Table 192024-009-01 – Discontinued Patients and Reason Continued

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 BID 4 days	0169	A25	Adverse event – conj hyperemia, eye dryness
AGN 192024 BID 2 days	0169	A30	Adverse event – epiphora, foreign body sensation, eye pain, photophobia
AGN 192024 BID 11 days	0296	Z05	Adverse event – conj hyperemia, foreign body sensation
AGN 192024 BID 37 days	0296	Z11	Other – patient unhappy with perceived side effects
AGN 192024 BID 54 days	0359	B53	Non-compliance – dosing OS only
AGN 192024 BID 20 days	0526	M09	Personal reasons
AGN 192024 BID 21 days	1584	J08	Adverse event – epiphora, conj hyperemia, eye pruritus
AGN 192024 BID 81 days	1584	J22	Personal reasons – no time to continue study
AGN 192024 BID 11 days	1634	K18	Adverse event – conj hyperemia, burning sensation in eye
AGN 192024 BID 33 days	1634	K19	Adverse event – foreign body sensation
AGN 192024 BID 6 days	1634	K58	Adverse event – conj hyperemia, eye pain, eye pruritus, photophobia
AGN 192024 BID 89 days	2005	W16	Adverse event – skin hypertrophy, growth of eyelashes
AGN 192024 BID 70 days	2005	W23	Adverse event – VF defect
AGN 192024 BID 5 days	2005	W24	Adverse event – allergic conjunctivitis, eye pain
AGN 192024 BID 18 days	2450	B26	Adverse events – conj hyperemia, photophobia
AGN 192024 BID 3 days	2666	T09	Adverse event – conj hyperemia, eye pruritus
AGN 192024 BID 5 days	2710	L60	Adverse event – conj hyperemia
AGN 192024 BID 27 days	2955	P13	Adverse event – conj hyperemia
AGN 192024 BID 84 days	2957	D03	Adverse event – conj hemorrhage
AGN 192024 BID 82 days	2957	D10	Adverse event – coronary artery disorder
AGN 192024 BID 14 days	2957	D15	Adverse event – allergic conjunctivitis
AGN 192024 BID 32 days	2958	H06	Subject relocated
AGN 192024 BID ? days	2991	D52	Lost to follow-up – unable to attend visits due to new job
AGN 192024 BID 14 days	3185	J69	Adverse event – headache, conj hyperemia, eye pruritus, eye pain
AGN 192024 BID 15 days	3209	C57	Personal reasons

Table 192024-009-01 – Discontinued Patients and Reason Continued

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 BID 58 days	3219	M67	Lack of efficacy
TIM BID 43 days	2008	S04	Adverse event – conj hyperemia, conj edema
TIM BID 50 days	2666	T15	Adverse event – chest pain
TIM BID 15 days	2710	L19	Adverse event – accidental injury (MVA)
TIM BID 92 days	2710	L36	Lack of efficacy

Reviewer's Comments:

Subject 0526-M09 (AGN192024 BID) is listed in the preceding table as discontinuing the trial for personal reasons. The exit CRF states the subject was unhappy with medication side effects (redness, itching, discharge, and lid discoloration).

Of the 596 patients enrolled in the study, 591 were included in the per-protocol analysis of the primary efficacy objective. All patients (596) were included in the ITT analysis and in the presentation of safety results.

Table 192024-009-02 – Number of Patients Included in the ITT, PP, and Safety Populations

Population	AGN 192024 QD	AGN 192024 BID	Timolol	All
ITT	234	243	119	596
Per-protocol	233	241	117	591
Safety	234	243	119	596

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown on the next page in **Table 192024-009-03**.

Reviewer's Comments:

As noted in Protocol 192024-008, the demographic statistics for all randomized patients found in **Table 192024-009-03** *only list the entry diagnoses of glaucoma, ocular hypertension, or mixed diagnosis. The diagnosis of glaucoma is not broken down by* type.

Table 192024-009-03– Demographic Statistics for
All Randomized Patients
$N_{AGN\ QD} = 234$, $N_{AGN\ BID} = 243$, $N_{TIM} = 119$

	Age				
	Mean	Std	N	Min	Max
Treatment					
AGN 192024 QD	63	13	234	26	92
AGN 192024 BID	62	12	243	32	91
Timolol	62	11	119	36	83

	Treatment Group					
	AGN 192024 QD		AGN 192024 BID		Timolol	
	N	%	N	%	N	%
Sex						
Male	98	42	117	48	47	40
Female	136	58	126	52	72	60
Age Class						
< 45 yrs	23	10	21	9	9	8
45 - 65 yrs	90	39	117	48	58	49
> 65 yrs	121	52	105	43	52	44
Race						
Caucasian	177	76	180	74	88	74
Black	47	20	45	19	20	17
Asian	6	3	12	5	4	3
Hispanic	4	2	5	2	6	5
Other	0	0	1	< 1	1	1
Black	47	20	45	19	20	17
Non-Black	187	80	198	81	99	83
Iris Color						
Light	121	52	129	53	64	54
Dark	113	48	114	47	55	46
Ophthalmic Diagnosis						
Glaucoma	147	63	148	61	78	66
Ocular Hypertension	85	36	92	38	41	34
Mixed	2	1	3	1	0	0

Table 192024-009-04 – Mean IOP Values at Each Timepoint at Baseline (ITT-LOCF)

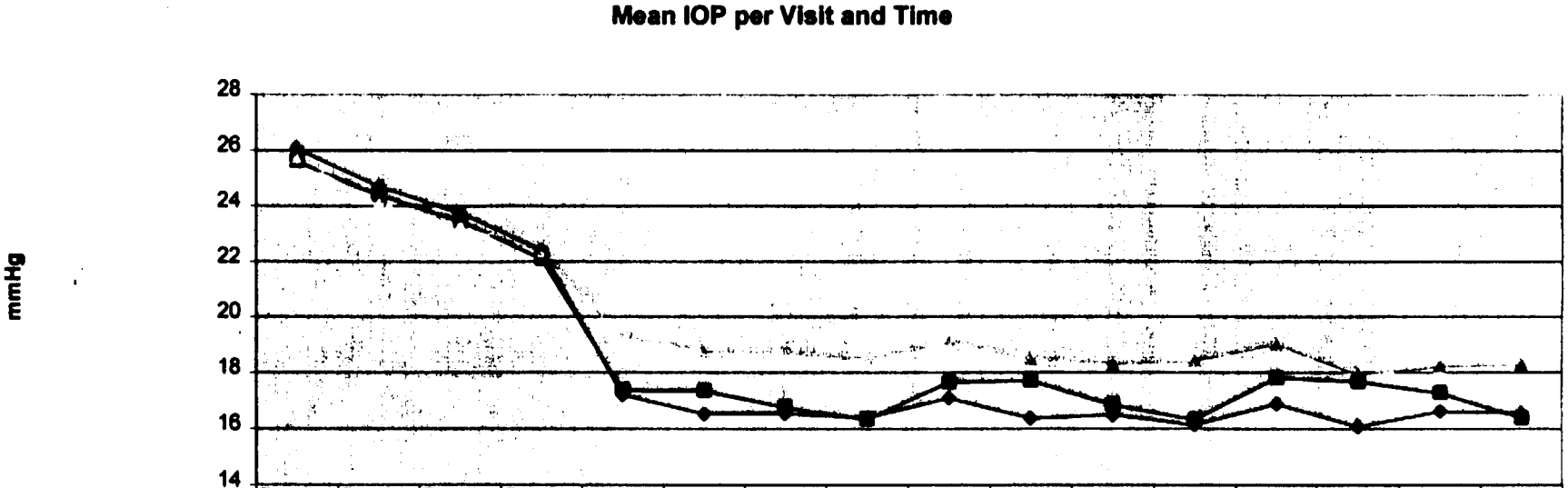
Timepoint	AGN 192024 QD	AGN 192024 BID	TIM
Hour 0	26.05	25.59	25.71
Hour 2	24.70	24.39	24.11
Hour 8	23.73	23.44	23.30
Hour 12 (selected sites)	22.38	22.06	22.32

Reviewer's Comments:

There are no statistically significant differences in Baseline IOP between the treatment groups at any timepoint.

8.1.2 Efficacy – Protocol 192024-009 Intent-to-Treat Population (LOCF)

Primary Efficacy Variable

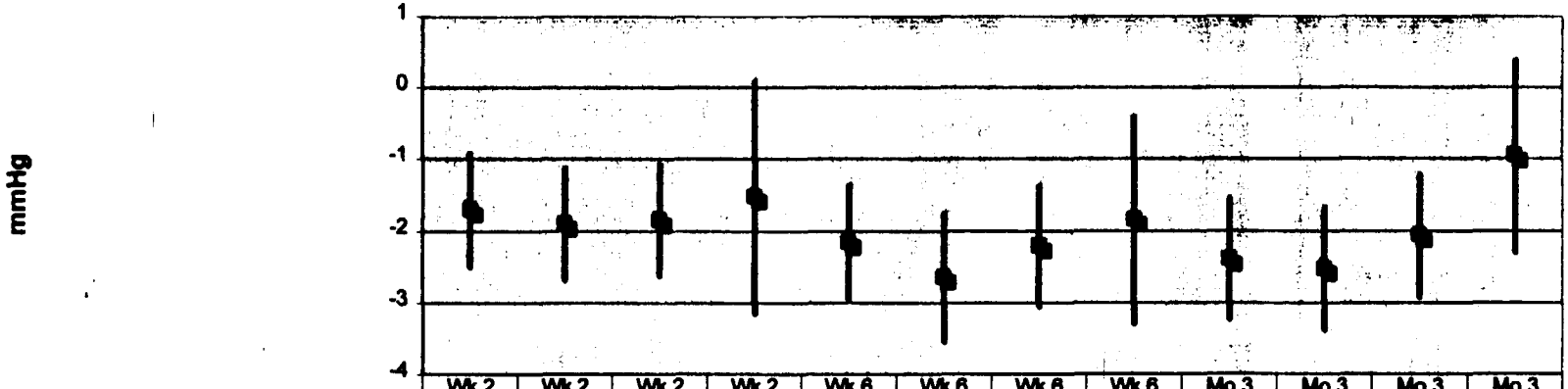


	Baseline Hour 0	Baseline Hour 2	Baseline Hour 8	Baseline Hour 12	Wk 2 Hour 0	Wk 2 Hour 2	Wk 2 Hour 8	Wk 2 Hour 12	Wk 6 Hour 0	Wk 6 Hour 2	Wk 6 Hour 8	Wk 6 Hour 12	Mo 3 Hour 0	Mo 3 Hour 2	Mo 3 Hour 8	Mo 3 Hour 12
AGN 192024 QD	26.05	24.7	23.73	22.38	17.2	16.52	16.53	16.39	17.1	16.37	16.48	16.14	16.89	16.08	16.62	16.54
AGN 192024 BID	25.59	24.39	23.44	22.06	17.36	17.34	16.76	16.33	17.65	17.71	16.84	16.32	17.81	17.67	17.26	16.38
Timolol BID	25.71	24.11	23.3	22.32	19.18	18.7	18.7	18.38	19.08	18.46	18.29	18.4	18.97	17.93	18.2	18.27

Reviewer's Comments:

Mean IOPs per visit and time are lower for AGN 192024 0.03% QD than for timolol 0.5% BID at all measured timepoints beginning at Week 2. Hour 12 IOP measurements are inadequately powered to establish equivalence due to small sample size.

