Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

October 13, 2017

Netarsudil Ophthalmic Solution 0.02%

FDA Clinical Presentation

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US Food and Drug Administration
Medical Officer

Introduction

Applicant	Aerie Pharmaceuticals, Inc.
Proposed Proprietary Name	Rhopressa
Established name	Netarsudil ophthalmic solution 0.02%
Pharmacologic Category	Rho kinase inhibitor
Dosage Form and Route of Administration	Topical ophthalmic solution
Dosing Regimen	Instill one drop into the affected eye once daily in the evening
Proposed Indication	Indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Table of Clinical Trials

Study Title	Study Design	Test product	Number of Subjects	Duration of Treatment	Baseline IOP
AR-13324-CS301	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	411	3 months	<27 mmHg
AR-13324-CS302	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Netarsudil ophthalmic solution 0.02% 1 gtt OU BID Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	756	12 months	<27 mmHg

Table of Clinical Trials

Study Title	Study Design	Test Product	Number of Subjects	Duration of Treatment	Baseline IOP
AR-13324-CS304	Double-masked, randomized, multi-center, active controlled, parallel study	Netarsudil ophthalmic solution 0.02% 1 gtt OU QPM Timolol maleate ophthalmic solution 0.5% 1 gtt OU BID	708	6 months	<30 mmHg
AR-13324-OBS01	Observational, prospective, targeted	None (Non-interventional)	45	No set duration	

Study AR-13324-CS301: Subject Disposition

Number of Randomized Subjects	**Netarsudil 0.02% QD N=202**	**Timolol 0.5% BID N=209**
Study Completion		
Completed	171 (85%)	196 (94%)
Discontinued	31 (15%)	13 (6%)
Reason for Subject Discontinuation		
Adverse Event	20 (65%)	4 (31%)
Withdrawal of Consent	3 (10%)	2 (15%)
Non-compliant	0	1 (8%)
Lost to Follow-up	0	1 (8%)
Lack of Efficacy	3 (10%)	0
Investigator Decision	2 (7%)	0
Protocol Violation	3 (10%)	5 (39%)

Study AR-13324-CS302: Subject Disposition

Number of Randomized Subjects	**Netarsudil 0.02% QD N=251**	**Netarsudil 0.02% BID N=254**	**Timolol 0.5% BID N=251**
Study Completion			
Completed Month 3	205 (82%)	153 (60%)	237 (94%)
Discontinued Prior to Month 3	46 (18%)	101 (40%)	14 (6%)
Completed Month 12	146 (58%)	86 (34%)	204 (81%)
Discontinued Prior to Month 12	105 (42%)	168 (66%)	47 (19%)
Reason for Subject Discontinuation			
Adverse Event	71 (67%)	132 (79%)	15 (32%)
Withdrawal of Consent	9 (9%)	13 (8%)	9 (19.%)
Non-compliant	3 (3%)	1 (1%)	3 (6%)
Lost to Follow-up	1 (1%)	3 (2%)	0
Lack of Efficacy	10 (10%)	4 (2%)	2 (4%)
Disallowed Concurrent Medication	2 (2%)	2 (1%)	5 (11%)
Investigator Decision	1 (1%)	2 (1%)	2 (4%)
Protocol Violation	4 (4%)	6 (4%)	10 (21%)
Death	2 (2%)	0	0
Other	2 (2%)	5 (3%)	1 (2%)

Study AR-13324-CS304: Subject Disposition

Number of Randomized Subjects	Netarsudil 0.02% QD N=351	Timolol 0.5% BID N=357
Study Completion		
Completed	243 (69%)	314 (88%)
Discontinued	108 (31%)	43 (12%)
Reason for Subject Discontinuation		
Adverse Event	68 (63%)	8 (19%)
Withdrawal of Consent	12 (11%)	16 (37%)
Non-compliant	1 (1%)	2 (5%)
Lost to Follow-up	1 (1%)	3 (7%)
Lack of Efficacy	12 (11%)	1 (2%)
Disallowed concurrent Medication	1 (1%)	3 (7%)
Investigator Decision	2 (2%)	4 (9%)
Protocol Violation	5 (5%)	4 (9%)
Death	1 (1%)	0
Other	5 (5%)	2 (5%)

Study AR-13324-CS301:
Primary Efficacy Endpoint

- The primary efficacy outcome was the mean IOP at 08:00, 10:00, and 16:00 hours at the Week 2 (Day 15), Week 6 (Day 43), and Month 3 (Day 90) visits.

Criteria for Non-inferiority

- Based on the upper limits of the 95% CIs for the treatment difference (netarsudil – timolol)
  - Within **1.5 mmHg** for all 9 time points
  - Within **1.0 mmHg** for at least 5 out of 9 time points

AR-13324-CS301: Results

- Study AR-13324-CS301 **DID NOT** meet the pre-specified endpoint with the PP or the ITT analysis.

Results of Study AR-13324-CS301: Study Eye Mean IOP PP Population With Observed Data-Baseline IOP<27

Day and Time	Mean IOP Netarsudil N=182	Mean IOP Timolol N=188	Mean Difference	95% Confidence Interval
Baseline				
08:00	23.42 (N=182)	23.37 (N=188)	0.06	(-0.29, 0.41)
10:00	22.28 (N=182)	21.92 (N=188)	0.36	(-0.07, 0.79)
16:00	21.78 (N=182)	21.45 (N=188)	0.33	(-0.15, 0.82)
Day 15				
08:00	18.68 (N=177)	18.33 (N=187)	0.35	(-0.27, 0.96)
10:00	17.29 (N=176)	17.55 (N=186)	-0.26	(-0.87, 0.36)
16:00	17.24 (N=176)	17.70 (N=186)	-0.45	(-1.08, 0.17)
Day 43				
08:00	19.35 (N=170)	18.24 (N=184)	1.11	(0.42, 1.80)
10:00	18.14 (N=170)	17.44 (N=184)	0.70	(0.04, 1.36)
16:00	17.86 (N=170)	17.71 (N=183)	0.15	(-0.52, 0.83)
Day 90				
08:00	19.81 (N=157)	18.47 (N=181)	1.33	(0.64, 2.03)
10:00	18.92 (N=158)	17.96 (N=181)	0.96	(0.26, 1.66)
16:00	18.48 (N=158)	17.74 (N=181)	0.74	(0.07, 1.42)

