

OCULAR TOLERABILITY: Conjunctival hemorrhage

Observed sporadically in netarsudil groups using biomicroscopy.

- Seen in about one of ten patients.



MLR-0032 Data on File – an example of conjunctival hemorrhage.

Netarsudil/Latanoprost FDC 0.02%/0.005%

Interim 3-month PERFORMANCE SUMMARY

Met the criteria for demonstrating superiority over both latanoprost and netarsudil for the primary efficacy analysis

Statistical superiority demonstrated at all 9 time points

vs. latanoprost and versus netarsudil ($p<0.0001$)

IOP-lowering effect greater by 1–3 mmHg

vs. monotherapy with either latanoprost or netarsudil throughout the study

65% of Patients achieved IOP Reductions of ≥ 30%

61% of patients achieved mean diurnal IOPs of ≤ 16 mmHg

Percentages significantly higher than observed in for comparators

Anticipated completion of Mercury 1 - 1 year study in Q3 2017

 Product Candidates/Drug Names Have Not Been Approved by the FDA MLR-0032 Data on File, Based on Mercury 1 3-month Interim Analysis

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