Mean Difference (AGN 192024 QD - Timolol) in Mean Values at Each Timepoint with 95% Confidence Intervals

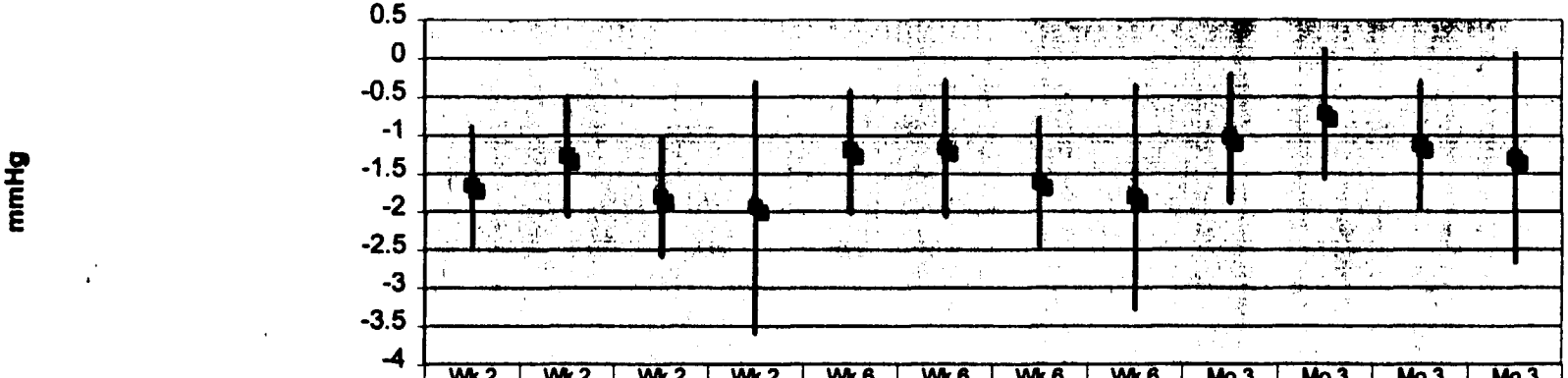


	Wk 2 Hour 0	Wk 2 Hour 2	Wk 2 Hour 8	Wk 2 Hour 12	Wk 6 Hour 0	Wk 6 Hour 2	Wk 6 Hour 8	Wk 6 Hour 12	Mo 3 Hour 0	Mo 3 Hour 2	Mo 3 Hour 8	Mo 3 Hour 12
Lower CI	-2.5	-2.69	-2.63	-3.15	-2.97	-3.55	-3.06	-3.29	-3.23	-3.38	-2.92	-2.3
Upper CI	-0.93	-1.13	-1.08	0.08	-1.36	-1.77	-1.38	-0.42	-1.57	-1.69	-1.23	0.38
Mean Difference (AGN QD - Timolol)	-1.71	-1.91	-1.86	-1.53	-2.17	-2.66	-2.22	-1.85	-2.4	-2.53	-2.07	-0.96

Reviewer's Comments:

When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% QD minus timolol 0.5% BID) is statistically significant at each remaining timepoint (i.e. confidence intervals do not cross 0).

Mean Difference (AGN 192024 BID - Timolol) in Mean Values at Each Timepoint with 95% Confidence Intervals

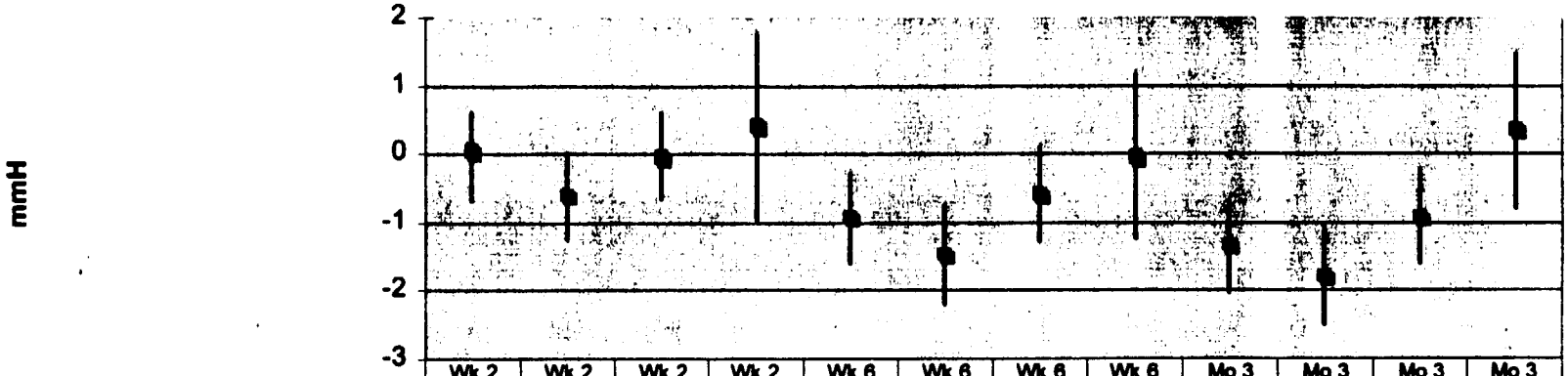


	Wk 2 Hour 0	Wk 2 Hour 2	Wk 2 Hour 8	Wk 2 Hour 12	Wk 6 Hour 0	Wk 6 Hour 2	Wk 6 Hour 8	Wk 6 Hour 12	Mo 3 Hour 0	Mo 3 Hour 2	Mo 3 Hour 8	Mo 3 Hour 12
Lower CI	-2.45	-2.06	-2.59	-3.59	-2.02	-2.06	-2.45	-3.28	-1.88	-1.57	-1.98	-2.67
Upper CI	-0.9	-0.51	-1.06	-0.32	-0.43	-0.31	-0.8	-0.36	-0.23	0.11	-0.31	0.05
Mean Difference (AGN BID - Timolol)	-1.67	-1.29	-1.82	-1.95	-1.22	-1.18	-1.63	-1.82	-1.05	-0.73	-1.14	-1.31

Reviewer's Comments:

When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% BID minus timolol 0.5% BID) is statistically significant at eight out of nine remaining timepoints (i.e. confidence intervals do not cross 0).

Mean Difference (AGN 192024 QD - AGN 192024 BID) in Mean Values at Each Timepoint with 95% Confidence Intervals

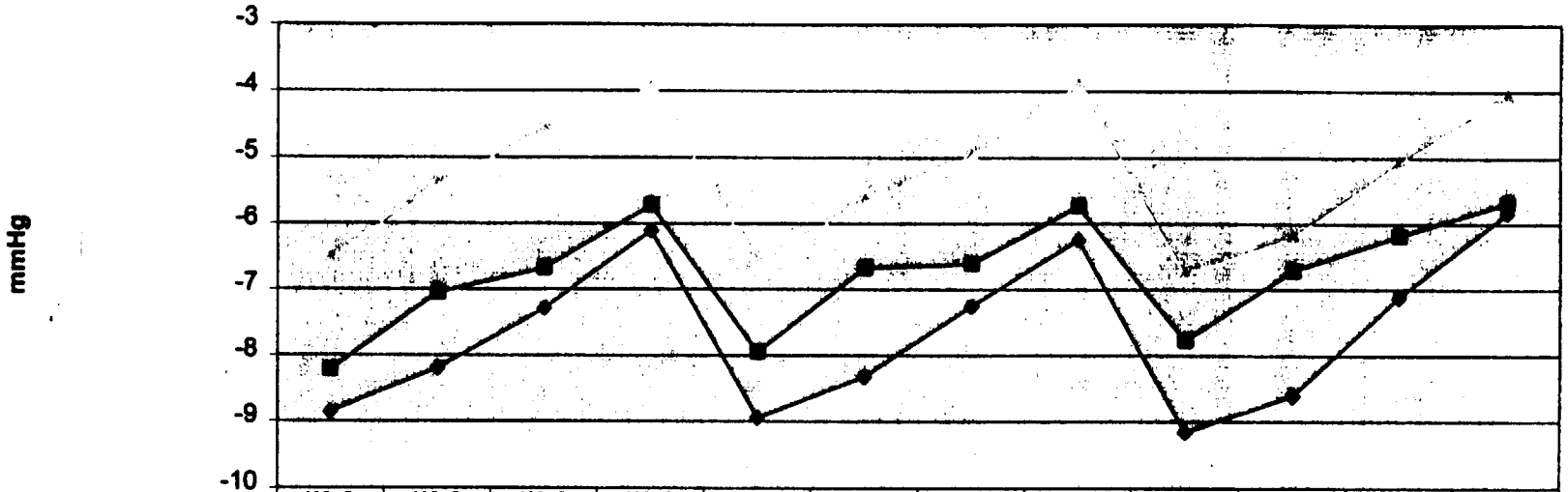


	Wk 2 Hour 0	Wk 2 Hour 2	Wk 2 Hour 8	Wk 2 Hour 12	Wk 6 Hour 0	Wk 6 Hour 2	Wk 6 Hour 8	Wk 6 Hour 12	Mo 3 Hour 0	Mo 3 Hour 2	Mo 3 Hour 8	Mo 3 Hour 12
Lower CI	-0.68	-1.26	-0.66	-0.95	-1.59	-2.2	-1.27	-1.23	-2.03	-2.49	-1.61	-0.79
Upper CI	0.59	0.01	0.6	1.78	-0.29	-0.76	0.09	1.17	-0.68	-1.12	-0.25	1.48
Mean Difference (AGN QD - AGN BID)	0.04	-0.62	-0.03	0.42	-0.94	-1.48	-0.59	-0.03	-1.35	-1.8	-0.93	0.35

Reviewer's Comments:

When Hour 12 measurements are excluded, the mean difference in mean values (AGN 192024 0.03% QD minus AGN 192024 0.03% BID) is statistically significant at five out of nine remaining timepoints (i.e. confidence intervals do not cross 0).

Mean IOP Change From Baseline at Each Timepoint



	Wk 2 Hour 0	Wk 2 Hour 2	Wk 2 Hour 8	Wk 2 Hour 12	Wk 6 Hour 0	Wk 6 Hour 2	Wk 6 Hour 8	Wk 6 Hour 12	Mo 3 Hour 0	Mo 3 Hour 2	Mo 3 Hour 8	Mo 3 Hour 12
AGN 192024 QD	-8.86	-8.2	-7.29	-6.11	-8.95	-8.33	-7.26	-6.25	-9.16	-8.62	-7.12	-5.84
AGN 192024 BID	-8.22	-7.05	-6.68	-5.73	-7.95	-6.68	-6.61	-5.74	-7.78	-6.72	-6.19	-5.68
Timolol BID	-6.53	-5.41	-4.6	-3.94	-6.63	-5.64	-4.97	-3.9	-6.74	-6.18	-5.06	-4.06

Reviewer's Comments:

When Hour 12 measurements are excluded, AGN 192024 0.3% QD lowers IOP between 7 and 9 mmHg from baseline. AGN 192024 0.03% BID lowers IOP between 6 and 8 mmHg from baseline. Timolol 0.5% BID lowers IOP between 5 and 7 mmHg from baseline.

8.1.2 Safety

Adverse Events

Serious adverse events were reported for 3.0% (7/234) of patients treated with AGN 192024 QD, 2.1% (5/243) of patients treated with AGN 192024 BID, and 1.7% (2/119) of patients treated with timolol 0.5% BID.

Table 192024-009-05 – Serious Adverse Events

Treatment	Investigator	Patient	AE Code	Patient Disposition at Month 3
AGN 192024 0.03% OD	1485	E15	Syncope	Completed
	1584	J06	Arthralgia	Discontinued
	2005	W12	Angina Pectoris Acute Kidney Failure Infection Bronchitis	Completed
	2005	W18	Arteritis Glossitis	Discontinued
	2005	W22	Infection	Completed
	2710	L14	Cholecystitis	Completed
	3225	105	Syncope	Completed
AGN 192024 0.03% BID	1634	K38	Accidental Injury	Completed
	2005	W17	Headache	Completed
	2671	U-05	Epistaxis	Completed
	2710	L154	Atrial Arrhythmia	Completed
	2957	D10	Coronary Artery Disorder	Discontinued
Timolol 0.05% BID	2710	L19	Accidental Injury	Discontinued
	2956	N19	Cerebrovascular Accident	Completed

There were no deaths during the initial 3 months of the study.

The most common adverse event was conjunctival hyperemia, which was reported for 46.6% (109/234) of patients treated with AGN 192024 QD, 60.5% (147/243) of patients treated with AGN 192024 BID, and 11.8% (14/119) of patients treated with timolol.

Other ocular adverse events reported for at least 5 patients (≥ 2%) treated with either AGN 192024 QD or BID were growth of eyelashes, eye pruritus, eye pain, eyelid erythema, foreign body sensation, eye dryness, visual disturbance, burning sensation in eye, blepharal pigmentation, eye discharge, epiphora, photophobia, allergic conjunctivitis, and eyelid pruritus.

The most common non-ocular adverse events reported for at least 5 patients (≥ 2%) treated with either AGN 192024 QD or BID were infection (primarily colds and upper respiratory tract infections), headache, hypertension, and accidental injury (e.g. sprains and bruises).