Results of Study AR-13324-CS301: Study Eye Mean IOP ITT With LOCF-Baseline IOP<27

Day and Time	Mean IOP Netarsudil N=202	Mean IOP Timolol N=209	Mean Difference	95% Confidence Interval
Baseline (Visit 3)				
08:00	23.41	23.34	0.07	(-0.27, 0.41)
10:00	22.30	21.87	0.43	(0.02, 0.84)
16:00	21.84	21.40	0.44	(-0.02, 0.90)
Day 15				
08:00	18.81	18.33	0.48	(-0.11, 1.07)
10:00	17.54	17.51	0.03	(-0.56, 0.61)
16:00	17.50	17.68	-0.17	(-0.77, 0.43)
Day 43				
08:00	19.46	18.26	1.21	(0.56, 1.86)
10:00	18.22	17.50	0.72	(0.10, 1.34)
16:00	18.07	17.79	0.28	(-0.36, 0.91)
Day 90				
08:00	19.97	18.48	1.48	(0.85, 2.12)
10:00	19.03	17.96	1.07	(0.43, 1.71)
16:00	18.68	17.85	0.83	(0.20, 1.46)

AR-13324-CS301: Results

- Although, Study AR-13324-CS301 **DID NOT** meet the pre-specified endpoint with the PP or the ITT analysis, when looking at a **POST HOC ANALYSIS** of patients with IOP <25, it did meet its endpoint in both PP and ITT populations.

Study AR-13324-CS301: Study Eye Mean IOP For Subjects With Baseline IOP <25 PP Population With Observed Data POST HOC ANALYSIS

Day and Time	Mean IOP Netarsudil	Mean IOP Timolol	Mean Difference	95% Confidence Interval
Baseline				
08:00	22.39 N=113	22.50 N=124	-0.11	(-0.39, 0.18)
10:00	21.28 N=113	21.07 N=124	0.21	(-0.21, 0.64)
16:00	20.62 N=113	20.52 N=124	0.10	(-0.36, 0.56)
Day 15				
08:00	17.34 N=108	17.78 N=123	-0.44	(-1.10, 0.22)
10:00	16.18 N=107	16.98 N=122	-0.81	(-1.44, -0.17)
16:00	16.22 N=107	17.14 N=122	-0.92	(-1.58, -0.26)
Day 43				
08:00	17.85 N=105	17.81 N=121	0.05	(-0.68, 0.77)
10:00	16.88 N=105	16.96 N=121	-0.08	(-0.74, 0.58)
16:00	16.57 N=105	17.26 N=120	-0.69	(-1.40, 0.02)
Day 90				
08:00	18.22 N=99	17.91 N=119	0.31	(-0.40, 1.02)
10:00	17.34 N=99	17.43 N=119	-0.09	(-0.82, 0.63)
16:00	17.02 N=99	17.37 N=119	-0.35	(-1.03, 0.34)

Study AR-13324-CS302: Primary Efficacy Endpoint

- The primary efficacy outcome was the mean IOP for subjects with baseline IOP > 20 mmHg (08:00 hours) and **< 25 mmHg** (08:00,10:00, and 16:00 hours) in the study eye at the following time points: 08:00, 10:00, and 16:00 hours at the Week 2, Week 6, and Month 3 visits.

Study AR-13324-CS302: Results

- Study AR-13324-CS302 **DID MEET** the pre-specified endpoint with the PP and the ITT analysis.

Study AR-13324-CS302: Study Eye Mean IOP
PP Population With Observed Data Subjects With Baseline IOP <25

Day and Time	Mean IOP Netarsudil 0.02% QD	Mean IOP Netarsudil 0.02% BID	Mean IOP Timolol 0.5% BID	Mean Difference Timolol-netarsudil 0.02% QD	95% CI	Mean Difference Timolol-netarsudil 0.02% BID	95% CI
Baseline							
08:00	22.54 N=129	22.55 N=132	22.54 N=142	0	(-0.25, 0.25)	0.01	(-0.24, 0.26)
10:00	21.29 N=129	21.27 N=132	21.27 N=142	0.02	(-0.37, 0.41)	-0.01	(-0.40, 0.38)
16:00	20.43 N=129	20.56 N=132	20.71 N=142	-0.28	9-0.71, 0.14)	-0.15	(-0.58, 0.29)
Day 15							
08:00	18.07 N=127	17.21 N=122	17.69 N=142	0.37	(-0.25, 0.99)	-0.48	(-1.19, 0.22)
10:00	16.72 N=126	16.35 N=120	16.93 N=141	-0.21	(-0.82, 0.41)	-0.57	(-1.24, 0.09)
16:00	16.68 N=126	15.65 N=118	16.83 N=141	-0.15	(-0.75, 0.46)	-1.18	(-1.82, -0.54)
Day 43							
08:00	17.95 N=122	17.64 N=111	17.46 N=141	0.49	(-0.13, 1.12)	0.17	(-0.51, 0.86)
10:00	16.95 N=120	16.28 N=106	16.63 N=141	0.32	(-0.31, 0.95)	-0.34	(-1.02, 0.33)
16:00	17.00 N=120	15.75 N=106	16.60 N=141	0.40	(-0.22, 1.02)	-0.85	(-1.53, -0.17)
Day 90							
08:00	18.24 N=116	17.58 N=91	17.47 N=140	0.77	(0.03, 1.50)	0.11	(-0.64, 0.86)
10:00	17.03 N= 14	16.94 N=88	16.92 N=140	0.10	(-0.59, 0.80)	0.02	(-0.72, 0.77)
16:00	17.13 N=114	16.51 N=88	16.95 N=139	0.18	(-0.55, 0.91)	-0.44	(-1.16, 0.27)