Table 192024-009-06 – Number (%) of Patients with Adverse Events Reported by at Least 5 Patients (≥ 2%) in Either AGN 192024 Group

BODY SYSTEM Preferred Term	AGN 192024 QD (N = 234)	AGN 192024 BID (N = 243)	timolol (N = 119)	Among-group P-value[a]
BODY AS A WHOLE				
infection	13 (5.6%)	12 (4.9%)	3 (2.5%)	0.433
headache	7 (3.0%)	11 (4.5%)	4 (3.4%)	0.720[b]
accidental injury	6 (2.6%)	2 (0.8%)	1 (0.8%)	0.277[b]
CARDIOVASCULAR				
hypertension	6 (2.6%)	3 (1.2%)	2 (1.7%)	0.485[b]
SPECIAL SENSES (OCULAR)				
conjunctival hyperemia	109 (46.6%)	147 (60.5%)	14 (11.8%)	< 0.001
growth of eyelashes	60 (25.6%)	82 (33.7%)	2 (1.7%)	< 0.001
eye pruritus	21 (9.0%)	37 (15.2%)	4 (3.4%)	0.002
eye pain	13 (5.6%)	25 (10.3%)	5 (4.2%)	0.050
erythema eyelid	11 (4.7%)	8 (3.3%)	0 (0.0%)	0.030[b]
foreign body sensation	9 (3.8%)	24 (9.9%)	1 (0.8%)	< 0.001
eye dryness	9 (3.8%)	17 (7.0%)	2 (1.7%)	0.059
visual disturbance	9 (3.8%)	13 (5.3%)	4 (3.4%)	0.606
burning sensation in eye	8 (3.4%)	9 (3.7%)	11 (9.2%)	0.032
blepharal pigmentation	5 (2.1%)	11 (4.5%)	1 (0.8%)	0.139[b]
eye discharge	4 (1.7%)	8 (3.3%)	1 (0.8%)	0.308[b]
epiphora	4 (1.7%)	7 (2.9%)	2 (1.7%)	0.713[b]
photophobia	2 (0.9%)	15 (6.2%)	1 (0.8%)	0.001[b]
allergic conjunctivitis	1 (0.4%)	5 (2.1%)	1 (0.8%)	0.294[b]
eyelid pruritus	0 (0.0%)	8 (3.3%)	1 (0.8%)	0.008[b]

a Among-group p-value based on Pearson's chi-square test unless indicated otherwise.
b Among-group p-value based on Fisher's exact test.

Iris Color/Eyelash Assessment

234 subjects treated with AGN 192024 0.03% QD, 243 subjects treated with AGN 192024 0.03% BID, and 119 subjects treated with timolol 0.5% BID were assessed for potential iris color changes. Iris photographs were performed at Baseline (Day 0), Weeks 2 and 6, and Month 3 (and planned for Months 6, 9 and 12).

Investigators were instructed to note any ocular changes from Baseline (e.g. iris color, lashes, etc.) on the Adverse Event Form.

One patient receiving AGN 192024 BID (2846-Y01) was noted to have a darker iris OU (COSTART preferred term iris disorder) at the month 3 exam. The patient continued in the study.

Table 192024-009-07 – Summary of Specific Ocular Adverse Events by Severity and Percent of Patients

Adverse Event	Severity	AGN 192024 0.3% QD (N = 240)	AGN 192024 0.3% BID (N = 240)	Timolol 0.5% BID (N = 122)
Growth of eyelashes	Overall	60 (25.6%)	82 (33.7%)	2 (1.7%)
	Mild	54 (23.1%)	69 (28.4%)	1 (0.8%)
	Moderate	5 (2.1%)	10 (4.1%)	1 (0.8%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
	N/A*	1 (0.4%)	3 (1.2%)	0 (0.0%)
Eyelash discoloration	Overall	1 (0.4%)	4 (1.6%)	0 (0.0%)
	Mild	0 (0.0%)	2 (0.8%)	0 (0.0%)
	Moderate	0 (0.0%)	1 (0.4%)	0 (0.0%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
	N/A*	1 (0.4%)	1 (0.4%)	0 (0.0%)
Blepharal pigmentation	Overall	5 (2.1%)	11 (4.5%)	1 (0.8%)
	Mild	5 (2.1%)	10 (4.1%)	0 (0.0%)
	Moderate	0 (0.0%)	1 (0.4%)	1 (0.8%)
	Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)
	N/A*	0 (0.0%)	0 (0.0%)	0 (0.0%)

* N/A: not applicable for severity

Reviewer's Comments:

Changes in eyelash growth are consistent with an ocularly administered prostaglandin-type effect.

Laboratory Parameters

At baseline, there were no statistically significant differences among the 3 treatment groups for any hematology, chemistry, or urinalysis parameter.

Within-group changes from baseline to month 3 were statistically significant as follows: in the AGN 192024 QD group for hemoglobin, red blood cell count (RBC), mean corpuscular volume (MCV), urea nitrogen, creatinine, uric acid, calcium, cholesterol, and chloride; in the AGN 192024 BID group for hemoglobin, RBC, alkaline phosphatase, urea nitrogen, creatinine, uric acid, calcium, chloride, and bicarbonate; and in the timolol group for RBC, albumin, urea nitrogen, calcium, inorganic phosphorus, and sodium. These changes were generally small and were not clinically relevant.

Reviewer's Comments:

Agree. There does not appear to be a clinically significant difference between treatment groups in any of the hematology, chemistry, or urinalysis parameters evaluated.

Visual Acuity

Table 192024-009-08 – Visual Acuity Tabulated by Changes in Line Number Comparing Patient's Final Evaluation to Baseline[a]

Line Changes	HTL QD (N=234)	HTL BID (N=243)	TIM (N=119)
N	232	243	119
>= -2	16 (6.9%)	17 (7.0%)	6 (5.0%)
> -2 to <= -1	53 (22.8%)	55 (22.6%)	24 (20.2%)
> -1 to < 0	17 (7.3%)	24 (9.9%)	10 (8.4%)
0	104 (44.8%)	108 (44.4%)	64 (53.8%)
> 0 to < +1	14 (6.0%)	10 (4.1%)	6 (5.0%)
>= +1 to < +2	22 (9.5%)	26 (10.7%)	7 (5.9%)
>= +2	6 (2.6%)	3 (1.2%)	2 (1.7%)

[a] The final evaluation at or prior to month 3. Tabulation was based on the eye with worse change comparing to the fellow eye.

Cup/Disc Ratio

Table 192024-009-09 – Cup/Disc Ratio Change from Baseline[a]

Change from Baseline	HTL QD (N=234)	HTL BID (N=243)	TIM (N=119)
N	225	239	115
<= -0.2	3 (1.3%)	2 (0.8%)	4 (3.5%)
>= +0.2	4 (1.8%)	3 (1.3%)	5 (4.3%)

[a] The final evaluation at or prior to month 3. Tabulation was based on the eye with worse change compared to the fellow eye.

Reviewer's Comments:

There are no clinically significant differences in visual acuity or cup/disc ratio between treatment groups.

Biomicroscopy

An increase from the baseline severity of conjunctival erythema was reported for 34.2% (80/234) of patients in the AGN 192024 QD group, 39.9% (97/243) of patients in the AGN 192024 BID group, and 6.7% (8/119) of patients in the timolol group ($p < 0.001$).

Eyelash growth was reported for 10.7% (25/234) of patients in the AGN 192024 QD group, 16.9% (41/243) of patients in the AGN 192024 BID group, and 0.8% (1/119) of patients in the timolol group ($p < 0.001$).

An increase from the baseline severity of lid erythema was reported for 6.8% (16/234) of patients in the AGN 192024 QD group, 7.8% (19/243) of patients in the AGN 192024 BID group, and 0 patients in the timolol group ($p = 0.009$).

Pairwise comparisons of both AGN 192024 QD and BID versus timolol were statistically significant ($p \leq 0.004$) for each of these findings.

Conjunctival hyperemia/erythema and eyelash growth were reported more frequently as adverse events than noted on the biomicroscopy evaluations.

Reviewer's Comments:

Agree. Growth of eyelashes was reported more frequently as an adverse event than noted on biomicroscopy evaluations.

Note, however, the percentage of each treatment group reporting growth of eyelashes in **Table 192024-009-07**, *page 47.*

Laser Flare Meter Reading

Laser flare meter data were collected for a subset of 187 patients at selected centers. The laser flare meter readings at baseline ranged from 2.81 to 88.90 p/msec, and were similar across the 3 treatment groups.

Endothelial Cell Counts

Endothelial cell counts were collected for a subset of 217 patients at selected centers. The cell counts at baseline ranged from 1209.5 to 3308.5 cells, and were similar across the 3 treatment groups. There were no statistically significant within-group changes from baseline to month 3 in any treatment group.

Visual Fields

Patients' final visual fields mean deviation at or prior to month 3 was compared to baseline, based on the eye with the worst change. The changes from baseline in the

visual fields mean deviation ranged from –12.2 to +8.1 dB, and were similar across the 3 treatment groups (p = 0.607).

Patient 2005-W23 discontinued AGN 192024 BID after 70 days due to visual field defect. On fluorescein angiography a low-grade leak was seen in an area of preretinal fibrosis. The scotoma resolved following discontinuation of the study medication. No clinical macular edema was seen.

Reviewer's Comments:

There are no clinically significant differences in laser flare meter data, endothelial cell counts, or visual fields between treatment groups.

Heart Rate/Blood Pressure

Heart rate at baseline ranged from 48 to 110 bpm, and was similar across the 3 treatment groups. The mean changes from baseline were generally small with AGN 192024, ranging from –1.40 to +0.87 bpm, and not clinically relevant.

Systolic blood pressure at baseline ranged from 80 to 195 mm Hg, and was similar across the 3 treatment groups. The mean changes from baseline were generally small, ranging from –2.48 to –0.53 mm Hg, and not clinically relevant.

Diastolic blood pressure at baseline ranged from 48 to 110 mm Hg, and was similar across the 3 treatment groups. The mean changes from baseline were generally small, ranging from –1.28 to +0.48 mm Hg, and not clinically relevant.

Reviewer's Comments:

Agree. Mean changes from baseline in heart rate and blood pressure were not clinically significant with either AGN 192024 0.03% QD or BID.

8.1.2 Reviewer's Summary of Efficacy and Safety

AGN 192024 0.03% administered QPM did not demonstrate equivalence to AGN 192024 0.03% administered BID in the ability to lower intraocular pressure.

When Hour 12 measurements are excluded, AGN 192024 0.3% QD lowers IOP between 7 and 9 mmHg from baseline. AGN 192024 0.03% BID lowers IOP between 6 and 8 mmHg from baseline. Timolol 0.5% BID lowers IOP between 5 and 7 mmHg from baseline.

The IOP lowering ability of AGN 192024 0.03% (either QD or BID) is not superior to timolol 0.5% BID by a clinically significant amount.

Both AGN 192024 0.03% QD and BID regimens are associated with conjunctival hyperemia, at 47% and 61% respectively.

Changes in iris color may signal the ability of AGN 192024 to increase the number of melanosomes (pigment granules) in melanocytes. Changes in eyelash growth are consistent with an ocularly administered prostaglandin-type effect.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

8 Clinical Studies

8.1.3 Study #3 Protocol 192024-001

Title: A One Month, Investigator-masked, Parallel, Randomized, Safety and Efficacy Study of AGN 192024 0.003%, 0.01% and 0.03% Ophthalmic Solutions Compared to its (sic) Vehicle and Timolol 0.5%, in Subjects with Open-angle Glaucoma or Ocular Hypertension

Study Design: A single center, double-masked, randomized, parallel-group, active- and inactive-controlled comparison study.

Test Drug Schedule: The study coordinator instilled one drop of study medication into each subject's eye, twice daily, at twelve hour intervals (between 7:30 am and 9:30 am, and between 7:30 pm and 9:30 pm), for five and one-half days.

Because the medication was not preserved, a new bottle of medication was used at each instillation (i.e., two bottles per day).

Investigator Number	Investigator	Number Randomized
1438	Robert A. Laibovitz, M.D. Austin, Texas 78731 USA	60

8.1.3 Study Design

This study was a single-site, double-masked, evenly-randomized, parallel-group, active- and inactive-controlled comparison consisting of eight (8) scheduled visits. Following an appropriate washout period, sixty subjects with open-angle glaucoma or ocular hypertension were randomly assigned to one of the five treatment groups: AGN 192024 0.01%, 0.03%, 0.1%, vehicle or timolol 0.5%. Medications were instilled twice-daily for five and one-half days. Subjects were evaluated at Prestudy, Day 0 (Baseline), and Days 1, 2, 3, 5, 6, and 7 (24 hours post-instillation).

Intraocular pressure measurements were collected for each eye and analyzed as an average of both eyes.

The sole efficacy variable was intraocular pressure [change from Day 0 (Baseline) IOP]. This variable was evaluated by the investigator at Prestudy (prior to washout), Baseline (after washout) and at the appropriate follow-up visits during the treatment period.

Study Medications

Each identically masked bottle of test medication was coded with a shipment number and was labeled with the number of the subject to whom the bottle was assigned.

- AGN 192024 0.01% (Allergan formulation number 8765X):
- AGN 192024 0.03% (Allergan formulation number 8824X):
- AGN 192024 0.1% (Allergan formulation number 8766X):
- AGN 192024 vehicle (Allergan formulation number 8763X):
- Timolol maleate 0.5% ophthalmic solution (Allergan formulation number 6151X):

Study Population – Inclusion and Exclusion Criteria

Key Inclusion Criteria: Male or female subjects (females not of child-bearing potential), 21 years of age or older, with ocular hypertension or open-angle glaucoma in each eye; Day 0, hour 0 (post-washout) intraocular pressures (IOPs) of greater than or equal to 23 mm Hg and less than or equal to 34 mm Hg in each eye and between eye asymmetry of IOP not greater than 5 mm Hg; corrected visual acuity of 20/80 or better in each eye.