Results of Study AR-13324-CS302: Mean IOP ITT With LOCF With Baseline IOP <25

Day and Time	Mean IOP Netarsudil 0.02% QD	Mean IOP Netarsudil 0.02% BID	Mean IOP Timolol 0.5% BID	Mean Difference Timolol-netarsudil 0.02% QD	95% CI	Mean Difference Timolol-netarsudil 0.02% BID	95% CI
Baseline							
08:00	22.54	22.56	22.41	0.13	(-0.10, 0.37)	0.15	(-0.10, 0.39)
10:00	21.23	21.28	21.16	0.07	(-0.28, 0.42)	0.11	(-0.24, 0.47)
16:00	20.40	20.59	20.60	-0.20	(-0.60, 0.20)	-0.01	(-0.41, 0.40)
Day 15							
08:00	17.91	17.69	17.61	0.30	(-0.28, 0.88)	0.07	(-0.58, 0.73)
10:00	16.75	16.81	16.92	-0.17	(-0.74, 0.41)	-0.11	(-0.74, 0.52)
16:00	1.673	16.34	16.83	-0.10	(-0.67, 0.47)	-0.49	(-1.12, 0.14)
Day 43							
08:00	17.85	17.97	17.38	0.47	(-0.09, 1.04)	0.60	(-0.03, 1.22)
10:00	16.93	17.06	16.54	0.39	(-0.18, 0.97)	0.52	(-0.10, 1.14)
16:00	16.96	16.38	16.56	0.40	(-0.16, 0.97)	-0.18	(-0.82, 0.46)
Day 90							
08:00	18.16	18.13	17.36	0.80	(0.15, 1.45)	0.77	(-0.09, 1.44)
10:00	17.15	17.35	16.77	0.38	(-0.25, 1.01)	0.58	(-0.06, 1.21)
16:00	17.11	16.80	16.79	0.31	(-0.32, 0.95)	0.00	(-0.63, 0.64)

U.S. FOOD & DRUG ADMINISTRATION

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

October 13, 2017

Netarsudil Ophthalmic Solution 0.02%

FDA Statistical Presentation

Reviewer: Yunfan Deng, PhD
Team Leader: Yan Wang, PhD
Division of Biometrics IV

Design of Phase 3 Efficacy Studies

(AR-13324-CS301, AR-13324-CS302, AR-13324-CS304)

- Multi-center, double-masked, active-controlled non-inferiority

Study	Treatment Arm	Treatment Duration	Baseline IOP
301	Netarsudil QD Timolol BID	3 months	20 mmHg < IOP < 27 mmHg at 8am 17 mmHg < IOP < 27 mmHg at 10am and 4pm
302	Netarsudil QD Netarsudil BID Timolol BID	12 months	Same as 301
304	Same as 301	6 months	20 mmHg < IOP < 30 mmHg at 8am 17 mmHg < IOP < 30 mmHg at 10am and 4pm

Efficacy Endpoints and Analysis Populations

- Primary endpoint: mean IOP in the study eye at 8am, 10am, and 4pm at Days 15, 43, and 90
- Secondary endpoint: mean IOP change from baseline in the study eye at each post-baseline time point
- Analysis populations: Intent-to-treat (ITT) and Per Protocol (PP)
  - ITT population: all randomized subjects who received at least 1 dose of study drug
  - PP population: all ITT subjects who did not have major protocol violations likely to seriously affect the primary outcome of the study

Analysis Methods

- Treatment difference evaluated using a 95% CI based on 2-sample t-distribution for each individual time point
- Primary analysis conducted on the PP population using observed data
  - 301: all subjects (maximum baseline IOP <27 mmHg)
  - 302 and 304: subjects with maximum baseline IOP < 25 mmHg
- Analyses also conducted based on ITT population and using various methods of handling missing data under varying assumptions

Study Success Criteria for Non-inferiority

- The upper limits of the 95% CIs for the treatment difference (netarsudil – timolol) need to be
  - within **1.5** mmHg for all 9 time points
  - within **1.0** mmHg for at least 5 out of 9 time points

Subject Disposition

		Netarsudil QD n (%)	Timolol BID n (%)
Study 301	**ITT**	202	209
	Discontinued prior to Month 3 due to AE	20 (10%)	4 (2%)
Study 302	**ITT**	251	251
	Discontinued prior to Month 3 due to AE	31 (12%)	2 (1%)
	Discontinued prior to Month 12 due to AE	71 (28%)	15 (6.0)
Study 304	**ITT**	351	357
	Discontinued prior to Month 3 due to AE	39 (11%)	6 (2%)
	Discontinued prior to Month 6 due to AE	68 (19%)	8 (2%)
Study 301	**PP**	182 (90%)	188 (90%)
Study 302	**PP**	206 (82%)	217 (86%)
Study 304	**PP**	306 (87%)	317 (89%)