Key Exclusion Criteria: Any uncontrolled systemic disease; known allergy or sensitivity to the study medication; abnormally low or high heart rate or blood pressure for age; any contraindications to beta-blocker therapy; anticipated alteration during the study of existing chronic therapy with agents which could have a substantial effect on IOP; anticipated use of any topical dermatologic or systemic steroids during the study; glaucomas other than primary, pseudoexfoliative or pigmentary (including lens induced and chronic angle closure); functional vision in only one eye.

Safety Measures

Ocular and systemic safeties were determined from adverse event reports, biomicroscopy, ophthalmoscopy, visual acuity, heart rate/blood pressure, and visual field data.

Table 192024-001-01 – Schedule of Assessments for Protocol 192024-001

Visit #/ Day	Time	Pupil Size/ IOP/ Heart Rate/ Blood Pressure	Biomi-croscopy/ Visual Acuity	Subjective Assessment of Study Med	Ophthal-moscopy †	Study Med Instillation (immediately following examination)	Visual Field	CRFs to be completed
1 Prestudy*	Hour 0	X	X		X		X	D,E
WASHOUT PERIOD (if necessary) OR WAITING PERIOD								
2 (Day 0-baseline)	Hour 0	X	X					D,E
	Hour 1	X						D,E
	Hour 2	X						D,E
	Hour 4	X						D,E
	Hour 6	X						D,E
	Hour 12	X						D,E
3 (Day 1)	Hour -0.5	X						D,E
	Hour 0		X	X§		X	X	
	1-5 mins		X	X				D,E
	20-30 mins		X	X				D,E
	Hour 1	X	X	X				D,E
	Hour 2	X						D,E
	Hour 4	X						D,E
	Hour 6	X	X	X				D,E
	Hour 12	X		X		X	X	D,E
4 (Day 2)	Hour 0	X	X	X		X	X	D,E
	Hour 12					X	X	
5 (Day 3)	Hour 0	X	X	X		X	X	D,E
	Hour 12					X	X	
6 (Day 5)	Hour 0	X	X	X		X	X	D,E
	Hour 12					X	X	
7 (Day 6)	Hour -0.5	X		X				D,E
	Hour 0		X			X	X	
	1-5 mins		X	X				D,E
	20-30 mins		X	X				D,E
	Hour 1	X	X	X				D,E
	Hour 2	X						D,E
	Hour 4	X						D,E
	Hour 6	X	X	X				D,E
	Hour 12	X		X		No Instillation	No Instillation	D,E
8 (Day 7)	Hour 0 (24 hours following final instillation)	X	X	X	X			D,E,X

Key to Abbreviations:
CRF = Case Report Form(s) to be completed
IOP = Intraocular Pressure
* = Prestudy History including a complete medical and ophthalmological history, visual field and informed consent.
† = Ophthalmoscopy will be performed 30 minutes or more after the IOP measurement has been taken.
§ = Subjective evaluation of ocular and general comfort (pre-instillation)

Subject Disposition and Demographics

All enrolled subjects completed the study as planned.

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown on the next page in **Table 192024-001-02.**

Table 192024-001-02– Demographic Statistics for
All Randomized Patients
$N_{AGN\ 0.01\%} = 12$, $N_{AGN\ 0.03\%} = 12$, $N_{AGN\ 0.1\%} = 12$, $N_{TIM} = 12$, $N_{VEH} = 12$

	Age				
	Mean	SE	N	Min	Max
Treatment					
AGN 192024 0.01%	56	2.8	12	40	72
AGN 192024 0.03%	63	2.8	12	44	79
AGN 192024 0.1%	61	2.3	12	48	79
Timolol 0.5%	64	2.9	12	48	79
Vehicle	55	3.4	12	31	69

	Treatment Group									
	AGN 0.01%		AGN 0.03%		AGN 0.1%		Timolol		Vehicle	
	N	%	N	%	N	%	N	%	N	%
Sex										
Male	4	33	4	33	4	33	3	25	5	42
Female	8	67	8	67	98	67	9	75	7	58
Age Class										
< 45 yrs	1	8	1	8	0	0	0	0	2	17
45 - 65 yrs	9	75	6	50	10	83	7	58	7	58
> 65 yrs	2	17	5	42	2	17	5	42	3	25
Race										
Caucasian	10	83	8	67	11	92	9	75	11	92
Non-Caucasian	2	17	4	33	1	8	3	25	1	8
Iris Color										
Light	5	42	7	58	9	75	6	50	4	33
Dark	7	58	5	42	2	25	6	50	8	67
Ophthalmic Diagnosis										
POAG	1	8	1	8	0	0	0	0	1	8
Ocular Hypertension	11	92	11	92	12	100	12	100	10	83
Mixed	0	0	0	0	0	0	0	0	1	8

Table 192024-001-03 – Mean IOP Values at Each Timepoint at Baseline (Day 0)

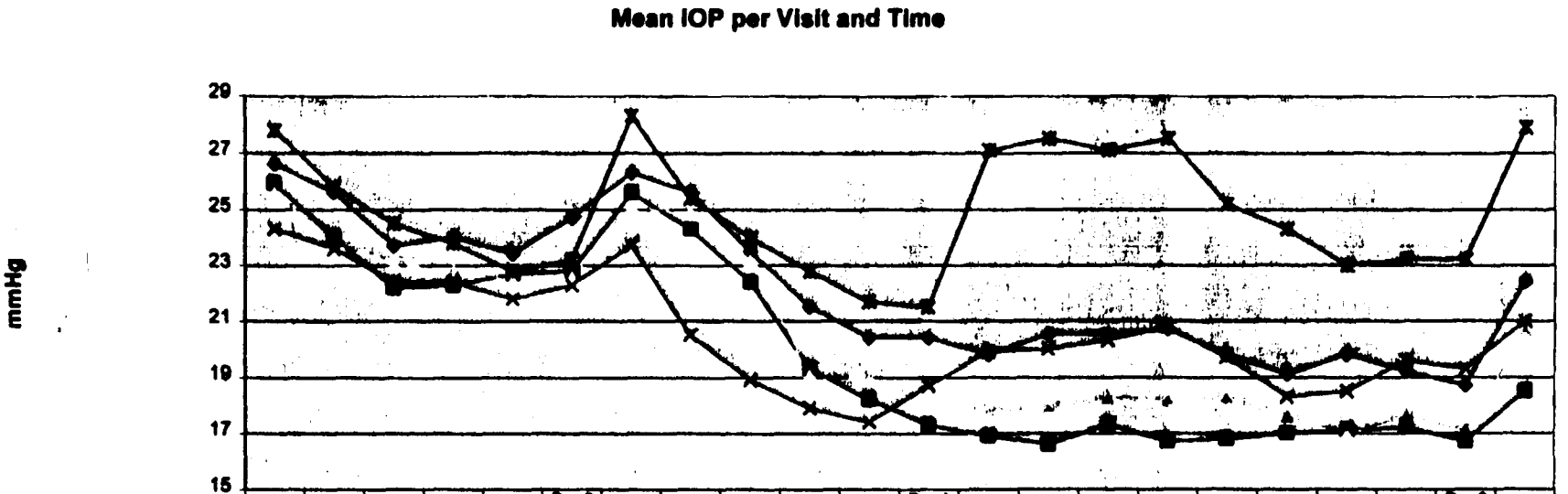
Timepoint	AGN 192024 0.01%	AGN 192024 0.03%	AGN 192024 0.1%	TIM	Vehicle
Hour 0	26.58	25.88	25.58	24.25	27.79
Hour 1	25.63	24.00	23.75	23.63	25.83
Hour 2	23.71	22.17	23.08	22.42	24.5
Hour 4	23.96	22.29	22.83	22.38	23.83
Hour 6	23.38	22.67	22.46	21.83	22.79
Hour 12	24.71	22.75	22.63	22.25	23.21

Reviewer's Comments:

There are no statistically significant differences in Baseline IOP between the treatment groups at any timepoint.

8.1.3 Efficacy – Protocol 192024-001

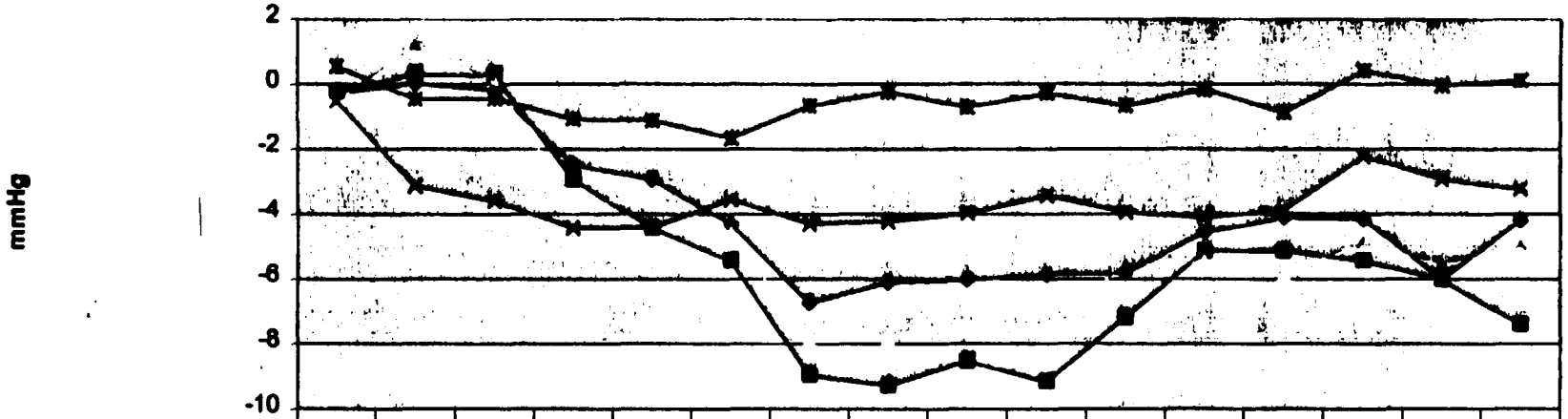
Primary Efficacy Variable



	Day 0 Hour 0	Day 0 Hour 1	Day 0 Hour 2	Day 0 Hour 4	Day 0 Hour 8	Day 0 Hour 12	Day 1 Hour 0	Day 1 Hour 1	Day 1 Hour 2	Day 1 Hour 4	Day 1 Hour 8	Day 1 Hour 12	Day 2 Hour 0	Day 3 Hour 0	Day 5 Hour 0	Day 6 Hour 0	Day 6 Hour 1	Day 6 Hour 2	Day 6 Hour 4	Day 6 Hour 8	Day 6 Hour 12	Day 7 Hour 0
AGN 192024 0.01%	26.6	25.6	23.7	24	23.4	24.7	26.3	25.6	23.5	21.5	20.4	20.4	19.8	20.5	20.5	20.7	19.8	19.1	19.8	19.2	18.7	22.4
AGN 192024 0.03%	25.9	24	22.2	22.3	22.7	22.8	25.6	24.3	22.4	19.3	18.2	17.3	16.9	16.6	17.3	16.7	16.8	17	17.1	17.2	16.7	18.5
AGN 192024 0.1%	25.6	23.8	23.1	22.8	22.5	22.6	25.1	24.9	23.2	19.1	19	18	17.7	17.8	18.2	18.1	18.2	17.6	17	17.6	17.1	20.6
Timolol	24.3	23.6	22.4	22.4	21.8	22.3	23.7	20.5	18.9	17.9	17.4	18.7	19.9	20	20.3	20.8	19.7	18.3	18.5	19.6	19.3	21
Vehicle	27.8	25.8	24.5	23.8	22.8	23.2	26.3	25.4	24	22.8	21.7	21.5	27.1	27.5	27.1	27.5	25.2	24.3	23	23.2	23.2	27.9

Reviewer's Comments: *This study is limited by its short duration and limited number of patients. AGN 192024 0.03% BID produced the lowest mean IOPs and demonstrated the greatest IOP lowering efficacy compared to the AGN 192024 0.01% and 0.1% formulations. Because the peak effect of AGN 192024 is approximately twelve (12) hours after administration, timolol produced lower IOPs than AGN 192024 0.03% until the Hour 12 timepoint on Day 1.*

Mean IOP Change From Baseline at Each Timepoint



	Day 1 Hour 0	Day 1 Hour 1	Day 1 Hour 2	Day 1 Hour 4	Day 1 Hour 8	Day 1 Hour 12	Day 2 Hour 0	Day 3 Hour 0	Day 5 Hour 0	Day 6 Hour 0	Day 6 Hour 1	Day 6 Hour 2	Day 6 Hour 4	Day 6 Hour 8	Day 6 Hour 12	Day 7 Hour 0
AGN 192024 0.01%	-0.29	0	-0.21	-2.5	-2.96	-4.33	-6.75	-6.13	-6.04	-5.88	-5.83	-4.58	-4.13	-4.17	-6.04	-4.21
AGN 192024 0.03%	-0.25	0.29	0.25	-2.96	-4.46	-5.46	-8.96	-9.29	-8.54	-9.17	-7.21	-5.17	-5.17	-5.46	-6.04	-7.42
AGN 192024 0.1%	-0.5	1.17	0.13	-3.71	-3.5	-4.58	-7.88	-7.79	-7.38	-7.46	-5.54	-5.46	-5.79	-4.88	-5.54	-5
Timolol	-0.54	-3.17	-3.63	-4.46	-4.46	-3.58	-4.33	-4.25	-4	-3.46	-3.96	-4.13	-3.92	-2.25	-2.96	-3.25
Vehicle	0.54	-0.46	-0.46	-1.08	-1.13	-1.67	-0.67	-0.25	-0.71	-0.29	-0.67	-0.17	-0.88	0.42	-0.04	0.13

Reviewer's Comments: *AGN 192024 0.03% appears to be at the top of the dose-response curve.*

8.1.3 Safety

Adverse Events

No serious adverse events occurred during the study. All subjects completed the study as planned. No subjects were discontinued due to adverse events.