Analysis Population

	ITT		PP	
	Netarsudil QD	**Timolol BID**	**Netarsudil QD**	**Timolol BID**
Study 301	202	209	182	188
Maximum Baseline IOP < 25 mmHg	125 (62%)	138 (66%)	113 (62%)	124 (66%)
25 mmHg ≤ Maximum Baseline IOP < 27 mmHg	77 (38%)	71 (34%)	69 (38%)	64 (34%)
Study 302	251	251	206	217
Maximum Baseline IOP < 25 mmHg	155 (62%)	163 (65%)	129 (63%)	142 (65%)
25 mmHg ≤ Maximum Baseline IOP < 27 mmHg	96 (38%)	88 (35%)	77 (37%)	75 (35%)
Study 304	351	357	306	317
Maximum Baseline IOP < 25 mmHg	214 (61%)	209 (59%)	186 (61%)	187 (59%)
Maximum Baseline IOP ≥ 25 mmHg	137 (39%)	148 (41%)	120 (39%)	130 (41%)
25 mmHg ≤ Maximum Baseline IOP < 27 mmHg	60 (17%)	71 (20%)	54 (17%)	68 (21%)
27 mmHg ≤ Maximum Baseline IOP < 30 mmHg	77 (22%)	77 (21%)	66 (22%)	62 (20%)

Summary of Applicant's Key Efficacy Results

Non-inferiority of Netarsudil 0.02% QD to Timolol BID

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

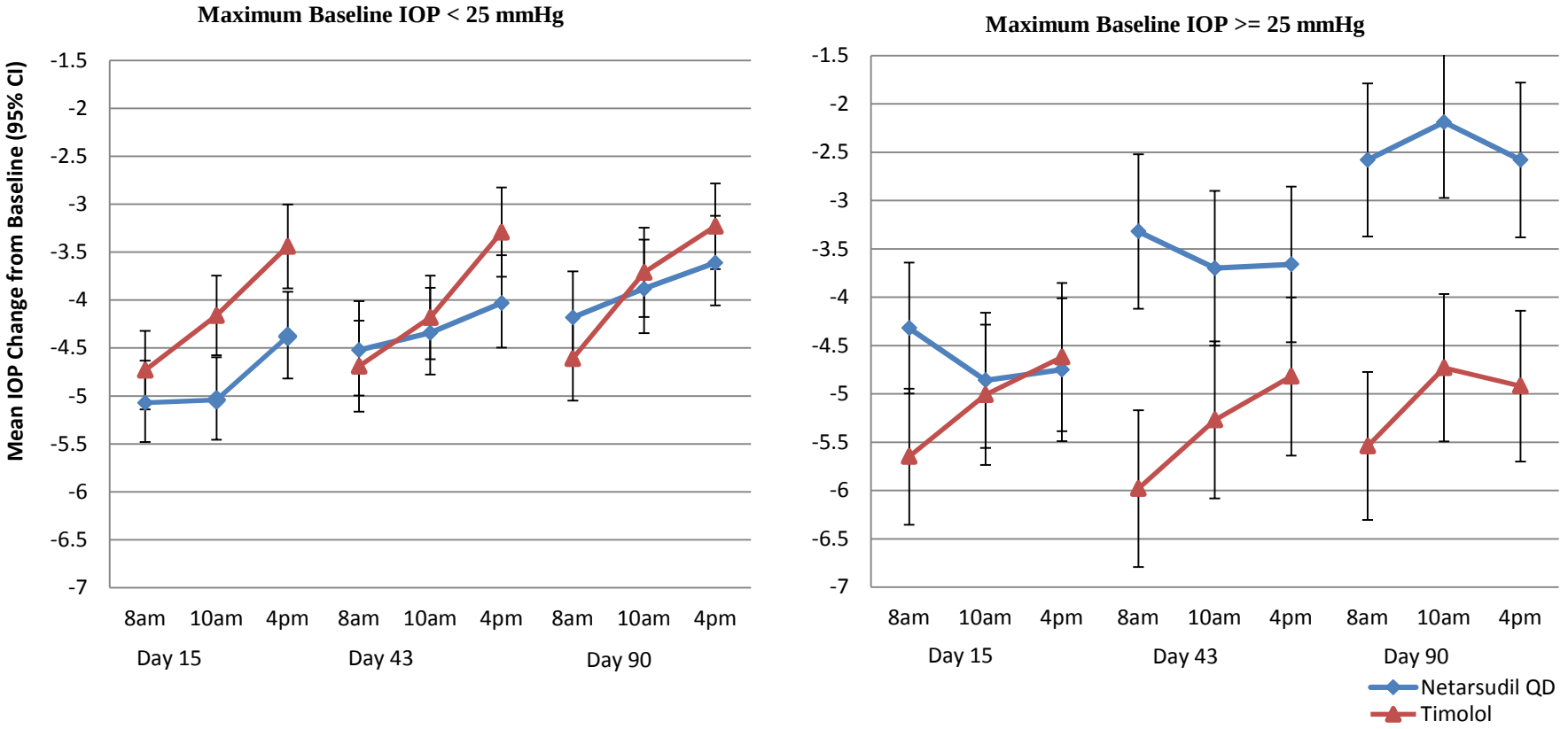
Mean IOP Change from Baseline

- Conducted analyses to gain insight into the treatment effect
  - Including analysis of covariance (ANCOVA) adjusted for baseline IOP
- Focused on two subgroups
  - Maximum baseline IOP < 25 mmHg
  - Maximum baseline IOP ≥ 25 mmHg

Study 301: Mean IOP Change from Baseline in Study Eye by Visit and Time

	Maximum Baseline IOP < 25 mm Hg			Maximum Baseline IOP ≥ 25 mmHg		
	Netarsudil QD	Timolol BID	Difference (95% CI)	Netarsudil QD	Timolol BID	Difference (95% CI)
	Mean	Mean		Mean	Mean	
Baseline						
08:00	22.4	22.5		25.1	25.1	
10:00	21.3	21.1		23.9	23.6	
16:00	20.6	20.5		23.7	23.3	
Day 15						
08:00	-5.1	-4.7	-0.3 (-0.9, 0.3)	-4.3	-5.7	**1.3 (0.4, 2.3)**
10:00	-5.0	-4.2	-0.9 (-1.5, -0.3)	-4.9	-5.0	0.1 (-0.9, 1.2)
16:00	-4.4	-3.4	-0.9 (-1.6, -0.3)	-4.7	-4.6	-0.1 (-1.2, 0.9)
Day 43						
08:00	-4.5	-4.7	0.2 (-0.5, 0.9)	-3.3	-6.0	**2.7 (1.5, 3.8)**
10:00	-4.3	-4.2	-0.2 (-0.8, 0.5)	-3.7	-5.3	**1.6 (0.4, 2.7)**
16:00	-4.0	-3.3	-0.7 (-1.4, 0.0)	-3.7	-4.8	**1.2 (0.0, 2.3)**
Day 90						
08:00	-4.2	-4.6	0.4 (-0.2, 1.1)	-2.6	-5.5	**3.0 (1.8, 4.1)**
10:00	-3.9	-3.7	-0.2 (-0.9, 0.5)	-2.2	-4.7	**2.5 (1.4, 3.6)**
16:00	-3.6	-3.2	-0.4 (-1.0, 0.3)	-2.6	-4.9	**2.3 (1.2, 3.5)**

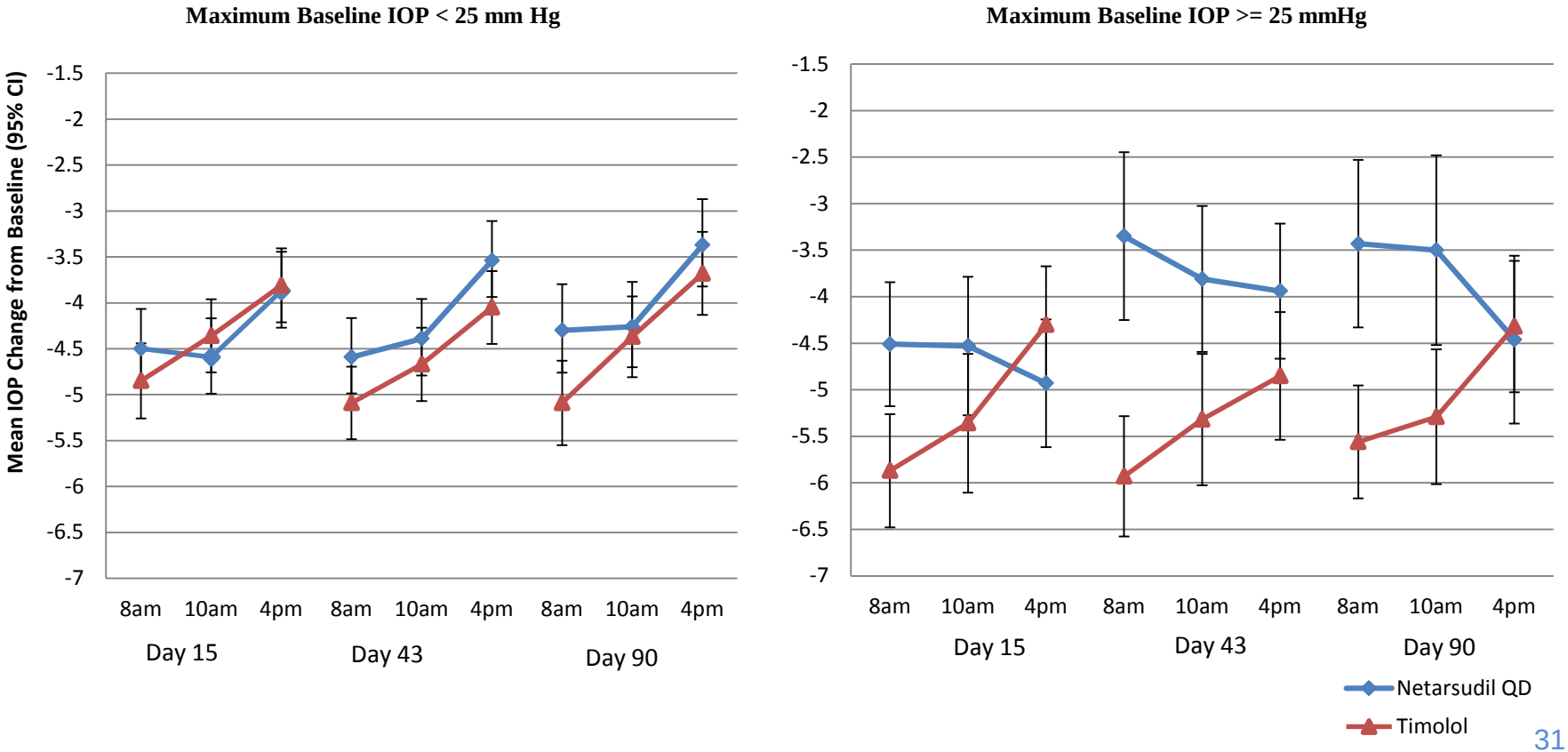
Study 301: Mean IOP Change from Baseline in Study Eye by Visit and Time