Ocular and/or systemic adverse occurred in 75.0% (9/12) of subjects in the 0.01% group, 66.7% (8/12) of subjects in the 0.03% group, 100% (12/12) of subjects in the 0.1% group, 58.3% (7/12) of subjects in the timolol group, and 25.0% (3/12) of subjects in the vehicle group. The only significant between-group difference in adverse event incidence was for conjunctival erythema. The number of subjects with conjunctival erythema was significantly greater in the 0.1% group compared with the 0.01%, timolol and vehicle groups.

Table 192024-001-04 – Number (%) of Patients with Adverse Events Regardless of Causality Reported by at Least 2 Patients in Any AGN 192024 Group

BODY SYSTEM Preferred Term	AGN 192024 0.01% (N = 12)	AGN 192024 0.03% (N = 12)	AGN 192024 0.1% (N = 12)	timolol (N = 12)	vehicle (N = 12)	Among-group P-value[a]
OVERALL	9 (75.0)	8 (66.7)	12 (100)	7 (58.3)	3 (25.0)	--
BODY AS A WHOLE						
fatigue/drowsiness	0 (0.0)	2 (16.7)	1 (8.3)	2 (16.7)	0 (0.0)	0.537
headache	3 (25.0)	1 (8.3)	4 (33.3)	0 (0.0)	0 (0.0)	0.050
other systemic[b]	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.186
DIGESTIVE						
gastrointestinal symptoms[c]	1 (8.3)	1 (8.3)	4 (33.3)	2 (16.7)	0 (0.0)	0.234
RESPIRATORY						
upper respiratory infection	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.495
SPECIAL SENSES (OCULAR)						
burning/stinging eye	2 (16.7)	0 (0.0)	2 (16.7)	2 (16.7)	0 (0.0)	0.336
conjunctival hyperemia	1 (8.3)	6 (50.0)	8 (66.7)	2 (16.7)	1 (8.3)	0.003
dry eye	1 (8.3)	2 (16.7)	4 (33.3)	1 (8.3)	0 (0.0)	0.234
epiphora	0 (0.0)	0 (0.0)	3 (25.0)	0 (0.0)	0 (0.0)	0.032
foreign body sensation	1 (8.3)	1 (8.3)	2 (16.7)	0 (0.0)	0 (0.0)	0.787
pain eye	1 (8.3)	3 (25.0)	2 (16.7)	0 (0.0)	0 (0.0)	0.278
photophobia	1 (8.3)	1 (8.3)	3 (25.0)	0 (0.0)	0 (0.0)	0.250
pruritus eye	0 (0.0)	2 (16.7)	3 (25.0)	0 (0.0)	0 (0.0)	0.076

a Among-group p-value based on Fisher's exact test.
b One report of sweating and one report of nasal burning
c Gastrointestinal symptoms included diarrhea, nausea, and abdominal pain

Biomicroscopy

The only statistically significant slit-lamp finding reported by the investigator was conjunctival erythema. Subjects began to show increases in conjunctival erythema at Day 1 Hour 6. This increase in incidence was significant ($p = 0.001$) starting on Day 1 Hour 6, and continuing to the end of the study. The 0.03% and 0.1% groups had significantly greater increases from baseline conjunctival erythema than did the vehicle group.

Cup/Disc Ratio

There were no significant among-group differences or within-group changes from baseline during the study. No subjects had a clinically significant change in cup/disc ratio.

Visual Acuity

Changes in visual acuity from baseline were not felt to be clinically significant and there were no significant between-group differences.

Reviewer's Comments:

There are no clinically significant differences in cup/disc ratio or visual acuity between treatment groups.

Heart Rate/Blood Pressure

Baseline heart rates were similar among the five treatment groups ranging from 74.17 bpm to 85.42 bpm. Overall, mean heart rate remained relatively unchanged in the AGN 192024 treatment groups during the study.

Baseline systolic blood pressures were similar among the five treatment groups ranging from 130.08 mm Hg to 144.75 mm Hg. There were no significant among-group differences in mean decrease for systolic blood pressure.

Overall diastolic blood pressure remained unchanged in all five treatment of the groups.

Reviewer's Comments:

Agree. Mean changes from baseline in heart rate and blood pressure were not clinically significant in the AGN 192024 treatment groups.

8.1.3 Reviewer's Summary of Efficacy and Safety

This study is limited by its short duration and limited number of patients.

AGN 192024 0.03% BID produced the lowest mean IOPs and demonstrated the greatest IOP lowering efficacy compared to the AGN 192024 0.01% and 0.1% formulations.

AGN 192024 0.03% appears to be at the top of the dose-response curve.

AGN 192024 0.01% BID, AGN 192024 0.03% BID, and AGN 192024 0.1% BID regimens are associated with conjunctival hyperemia, at 8%, 50%, and 67% respectively.

APPEARS THIS WAY
ON ORIGINAL

8 Clinical Studies

8.1.4 Study #4 Protocol 192024-002

Title: A One Month, Investigator-Masked, Parallel, Randomized, Safety and Efficacy Study of AGN 192024 0.003%, 0.01% and 0.03% Ophthalmic Solutions Compared to its (sic) Vehicle and Timolol 0.5%, in Subjects with Open-angle Glaucoma or Ocular Hypertension

Study Design: A single center, investigator-masked, parallel-group, active- and inactive-controlled comparison study.

Test Drug Schedule: AGN 192024 0.003%, 0.01%, 0.03% administered once-daily for three weeks, then twice-daily for one week; or AGN 192024 vehicle or timolol 0.5% administered twice-daily for four weeks. The study coordinator performed all evening dosing on the days prior to scheduled visits

Because the medication was not preserved, a new bottle of medication was used at each instillation (i.e., two bottles per day).

Investigator Number	Investigator	Number Randomized
1438	**Robert A. Laibovitz, M.D.** Austin, Texas 78731 USA	100

8.1.4 Study Design

This study was a single-site, investigator-masked, even-randomized, parallel-group, vehicle- and active-controlled comparison. Following an appropriate washout period, subjects with open-angle glaucoma or ocular hypertension were randomly assigned to receive either AGN 192024 0.003%, 0.01%, 0.03% administered once-daily for three weeks, then twice-daily for one week; or AGN 192024 vehicle or timolol 0.5% administered twice-daily for four weeks. Subjects were evaluated at Prestudy, Day 0 (baseline), and Days 3, 7, 14, 21, 23, 28 and 30 (48 hours post-instillation).

The sole efficacy variable was intraocular pressure [change from Day 0 (Baseline) IOP]. This variable was evaluated by the investigator at Prestudy (prior to washout), Baseline (after washout) and at the appropriate follow-up visits during the treatment period.

Study Medications

Each identically masked bottle of test medication was coded with a shipment number and was labeled with the number of the subject to whom the bottle was assigned.

- AGN 192024 0.003% (Allergan formulation number 8929X):
- AGN 192024 0.01% (Allergan formulation number 8765X):
- AGN 192024 0.03% (Allergan formulation number 8824X):
- AGN 192024 vehicle (Allergan formulation number 8763X):
- Timolol maleate USP 0.5% sterile ophthalmic solution (Allergan formulation number 6151X):

Study Population – Inclusion and Exclusion Criteria

Key Inclusion Criteria: Male or female subjects, 21 years of age or older; ocular hypertension, chronic open-angle glaucoma, pseudoexfoliative glaucoma, or pigmentary glaucoma in each eye; newly diagnosed or likely to be controlled on monotherapy; corrected visual acuity of 20/100 or better in each eye; post-washout (8 AM) IOPs of greater than or equal to 23 mm Hg and less then or equal to 34 mm Hg in each eye and asymmetry of IOP between the eyes not greater than 5 mm Hg; 8 PM IOP on Day 0 no more than 4 mm Hg higher than the 8 AM IOP.

Key Exclusion Criteria: Women who were of child-bearing potential; contraindications to beta-adrenergic receptor blocking therapy; anticipated alteration during the study of existing chronic therapy with agents which could have a substantial effect on IOP or substantial interaction with study medications or study outcomes; functionally significant visual field loss; intraocular or refractive surgery within the past year, or laser surgery within the past three months; previous participation in any study involving 192024.

Safety Measures

Ocular and systemic safeties were determined from adverse event reports, biomicroscopy, ophthalmoscopy, visual acuity, heart rate/blood pressure, visual field data, and pharmacokinetic sampling

Table 192024-002-01 – Schedule of Assessments for Protocol 192024-002

Day	Time*	IOP/ Heart Rate/ Blood Pressure/ Erythema†	Visual Acuity/ Biomicro-scopy	Laser Flaremeter§	Ophthal-moscopy	Visual Field	Blood Draw for PK**
Prestudy¶		X	X		X	X	
		washout period 2-28 days (if required) or waiting period					
Day 0	8 AM	X	X	X			
	Noon	X					
	4 PM	X					
	8 PM	X	X				X
		Instill medication immediately following the 8 PM exam and blood draw					
	8:30 PM						X
	10 PM	X	X				X
		To qualify, IOP at 8 AM must be ≥23 mm Hg and ≤34 mm Hg. At 8 PM, IOP must be no higher than 4 mm Hg above the 8 AM measurement					
Day 3††	8 AM	X	X	X			
Day 7	8 AM	X	X	X			
Day 14	8 AM	X	X	X			
	Noon	X					
	4 PM	X					
	8 PM	X					
Day 21	8 AM	X	X	X			
	Noon	X					
	4 PM	X					
	8 PM	X					X
	8:30 PM						X
	10 PM	X	X				X
		AGN active compounds dosed now: switch from QD dosing to BID dosing on Day 21					
Day 23	8 AM	X	X	X			
Day 28	8 AM	X	X	X			
		Last dose of study medications given after 8 AM exam					
	Noon	X					
	4 PM	X					
	8 PM	X					X
	8:30 PM						X
	10 PM	X	X				X
Day 30	8 AM	X	X	X	X		

*Time of examination = time ±30 minutes. All patients will have their visits at the same time during the study.
†Conjunctival erythema will be evaluated by gross inspection.
§Laser flare meter measurements must be performed prior to any pupil dilation
**Blood drawn from the first 15 subjects receiving active AGN 192024 concentrations [i.e. QD group]).
¶Includes written informed consent, and complete medical and ophthalmological history.
††Study coordinator will perform all PM dosing on the days prior to a scheduled visit (e.g., Days 2, 6, 13, 20, 22, and 27)

Subject Disposition and Demographics

All enrolled subjects completed the study as planned.

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown on the following table.