Study 302: Mean IOP Change from Baseline in Study Eye by Visit and Time

	Maximum Baseline IOP < 25 mm Hg			Maximum Baseline IOP ≥ 25 mmHg		
	Netarsudil QD	Timolol BID	Difference (95% CI)	Netarsudil QD	Timolol BID	Difference (95% CI)
	Mean	Mean		Mean	Mean	
Baseline						
08:00	22.5	22.5		25.1	25.2	
10:00	21.3	21.3		24.0	23.9	
16:00	20.4	20.7		23.5	23.3	
Day 15						
08:00	-4.5	-4.9	0.4 (-0.2, 1.0)	-4.5	-5.9	**1.4 (0.5, 2.3)**
10:00	-4.6	-4.4	-0.2 (-0.8, 0.4)	-4.5	-5.4	0.9 (-0.1, 1.9)
16:00	-3.9	-3.8	-0.1 (-0.6, 0.5)	-4.9	-4.3	-0.6 (-1.5, 0.3)
Day 43						
08:00	-4.6	-5.1	0.5 (-0.1, 1.1)	-3.4	-5.9	**2.6 (1.5, 3.7)**
10:00	-4.4	-4.7	0.3 (-0.3, 0.9)	-3.8	-5.3	**1.5 (0.5, 2.6)**
16:00	-3.5	-4.0	0.5 (-0.1, 1.1)	-3.9	-4.9	**0.9 (0.0, 1.9)**
Day 90						
08:00	-4.3	-5.1	0.8 (0.1, 1.5)	-3.4	-5.6	**2.1 (1.1, 3.2)**
10:00	-4.3	-4.4	0.1 (-0.5, 0.8)	-3.5	-5.3	**1.7 (0.6, 2.8)**
16:00	-3.4	-3.7	0.3 (-0.4, 1.0)	-4.4	-4.3	-0.1 (-1.2, 1.0)

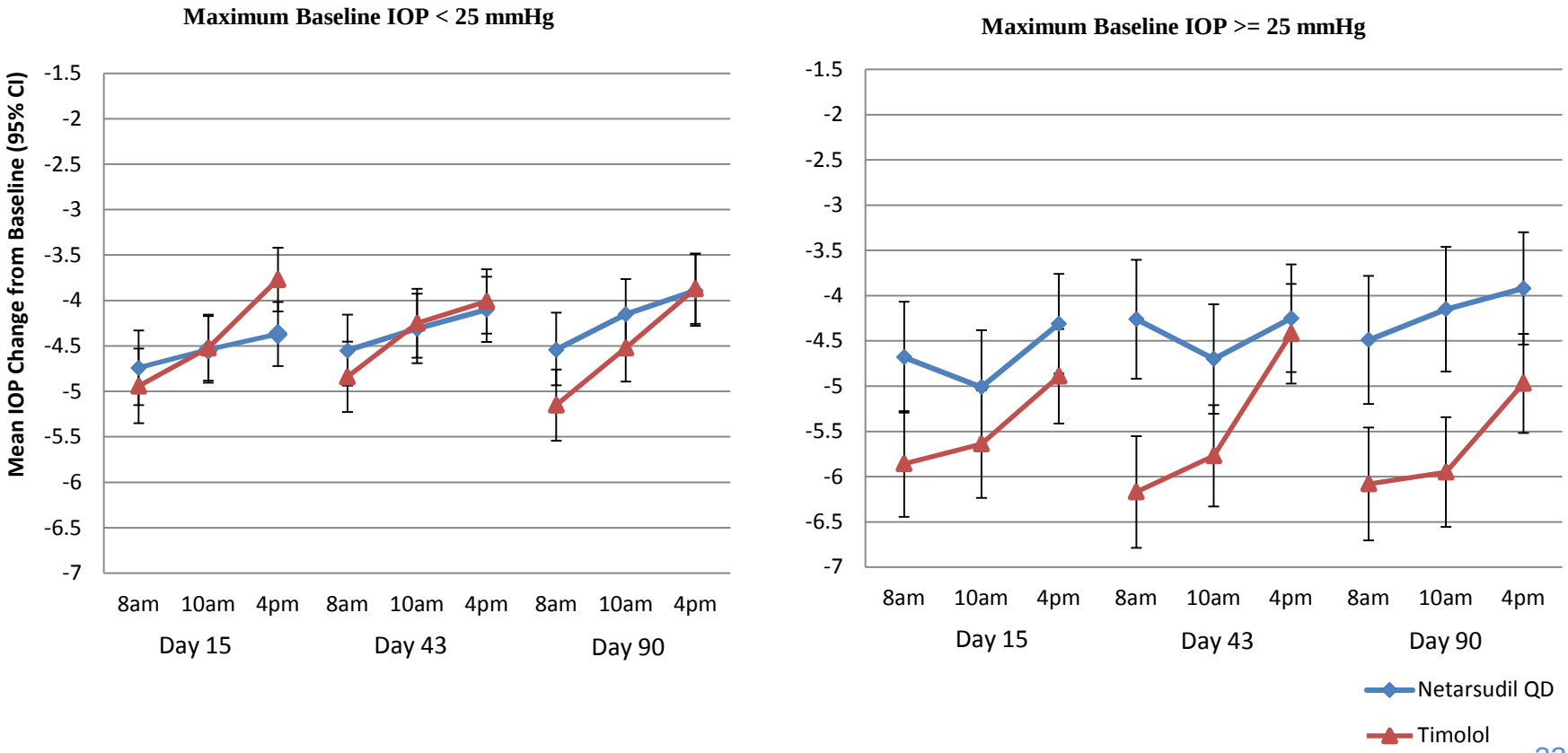
Study 302: Mean IOP Change from Baseline in Study Eye by Visit and Time



Study 304: Mean IOP Change from Baseline in Study Eye by Visit and Time

	Maximum Baseline IOP < 25 mmHg			Maximum Baseline IOP ≥ 25 mmHg		
	Netarsudil QD	Timolol BID	Difference (95% CI)	Netarsudil QD	Timolol BID	Difference (95% CI)
	Mean	Mean		Mean	Mean	
Baseline						
08:00	22.4	22.4		26.3	26.0	
10:00	21.1	21.3		25.2	24.9	
16:00	20.7	20.7		24.5	24.0	
Day 15						
08:00	-4.7	-4.9	0.2 (-0.4, 0.8)	-4.7	-5.9	**1.2 (0.3, 2.0)**
10:00	-4.5	-4.5	0.0 (-0.5, 0.5)	-5.0	-5.6	0.6 (-0.2, 1.5)
16:00	-4.4	-3.8	-0.6 (-1.1, -0.1)	-4.3	-4.9	0.6 (-0.2, 1.3)
Day 43						
08:00	-4.6	-4.8	0.3 (-0.3, 0.8)	-4.3	-6.2	**1.9 (1.0, 2.8)**
10:00	-4.3	-4.3	-0.1 (-0.6, 0.5)	-4.7	-5.8	**1.1 (0.2, 1.9)**
16:00	-4.1	-4.0	-0.1 (-0.6, 0.4)	-4.3	-4.4	0.2 (-0.6, 1.0)
Day 90						
08:00	-4.5	-5.2	0.6 (0.0, 1.2)	-4.5	-6.1	**1.6 (0.6, 2.5)**
10:00	-4.1	-4.5	0.4 (-0.2, 0.9)	-4.1	-5.9	**1.8 (0.9, 2.7)**
16:00	-3.9	-3.9	0.0 (-0.6, 0.5)	-3.9	-5.0	**1.1 (0.2, 1.9)**

Study 304: Mean IOP Change from Baseline in Study Eye by Visit and Time



Summary

- For subjects with maximum baseline IOP < 25 mmHg, overall netarsudil and timolol appeared to have similar mean IOP reductions on Days 15, 43, and 90
- For subjects with higher maximum baseline (≥ 25 mmHg), netarsudil had smaller mean IOP reductions
  - Difference was most noticeable at 8am and 10am on Days 43 and 90

Dermatologic and Ophthalmic Drugs Advisory Committee Meeting

October 13, 2017

Netarsudil Ophthalmic Solution 0.02%

Sonal D. Wadhwa, MD
US Food and Drug Administration
Medical Officer

Safety

- Study AR-13324-CS301
- Study AR-13324-CS302
- Study AR-13324-CS304
- Study AR-13324-OBS01

Deaths

- Study AR-13324-CS301: No deaths occurred during the study.
- Study AR-13324-CS302: Two subjects in the Netarsudil QD treatment group died during the course of the study secondary to a myocardial infarction.
- Study AR-13324-CS304: One subject in the Netarsudil QD group died during the course of the study secondary to a cardiac arrest.

Adverse Events
Studies AR-13324-CS301 and AR-13324-CS302
(Pooled Safety Population)

- Conjunctival hyperemia was the most common ocular AE (57%)

- Other common ocular AEs:
  - Conjunctival hemorrhage (18%)
  - Corneal verticillata (17%)
  - Instillation site pain (17%)
  - Vision blurred (8%)
  - Instillation site erythema (8%)
  - Visual acuity reduced (7%)
  - Vital dye cornea present (7%)
  - Eyelid erythema (6%)

Adverse Events
Study AR-13324-CS304

- Conjunctival hyperemia was the most common ocular AE (48%)

- Other common ocular AEs:
  - Corneal verticillata (25%)
  - Instillation site pain (23%)
  - Conjunctival hemorrhage (16%)
  - Instillation site erythema (10%)
  - Vital dye cornea present (10%)
  - Lacrimation increased (7%)
  - Eyelid erythema (7%)
  - Vision blurred (6%)

Corneal Verticillata

- Whorl-like pattern of golden brown or gray deposits in the epithelium of the cornea
- This is secondary to intracellular phospholipid accumulation (phospholipidosis) in the lysosomes
- Usually bilateral
- Usually patients have no visual symptoms

Corneal Verticillata

- Amiodarone is the most common cause of corneal verticillata.

- Other drugs which are known to cause corneal verticillata:
  - Chloroquine
  - Hydroxychloroquine
  - Indomethacin
  - Phenothiazines

Corneal Verticillata

- Netarsudil is the first topical ophthalmic known to cause corneal verticillata.

- Because of the finding of corneal verticillata in these studies there was a safety study to further investigate this finding (Study AR-13324-OBS01).

Incidence of Corneal Verticillata

Study	Number of Subjects with Corneal Verticillata in Netarsudil Group	Number of Subjects with Corneal Verticillata in Timolol Group
AR-13324-CS301	11/203 (5%)	0/208
AR-13324-CS302	64/251 (26%) in QD group 64/253 (25%) in BID group	2/251 (1%)
AR-13324-CS304	86/351 (25%)	0/357

Study AR-13324-OBS01: A Prospective, Targeted, Non-interventional (Observational) Study of Subjects Who Developed Corneal Deposits in Clinical Trials AR-13324-CS301 and AR-13324-CS302

- Designed to follow up and collect additional safety data in subjects who developed corneal verticillata in clinical trials AR-13324-CS301 and AR-13324-CS302.

- Subjects in clinical trials AR-13324-CS301 or AR-13324-CS302 identified by verbatim adverse event (AE) terms of:
  - corneal whorls
  - corneal haze
  - subepithelial corneal deposits
  - vortex epitheliopathy
  - cornea verticillata/corneal verticillata

- Any of the above in one or both eyes were eligible to participate in this study.

Study AR-13324-OBS01: A Prospective, Targeted, Non-interventional (Observational) Study of Subjects Who Developed Corneal Deposits in Clinical Trials AR-13324-CS301 and AR-13324-CS302

- This observational study had no set duration.
- The expectation was that subjects whom consented would participate until resolution or stabilization of corneal verticillata.
- Subjects participating in this observational study were not treated with any investigational products during this study. They did, however, re-start or continue treatment with IOP-lowering agents or other topical ocular medications (Rx or OTC) as recommended by their eye care provider/practitioner.