Table 192024-002-02– Demographic Statistics for
All Randomized Patients
$N_{AGN\ 0.003\%} = 20$, $N_{AGN\ 0.01\%} = 20$, $N_{AGN\ 0.03\%} = 20$, $N_{TIM} = 20$, $N_{VEH} = 20$

	Age				
	Mean	SE	N	Min	Max
Treatment					
AGN 192024 0.003%	59.09	1.999	20	37	76
AGN 192024 0.01%	60.73	2.407	20	40	77
AGN 192024 0.03%	58.00	1.953	20	40	77
Timolol 0.5%	59.84	2.663	20	43	84
Vehicle	61.82	2.418	20	46	90

	Treatment Group									
	AGN 0.003%		AGN 0.01%		AGN 0.03%		Timolol		Vehicle	
	N	%	N	%	N	%	N	%	N	%
Sex										
Male	9	45	8	40	11	55	10	50	8	40
Female	11	55	12	60	9	45	10	50	12	60
Age Class										
< 45 yrs	2	10	2	10	3	15	2	10	0	0
45 - 65 yrs	14	70	9	45	16	80	11	55	13	65
> 65 yrs	4	20	9	45	1	5	7	35	7	35
Race										
Caucasian	17	85	18	90	13	65	16	80	13	65
Non-Caucasian	3	15	2	10	7	35	4	20	7	35
Iris Color										
Light	10	50	12	60	9	45	12	60	9	45
Dark	10	50	8	40	11	55	8	40	11	55
Ophthalmic Diagnosis										
POAG	1	5	2	10	3	15	1	5	2	10
Ocular Hypertension	19	95	17	85	15	75	19	95	17	85
Mixed	0	0	1	5	2	10	0	0	1	5

Table 192024-002-03 – Mean IOP Values at Each Timepoint at Baseline (Day 0)

Timepoint	AGN 192024 0.003%	AGN 192024 0.01%	AGN 192024 0.03%	TIM	Vehicle
8 AM	24.9	25.18	26.95	25.08	24.48
Noon	25.70	24.43	25.45	24.60	24.10
4 PM	24.18	23.85	25.45	23.78	24.03
8 PM	23.88	22.28	23.73	22.75	22.43
10 PM	22.9	21.93	23.33	22.20	22.38

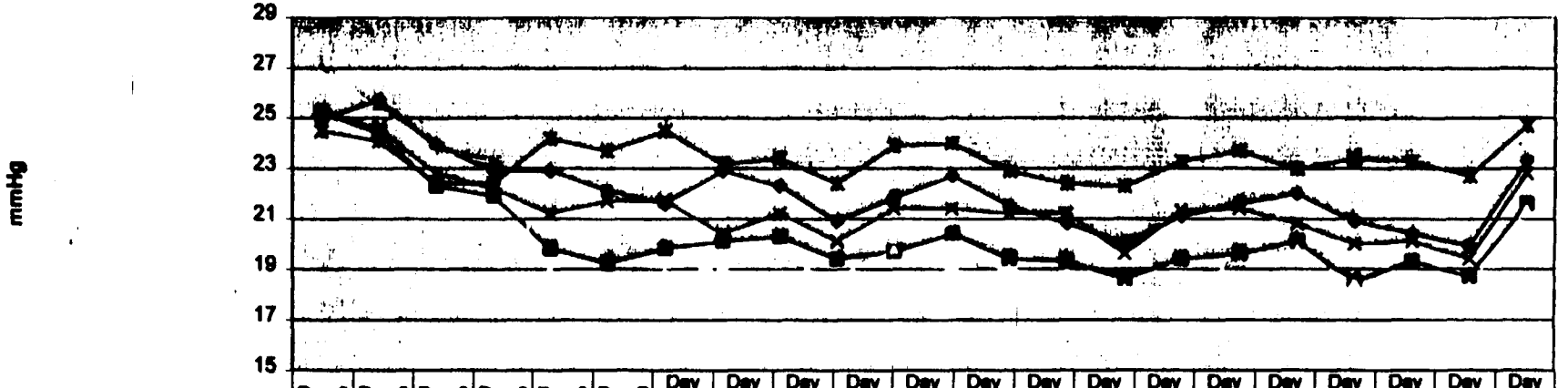
Reviewer's Comments:

There are no statistically significant differences in Baseline IOP between the treatment groups at any timepoint.

8.1.4 Efficacy – Protocol 192024-002

Primary Efficacy Variable

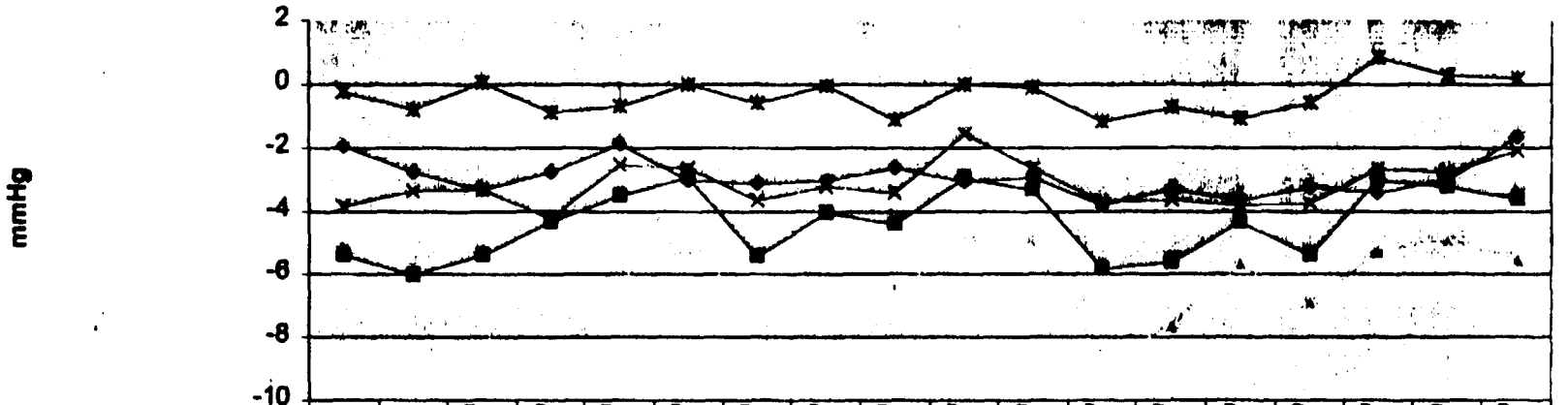
Mean IOP per Visit and Time



	Day 0 8AM	Day 0 12PM	Day 0 8PM	Day 0 10PM	Day 3 8AM	Day 7 8AM	Day 14 8AM	Day 14 12PM	Day 14 4PM	Day 14 8PM	Day 21 8AM	Day 21 4PM	Day 21 8PM	Day 21 10PM	Day 23 8AM	Day 28 8AM	Day 28 12PM	Day 28 4PM	Day 28 8PM	Day 28 10PM	Day 30 8AM
AGN 192024 0.003%	24.9	25.7	23.9	22.9	22.9	22.1	21.6	22.9	22.3	20.9	21.8	21.5	20.8	20	21.1	21.6	22	20.9	20.4	19.9	23.3
AGN 192024 0.01%	25.2	24.4	22.3	21.9	19.8	19.2	19.8	20.1	20.3	19.4	19.7	19.4	19.3	18.6	19.4	19.6	20.1	18.5	19.3	18.7	21.6
AGN 192024 0.03%	27	25.5	23.7	23.3	18.9	18.7	18.8	19.1	19.3	18.7	19.8	19	18.8	18.2	18.3	19.3	19.8	18.5	18.4	18.3	21.4
Timolol	25.1	24.6	22.8	22.2	21.2	21.7	21.7	20.4	21.2	20.1	21.4	21.2	21.2	19.6	21.3	21.4	20.8	20	20.1	19.4	22.8
Vehicle	24.5	24.1	22.4	22.4	24.2	23.7	24.5	23.2	23.4	22.4	23.9	22.9	22.4	22.3	23.3	23.7	23	23.4	23.3	22.7	24.7

Reviewer's Comments: *This study is limited by its short duration and limited number of patients. AGN 192024 0.03% QD (Days 3, 7, 14,and 21) and BID (Days 23, 28, and 30) produced the lowest mean IOPs overall and demonstrated the greatest IOP lowering efficacy compared to AGN 192024 0.003% and AGN 192024 0.01%.*

Mean IOP Change From Baseline at Each Timepoint



	Day 3 8AM	Day 7 8AM	Day 14 8AM	Day 14 12PM	Day 14 4PM	Day 14 8PM	Day 21 8AM	Day 21 12PM	Day 21 4PM	Day 21 8PM	Day 21 10PM	Day 23 8AM	Day 28 8AM	Day 28 12PM	Day 28 4PM	Day 28 8PM	Day 28 10PM	Day 30 8AM
AGN 192024 0.003%	-1.98	-2.6	-3.33	-2.6	-1.93	-3.03	-3.15	-3.03	-2.65	-3.1	-2.95	-3.83	-3.33	-3.68	-3.3	-3.45	-3.05	-1.65
AGN 192024 0.01%	-5.4	-6.03	-5.4	-4.35	-3.53	-2.93	-5.45	-4.06	-4.43	-3	-3.35	-5.83	-5.63	-4.35	-5.4	-3.03	-3.23	-3.63
AGN 192024 0.03%	-8.1	-8.23	-8.18	-8.38	-8.13	-5	-7.18	-8.23	-8.5	-4.98	-5.1	-8.65	-7.7	-5.7	-8.98	-5.35	-5	-5.6
Timolol	-3.68	-3.4	-3.35	-4.25	-2.55	-2.65	-3.68	-3.23	-3.45	-1.6	-2.65	-3.75	-3.7	-3.83	-3.8	-2.68	-2.78	-2.11
Vehicle	-0.25	-0.78	0.05	-0.88	-0.68	-0.03	-0.58	-0.08	-1.13	0	-0.13	-1.18	-0.75	-1.08	-0.6	0.83	0.28	0.18

Reviewer's Comments: *AGN 192024 0.03% appears to be at the top of the dose-response curve.*

8.1.4 Safety

Adverse Events

Only one subject had a serious adverse event. Subject 1438-113 in the 0.003% group was hospitalized for two days (starting on Day 10) for mild shortness of breath. The subject recovered without sequelae, and successfully completed the study.

All subjects completed the study as planned. No subjects were discontinued due to adverse events.

The most frequently reported adverse event within a treatment group was conjunctival hyperemia in 5% (1/20), 15% (3/20) and 5% (1/20) in the 0.003%, 0.01%, and 0.03% groups, respectively. Aside from conjunctival hyperemia, the most frequently reported adverse events in the active AGN 192024 groups included: ocular dryness, diarrhea, dyspnea, and foreign body sensation. All other adverse events occurred in less than two subjects within each treatment group.

Table 192024-002-04 – Number (%) of Patients with Adverse Events Regardless of Causality Reported by at Least 2 Patients in any AGN 192024 Group

BODY SYSTEM preferred term	AGN 192024 0.003% (N = 20)	AGN 192024 0.01% (N = 20)	AGN 192024 0.03% (N = 20)	timolol (N = 20)	vehicle (N = 20)	Among-group P-value[a]
OVERALL	3 (15.0)	8 (40.0)	8 (40.0)	3 (15.0)	0 (0.0)	0.003
DIGESTIVE						
diarrhea	0 (0.0)	1 (5.0)	2 (10.0)	0 (0.0)	0 (0.0)	0.505
RESPIRATORY						
dyspnea	2 (10.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	0.505
SPECIAL SENSES (OCULAR)						
conjunctival hyperemia	1 (5.0)	3 (15.0)	1 (5.0)	0 (0.0)	0 (0.0)	0.266
foreign body sensation	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0.505
dry eye	1 (5.0)	2 (10.0)	2 (10.0)	1 (5.0)	0 (0.0)	0.872

a Among-group p-value based on Fisher's exact test.

Biomicroscopy

Conjunctival hyperemia was observed post-treatment in all treatment groups. However, the mean values in the AGN 192024 groups, approximately trace to mild, were greater than in the timolol and vehicle groups (generally trace and less). This treatment difference was apparent at the first visit (Day 3), and continued throughout the study.

There was a slight increase in hyperemia during the period of twice-daily treatment in the 0.03% treatment group. The maximum hyperemia grade for the active AGN 192024 groups increased to severe during the BID dosing phase.

Cup/disc Ratio and Visual Acuity

There were no significant mean changes from baseline for either cup/disc ratio or visual acuity in any treatment group.

Laser Flare Meter

There was a significant increase in mean change from baseline laser flare measurements of approximately 25% in the timolol treatment group, and negligible changes in the active AGN 192024 and vehicle groups. This treatment effect was statistically significant ($P \leq 0.025$).

Heart Rate and Blood Pressure

There were no clinically significant changes in heart rate or blood pressure.

Reviewer's Comments:

There are no clinically significant differences between treatment groups in cup/disc ratio, visual acuity, laser flare meter measurements, heart rate, or blood pressure.

8.1.4 Reviewer's Summary of Efficacy and Safety

This study is limited by its short duration and limited number of patients.

AGN 192024 0.03% QD (Days 3, 7, 14,and 21) and BID (Days 23, 28, and 30) produced the lowest mean IOPs overall and demonstrated the greatest IOP lowering efficacy compared to AGN 192024 0.003% and AGN 192024 0.01%.

AGN 192024 0.003%, AGN 192024 0.01%, and AGN 192024 0.03% regimens are associated with conjunctival hyperemia, at 5%, 15%, and 5% respectively.

8 Clinical Studies

8.1.5 Study #5 Protocol 192024-003

Title: A One-Month, Single-Center, Double-Masked, Randomized, Parallel, Vehicle-Controlled, Morning Dosing, Pilot Study of the Safety and Efficacy of AGN 192024 0.03% Ophthalmic Solution in Subjects with Open-Angle Glaucoma or Ocular Hypertension

Study Design: A single-center, double-masked, randomized, parallel-group, vehicle control, comparison study.

Test Drug Schedule: One drop of AGN 192024 0.03% or vehicle was instilled into each eye in the morning (between 7 and 9 AM). Treatment with study medication was to continue for 1 month.

Investigator Number	Investigator	Number Randomized
1783	**William Stewart, M.D.** Charleston, South Carolina 29412 USA	32

8.1.5 Study Design

This study was single-center (US), double-masked, randomized, parallel, and vehicle-controlled with 6 scheduled visits. Patients with open-angle glaucoma or ocular hypertension were randomly assigned to receive either AGN 192024 0.03% or AGN 192024 vehicle, bilaterally administered QD in the morning for 1 month. Subjects were evaluated at Prestudy, Day 0 (Baseline), and Days 1, 14, 28, and 29.

Intraocular pressure measurements were collected for each eye and analyzed as an average of both eyes.

The sole efficacy variable was intraocular pressure [change from Day 0 (Baseline) IOP]. This variable was evaluated by the investigator at Prestudy (prior to washout), Baseline (after washout) and at the appropriate follow-up visits during the treatment period.

Study Medications

Each identically masked bottle of test medication was coded with a shipment number and was labeled with the number of the subject to whom the bottle was assigned.

- AGN 192024 0.03% preserved ophthalmic solution (Allergan formulation number 9106X, lot 11379C) contained 0.3 mg/mL AGN 192024
- AGN 192024 vehicle preserved ophthalmic solution (Allergan formulation number 9105X, lot 11427B)

Study Population – Inclusion and Exclusion Criteria

Key Inclusion Criteria: ≥ 21 years; post-washout intraocular pressure (IOP) ≥ 23 mm Hg and ≤ 34 mm Hg in each eye; between-eye asymmetry of IOP ≤ 5 mm Hg; best corrected visual acuity (VA) ≥ 20/80 in each eye

Key Exclusion Criteria: uncontrolled systemic disease or severe cardiovascular disease; clinically relevant low or high heart rate or blood pressure for age; anticipated alteration of existing chronic therapy with agents that could have a substantial effect on IOP, interaction with study medications, or interaction with study outcomes; anticipated wearing of contact lenses during the study; functionally significant visual field loss; laser or any other intraocular surgery within the past 3 months; and day 0 symptoms of ocular irritation greater than mild

Safety Measures

Ocular and systemic safeties were determined from adverse event reports, biomicroscopy, ophthalmoscopy, visual acuity, heart rate/blood pressure, and visual field data

Reviewer's Comments:

There were no repeat visual fields performed at the end of the study.

Table 192024-003-01 – Schedule of Assessments for Protocol 192024-003

Day	Time[a]	Visual Field	Laser Flare Meter	Hyperemia[b] Gross Ocular Photos[c]	Biomicro-scopy	IOP HR BP	Visual Acuity	Ophthal-moscopy	Preg-nancy Test[d]
Prestudy[e]		X			X	X	X	X	
	Washout period of 2-28 days for ocular dilating agents and/or IOP-lowering medications								
Day 0 (baseline)	8 AM		X	X	X	X	X		X
	Noon			X	X	X			
	4 PM			X	X	X			
	8 PM			X	X	X			
Day 1	8 AM		X	X	X	X	X		
	Dosing started the morning of day 1 following the 8 AM examination								
	Noon			X	X	X			
	4 PM			X	X	X			
	8 PM			X	X	X			
Day 14	8 AM		X	X	X	X	X		
	Study medication was administered after the 8 AM examination								
Day 28	8 AM		X	X	X	X	X		
	Last dose of study medication was administered after the 8 AM examination								
	Noon			X	X	X			
	4 PM			X	X	X			
	8 PM			X	X	X			
Day 29	8 AM		X	X	X	X	X	X	X

IOP = intraocular pressure, HR = heart rate, BP = systolic and diastolic blood pressure.

a Time of examination = time ± 30 minutes. Patients were seen at approximately the same time at each visit.

b Bulbar hyperemia was evaluated by gross inspection.

c Gross ocular photos were taken to document the bulbar hyperemia grading.

d Pregnancy tests were performed for women of childbearing potential.

e Included written informed consent, and complete medical and ophthalmological history.

Subject Disposition and Demographics

Thirty-two patients were enrolled, and 28 patients completed the study. One patient in each treatment group discontinued the study due to ocular adverse events. Two additional patients in the vehicle group discontinued due to uncontrolled IOP.

Table 192024-003-02 – Discontinued Patients and Reason

Treatment/Duration	Investigator	Patient	Reason
AGN 192024 QD 14 days	1783	128	Adverse event – uveitis, temporal pain, photophobia, cystoid macular edema
Vehicle QD 1 day	1783	109	Other – uncontrolled IOP
Vehicle QD 13 days	1783	110	Adverse event – ocular tenderness, uveitis
Vehicle QD 3 days	1783	114	Other – uncontrolled IOP

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown in the following table.

Table 192024-003-03– Demographic Statistics for
All Randomized Patients
$N_{AGN\ QD} = 16$, $N_{VEH\ QD} = 16$

	Age				
	Mean	Std	N	Min	Max
Treatment					
AGN 192024 0.03%QD	60.4	3.7	16	36.4	82.9
Vehicle QD	54.6	3.6	16	27.2	82.9

	Treatment Group			
	AGN 192024 QD		AGN 192024 BID	
	N	%	N	%
Sex				
Male	3	19	7	44
Female	13	81	9	56
Age Class				
< 45 yrs	3	19	5	31
45 - 65 yrs	6	38	7	44
> 65 yrs	7	44	4	25
Race				
Black	8	50	7	44
Non-Black	8	50	9	56
Iris Color				
Light	7	44	6	38
Dark	9	56	10	62
Ophthalmic Diagnosis				
POAG	2	13	3	19
Ocular Hypertension	14	87	13	81

Table 192024-003-04 – Mean IOP Values at Each Timepoint at Baseline (Day 0)

Timepoint	AGN 192024 0.03%	Vehicle
Hour 0 (8AM)	25.1	24.9
Hour 4 (Noon)	22.9	22.2
Hour 8 (4PM)	21.5	21.5
Hour 12 (8PM)	21.1	21.7

Reviewer's Comments:

There are no statistically significant differences in Baseline IOP between the treatment groups at any timepoint.

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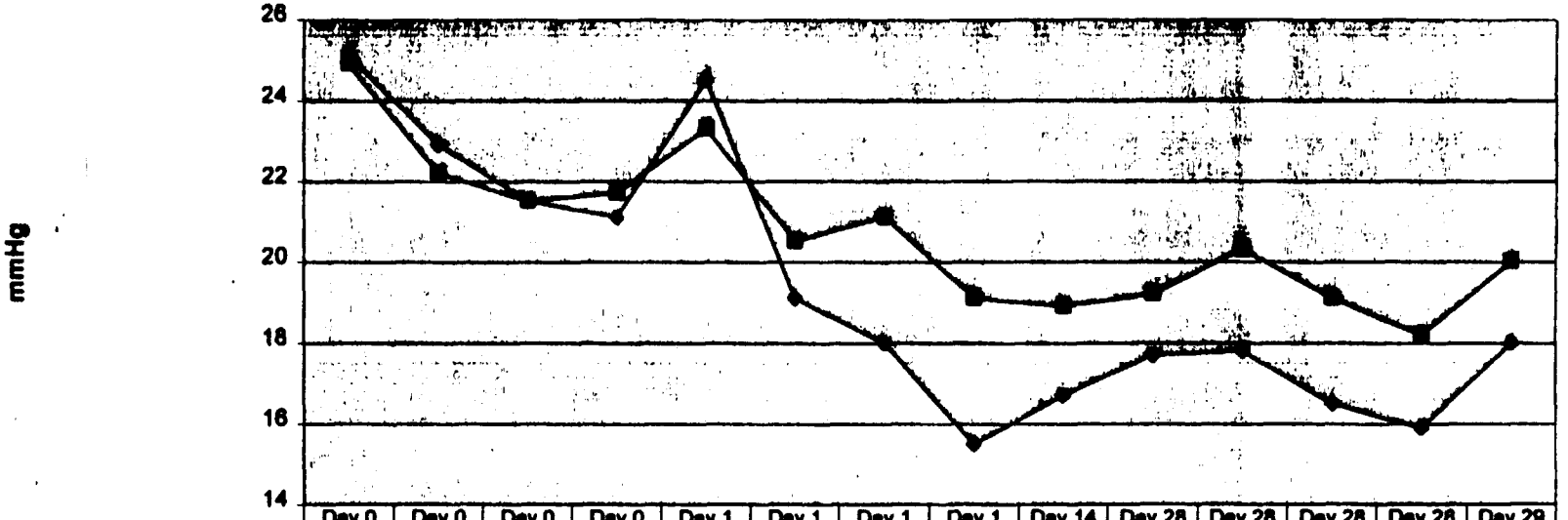
ON ORIGINAL

8.1.5 Efficacy – Protocol 192024-003

Primary Efficacy Variable

Mean IOP per Visit and Time

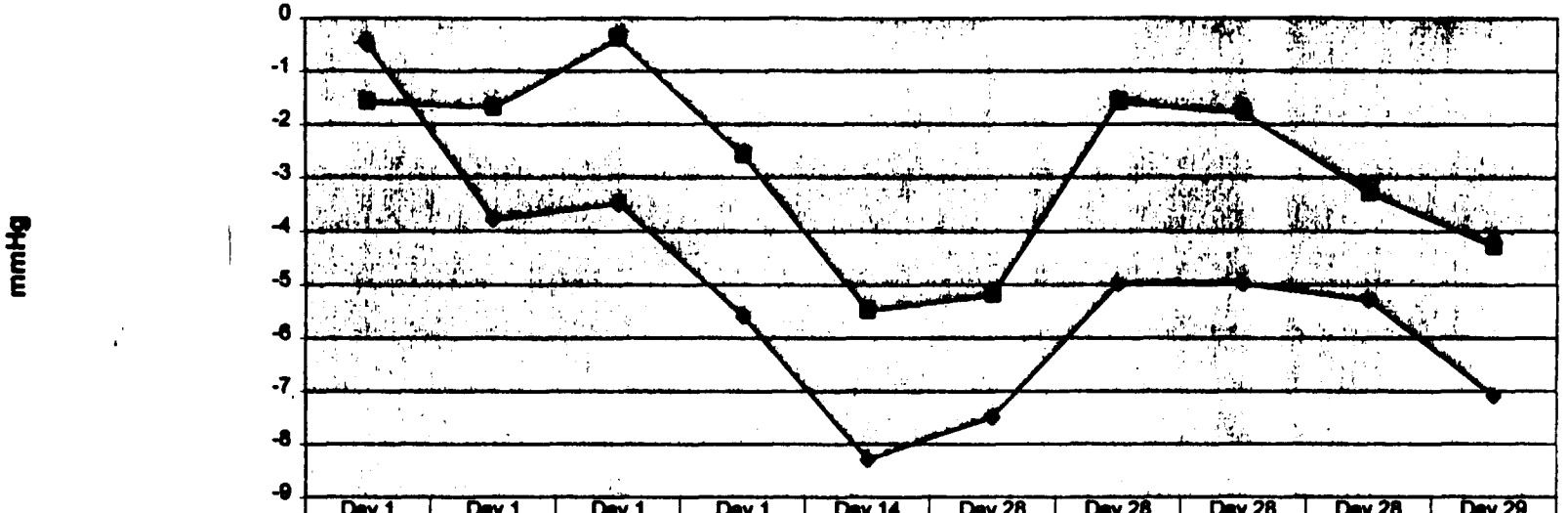


	Day 0 Hour 0	Day 0 Hour 4	Day 0 Hour 8	Day 0 Hour 12	Day 1 Hour 0	Day 1 Hour 4	Day 1 Hour 8	Day 1 Hour 12	Day 14 Hour 0	Day 28 Hour 0	Day 28 Hour 4	Day 28 Hour 8	Day 28 Hour 12	Day 29 Hour 0
AGN 192024 0.03%	25.1	22.9	21.5	21.1	24.5	19.1	18	15.5	16.7	17.7	17.8	16.5	15.9	18
Vehicle	24.9	22.2	21.5	21.7	23.3	20.5	21.1	19.1	18.9	19.2	20.3	19.1	18.2	20

Reviewer's Comments:

This study is limited by its short duration and limited number of patients. Beginning at Day 1 Hour 4, AGN 192024 0.3% QD (AM) produces lower IOPs than vehicle.

Mean IOP Change From Baseline at Each Timepoint



	Day 1 Hour 0	Day 1 Hour 4	Day 1 Hour 8	Day 1 Hour 12	Day 14 Hour 0	Day 28 Hour 0	Day 28 Hour 4	Day 28 Hour 8	Day 28 Hour 12	Day 29 Hour 0
AGN 192024 0.03%	-0.5	-3.8	-3.5	-5.6	-8.3	-7.5	-5	-5	-5.3	-7.1
Vehicle	-1.6	-1.7	-0.4	-2.6	-5.5	-5.2	-1.6	-1.8	-3.3	-4.3

Reviewer's Comments:

AGN 192024 0.03% QD (AM) lowers IOP between 0.5 and 8.3 mmHg from baseline. AGN 192024 vehicle QD (AM) lowers IOP between 1.6 and 5.5 mmHg from baseline.