Study AR-13324-OBS01

- The following assessments were performed in both eyes of all enrolled subjects:
  - Contrast Sensitivity (Pelli-Robson) testing
  - BCVA by ETDRS
  - VF-14 questionnaire
  - Corneal verticillata grading using a published grading scale for amiodarone-induced cornea verticillata (Orlando 1984)
  - Time to corneal verticillata resolution/stabilization

Corneal Verticillata Grading (Orlando 1984)

Grade	Description of Grade
Grade 1	The earliest changes are golden brown microdeposits in the epithelium just anterior to Bowman's membrane. These appear as a "dusting" of the cornea at the inferior pupillary margin in the mid-periphery. There is no fluorescein epithelial punctate staining, foreign body sensation, or other ocular symptoms.
Grade 2	The deposits become aligned in a more linear pattern and extend from the inferior pupillary margin towards the limbus. This gives the appearance much like that of a "cat's whisker." All patients had a clear zone between the margin of the deposits and the limbus.
Grade 3	The linear "filament-like" deposits seen in grade II increase in number and extend as branches from the inferior pupillary area into the visual axis. A whorled pattern is seen in the pupillary axis of the cornea.
Grade 4	Grade 3 with irregularly round "clumps" of golden-brown deposits.

Study AR-13324-OBS01

- Corneal verticillata were graded at Visit 1 and at all monthly/bi-monthly follow-up visits.

- Note that subjects were followed until corneal verticillata resolved in both eyes; therefore, an eye considered resolved at a prior visit was re-evaluated if corneal verticillata remained in the fellow eye.

Study AR-13324-OBS01

- All corneal verticillata cases reported in AR-13324-CS301 were resolved by the time AR-13324-OBS01 was initiated. Hence, no subjects from AR-13324-CS301 were enrolled.

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

	Netarsudil 0.02% QD N=25	Netarsudil 0.02% BID N=20
Have Corneal Verticillata at Study Entry		
OD only	0	0
OS only	0	0
OU	15	4
None	10	16
Duration of Investigation Product Prior to Start of Verticillata (Days) -OD		
Mean	166.0	110.0
Range	40, 368	41, 268
Duration of Investigation Product Prior to Start of Verticillata (Days) -OS		
Mean	165.2	108.6
Range	40, 368	41, 268

Study AR-13324-OBS01: Mean Change From Baseline (Visit 1) in Corneal Deposit Grading

Visit	Number of Eyes	Mean Improvement in Corneal Deposit Grading Score Compared to Visit 1	Number of Eyes With Ongoing Corneal Verticillata	Mean Improvement in Corneal Deposit Grading Score Compared to Visit 1
Visit 3	34	-0.47	25	-0.20
Visit 4	26	-0.35	25	-0.28
Visit 5	26	-0.73	19	-0.26
Visit 6	20	-1.40	5	-0.20
Visit 7	6	-0.83	4	-0.75
Visit 8	4	-1.00	2	-1.00

Study AR-13324-OBS01:
Mean Change From Baseline (Visit 1) in Visual Acuity

	Netarsudil 0.02% QD N=25		Netarsudil 0.02% BID N=20	
	Value	Change From Baseline	Value	Change From Baseline
Visit 2				
N (Eyes)	28	28	8	8
Mean	0.084	0.018	-0.38	-0.033
Range	-0.20, 0.32	-0.20, 0.20	-0.20, 0.10	-0.14, 0.08
Final Visit: After Resolution/Stabilization of Corneal Verticillata				
N (Eyes)	24	24	8	8
Mean	0.020	-0.0388	0.003	0.008
Range	-0.26, 0.32	-0.26, 0.22	-0.18, 0.16	-0.10, 0.10
Change From V2 to Final Visit				
N (Eyes)	24		8	
Mean	-0.063		0.040	
Range	-0.30, 0.14		-0.04, 0.12	

Study AR-13324-OBS01: Time From Corneal Verticillata Start to Resolution/Stabilization by Treatment Group

	Netarsudil 0.02% QD N=25	Netarsudil 0.02% BID N=20
N (Eyes)	26	8
Mean Time in Days to Corneal Verticillata Resolved/ Stabilized (sd)	496.7 (117.47)	517.0 (145.17)
Range (Min, Max)	302, 774	329, 712

Study AR-13324-OBS01: Time From Last Dose to Resolution/Stabilization by Treatment Group

	Netarsudil 0.02% QD N=25	Netarsudil 0.02% BID N=20
N (Eyes)	26	8
Mean Time From Last Dose in Days to Corneal Verticillata Resolution/Stabilization (sd)	317.2 (92.96)	419.0 (152.54)
Range (Min, Max)	189, 537	255, 631

Discontinuations

Study	Number of Patients in Netarsudil Group With Corneal Verticillata	Number of Patients With Corneal Verticillata That Discontinued Treatment
AR-13324-CS301	11	0
AR-13324-CS302	64 in QD group 64 in BID dosing group	13/64 (20%) in QD group 24/64 (38%) in BID group
AR-13324-CS304	86	14/86 (16%)

Corneal Verticillata

- At the completion of Study AR-13324-OBS01, corneal verticillata resolved in all subjects except for 3 subjects (4 out of the 6 eyes) where cornea verticillata remained stabilized but unresolved.

Study AR-13324-OBS01
Subjects Whose Corneal Verticillata Did Not Resolve

Patient/ Treatment Group	Corneal Verticillata Grade at Visit 1	Corneal Verticillata Grade at Stabilization	Treatment Duration (Days)	Comments
226-006 Netarsudil QD	OD-1 OS-2	OD-0 OS-1	357	This subject used concomitant medication Advil
263-001 Netarsudil QD	OD-2 OS-1	OD-1 OS-0	364	
263-002 Netarsudil BID	OD-1 OS-2	OU-1	124	This subject used concomitant medication naproxen

Points for Advisory Committee Consideration

- **VOTE #1 :** Do the clinical trials support the efficacy of netarsudil ophthalmic solution for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension?

  If no, what additional trials would you recommend?

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

  If no, what additional trials would you recommend?

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

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