8.1.5 Safety

Adverse Events

No serious adverse events occurred during the study.

Two patients discontinued treatment due to adverse events: 1 patient in the AGN 192024 group due to uveitis, temporal pain, photophobia, and cystoid macular edema with decreased visual acuity, and 1 patient in the vehicle group due to ocular tenderness and uveitis. See **Table 192024-003-02, page 72.**

Adverse events of any causality were reported for 68.8% (11/16) of patients treated with AGN 192024 and 37.5% (6/16) of patients treated with vehicle. The most frequent adverse event was conjunctival hyperemia, reported for 31.3% (5/16) of patients treated with AGN 192024 and 0 patients treated with vehicle (p = 0.043). The overall number of adverse events was not statistically different between the treatment groups.

Other ocular events reported for more than 1 patient in the AGN 192024 group were burning sensation in the eye (18.8%, 3/16), blepharitis (12.5%, 2/16), and visual disturbance (12.5%, 2/16). Ocular events reported for more than 1 patient in the vehicle group were blepharitis (12.5%, 2/16), and eye discharge (12.5%, 2/16).

Three patients (18.8%) in the AGN 192024 group reported non-ocular adverse events. These included foot infection, benign skin neoplasm, upper respiratory infection, and bacterial infection of the scalp.

Table 192024-003-05 - Number (%) of Patients with Adverse Events Regardless of Causality Reported by at Least 2 Patients in the AGN 192024 Group

BODY SYSTEM Preferred Term	AGN 192024 0.03% (N = 16)	vehicle (N = 16)	Between-group P-value[a]
OVERALL	11 (68.8)	6 (37.5)	0.156
BODY AS A WHOLE			
infection[b]	3 (18.8)	0 (0.0)	0.226
SPECIAL SENSES (OCULAR)			
conjunctival hyperemia	5 (31.3)	0 (0.0)	0.043
burning sensation in eye	3 (18.8)	1 (6.3)	0.600
blepharitis	2 (12.5)	2 (12.5)	>0.999
visual disturbance	2 (12.5)	0 (0.0)	0.484

a Between-group p-value based on Fisher's exact test.
b 1 patient each with foot infection, upper respiratory infection, and scalp bacterial infection.

Biomicroscopy

The most frequently reported findings were conjunctival erythema and lid erythema. Lid erythema was reported for 31.3% (5/16) of patients in the AGN 192024 group and 31.3% (5/16) of patients in the vehicle group. Conjunctival erythema was reported for 43.8% (7/16) of patients in the AGN 192024 group and 11.8% (3/16) of patients in the vehicle group.

Visual Acuity

There were no significant mean changes from baseline for visual acuity in any treatment group.

Laser Flare Meter

Mean changes from baseline ranged from 0.0 to 0.1p/msec in the AGN 192024 group and 0.0 to 0.2 in the vehicle group. There were no statistically significant differences between the AGN 192024 and vehicle groups at any timepoint.

Heart Rate and Blood Pressure

There were no clinically significant changes in heart rate or blood pressure.

Reviewer's Comments:

There are no clinically significant differences between treatment groups in visual acuity, laser flare meter measurements, heart rate, or blood pressure.

8.1.5 Reviewer's Summary of Efficacy and Safety

This study is limited by its short duration and limited number of patients.

Beginning at Day 1 Hour 4, AGN 192024 0.3% QD (AM) produces lower IOPs than vehicle.

AGN 192024 0.03% QD (AM) lowers IOP between 0.5 and 8.3 mmHg from baseline. AGN 192024 vehicle QD (AM) lowers IOP between 1.6 and 5.5 mmHg from baseline, thus raising questions about the interpretation of this study's results.

Conjunctival hyperemia is seen in 31% of subjects receiving AGN 192024 0.03% QD (versus 0% of subjects receiving placebo).

8 Clinical Studies

8.1.6 Study #6 Protocol 192024-004

Title: A One Month, Investigator-Masked, parallel, Randomized, Safety and Efficacy Study of AGN 192024 0.03% and AGN 192151 0.06% Ophthalmic Solutions Compared to Vehicle and Latanoprost 0.005% in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension

Study Design: A multi-site, randomized, investigator-masked, parallel comparison study.

Test Drug Schedule: All subjects were instructed to instill one drop of study medication in each eye once daily, in the evening, at around 8 PM (± 1 hour) for 28 days.

To maintain masking (since some of the medications were not preserved) all subjects were to use a new bottle of medication at each instillation (i.e., one bottle per day). Both eyes were to be instilled using this one bottle.

Investigator Number	Investigator	Number Randomized
2232	**David Cooke, MD** St. Joseph, MI 49085 USA	25
2078	**Monte Dirks, MD** San Antonio, TX 78234 USA	30
2450	**Harvey DuBiner, MD** Morrow, GA 30260 USA	25
1783	**William Stewart, MD** Charleston, SC 29412 USA	26

8.1.6 Study Design

This study was a multi-site, randomized, investigator-masked, parallel comparison consisting of four (4) scheduled visits. Subjects with primary open-angle glaucoma or ocular hypertension were randomly assigned to receive AGN 192024 0.03% (preserved), AGN 192024 0.03% (non-preserved), AGN 192151 0.06% (non-preserved), AGN 192024 vehicle (non-preserved), or latanoprost 0.005% administered once-daily, in the evening, for one month. Subjects were evaluated at Prestudy and follow-up visits at Days 0 (Baseline), 14, and 29.

IOP was collected bilaterally and analyzed as an average of two eyes.

The sole efficacy variable was intraocular pressure [change from Day 0 (Baseline) IOP]. This variable was evaluated by the investigators at Prestudy (prior to washout), after washout on Day 0 (Baseline) and at the appropriate follow-up visits during the treatment period.

Study Medications

Latanoprost bottles were the original, marketed container, with the labels removed and masked (investigational) labels applied. All other study medications were manufactured in Allergan's "Boston Round" bottle and masked with investigational labels. Each masked bottle of study medication (for all treatment groups) was coded with a shipment number and subject number.

- AGN 192024 0.03% preserved ophthalmic solution (Allergan Formulation Number 9106X)
- AGN 192024 0.03% non-preserved ophthalmic solution (Allergan Formulation Number 8824X)
- AGN 192151 0.06% non-preserved ophthalmic solution (Allergan Formulation Number 8940X)
- AGN 192024 vehicle non-preserved ophthalmic solution (Allergan Formulation Number 8763X)
- Latanoprost 0.005% ophthalmic solution (Allergan Formulation Number 9101X)

Study Population – Inclusion and Exclusion Criteria

Key Inclusion criteria: Male or female subjects, 21 years of age or older; likely to be controlled on monotherapy; best-corrected ETDRS visual acuity score equivalent to a Snellen score of 20/100 or better in each eye; Day 0 IOP at 8 AM greater than or equal to 23 mm Hg and less than or equal to 34 mm Hg in each eye and asymmetry of IOP between the eyes not greater than 5 mm Hg.

Key Exclusion criteria: Any uncontrolled systemic disease; female subjects who were pregnant, nursing, planning a pregnancy, or not using a reliable form of birth control; clinically significant abnormal blood parameters; any previous use of latanoprost; clinically relevant low or high heart rate, or blood pressure for age; known allergy or hypersensitivity to any of the study medication ingredients; anticipated use of topical or systemic steroids; anticipated alteration of existing chronic therapy with agents

which can have an effect in IOP; corneal abnormalities that would prevent accurate IOP readings with an applanation tonometer; anticipated wearing of contact lenses; presence of any other active ocular disease; required chronic use of other ocular medications; functionally significant glaucomatous visual field loss; intraocular surgery within the past three months; contraindications to pupil dilation; concurrent enrollment or participation within the last 30 days in any investigational study; previous participation in any AGN 192024, AGN 192151 or latanoprost study; situation or condition which could put the subject at significant risk, could confound the results or could interfere with the subject's participation in the study; at Day 0, subjects who were not properly washed out of their ocular medications.

Safety Measures

Ocular and systemic safeties were determined from adverse event reports, biomicroscopy, ophthalmoscopy, visual acuity, heart rate/blood pressure, and visual field data.

Reviewer's Comments:

There were no repeat visual fields performed at the end of the study.

Table 192024-004-01 – Schedule of Assessments for Protocol 192024-004

Day	Time*	IOP/ Heart Rate/ Blood Pressure	Bio-micro-scopy	Hyperemia†/ Gross Ocular Photos§	Visual Acuity	Blood Draw (fasting+)	Preg-nancy Test**	Ophthal-moscopy	Visual Field
Prestudy¶		X	X		X	X		X	X
washout period of 2-28 days (for ocular dilating agents and/or anti-glaucoma meds)									
Day 0	8 am	X	X	X	X	X	X		
	Noon	X	X	X					
	4 PM	X	X	X					
	8 PM	X	X	X					
Dosing starts the evening of Day 0 following the 8 PM exam									
Day 14	8 am	X	X	X	X				
Last dose instilled by the subject on the evening of Day 28									
Day 29	8 am	X	X	X	X	X	X-		
	Noon	X	X	X					
	4 PM	X	X	X					
	8 PM	X	X	X				X	

*Time of examination = time ±30 minutes. All patients should have their visits at the same time during the study.
†Conjunctival (bulbar) hyperemia was evaluated by gross inspection.
§Gross ocular photos will be taken to document the conjunctival (bulbar) hyperemia grading.
+Subjects must not ingest any food or liquids (other than water) for 8-10 hours prior to the first blood draw.
**Pregnancy test will be performed for women of child-bearing potential.
¶Includes written informed consent, and complete medical and ophthalmological history.

Subject Disposition and Demographics

A total of 106 subjects entered the study, 100 subjects completed the study as planned, and six subjects discontinued the study. Four subjects discontinued due to adverse events, and two subjects in the vehicle group discontinued due to lack of efficacy.

Table 192024-004-02 – Discontinued Patients and Reason

Treatment/Duration	Investigator	Patient	Reason
AGN 192151 0.06% non-preserved 35 days	2078	205	Adverse event – allergic reaction
AGN 192024 0.03% preserved 24 days	1783	409	Adverse event – eye pain, conj hyperemia, asthenopia, nausea
AGN 192024 0.03% preserved 8 days	2232	118	Adverse event – conj hyperemia, eyelid edema, foreign body sensation
Latanoprost QD 34 days	2232	34	Adverse event – pain
Vehicle Non-preserved 35 days	1783	406	Lack of efficacy
Vehicle Non-preserved 13 days	1783	411	Lack of efficacy

There were no statistically significant differences in demographic subgroup membership between the treatment groups for age, sex, race, iris color, or ophthalmic diagnosis. The demographic statistics for all randomized patients are shown on the following page.

Table 192024-004-03 – Demographic Statistics for All Randomized Patients

$N_{AGN\ 0.06\%\ NP} = 21$, $N_{AGN\ 0.03\%\ NP} = 21$, $N_{AGN\ 0.03\%\ P} = 21$, $N_{LAT} = 22$, $N_{VEH} = 21$

	Age				
	Mean	SE	N	Min	Max
Treatment					
AGN 192151 0.06% non-preserved	63.45	2.437	21	41	85
AGN 192024 0.03% non-preserved	65.07	2.208	21	47	83
AGN 192024 0.03% preserved	68.77	1.612	21	53	79
Latanoprost	64.26	2.130	22	43	77
Vehicle 192024 non-preserved	66.36	2.208	21	47	82

	Treatment Group									
	0.06% NP		0.03% NP		0.03% P		Latanoprost		Vehicle NP	
	N	%	N	%	N	%	N	%	N	%
Sex										
Male	5	24	7	33	11	52	10	46	8	38
Female	16	76	14	67	10	48	12	54	13	62
Age Class										
< 45 yrs	1	5	0	0	0	0	2	9	0	0
45 - 65 yrs	12	57	12	57	5	24	8	36	8	38
> 65 yrs	8	38	9	43	16	76	12	55	13	62
Race										
Caucasian	15	71	14	67	16	76	18	82	18	86
Non-Caucasian	6	29	7	33	5	24	4	18	3	14
Iris Color										
Light	9	43	12	57	14	67	11	50	13	62
Dark	12	57	9	43	7	33	11	50	8	38
Ophthalmic Diagnosis										
POAG	7	33	13	62	9	43	10	46	10	47
Ocular Hypertension	14	67	8	38	12	57	12	54	11	53

Table 192024-004-04 – Mean IOP Values at Each Timepoint at Baseline (Day 0)

Timepoint	0.06% NP	0.03% NP	0.03% P	Latanoprost	Vehicle NP
Hour 0 (8AM)	24.71	25.90	25.62	25.23	25.83
Hour 4 (Noon)	24.24	23.55	24.81	22.93	23.43
Hour 8 (4PM)	22.67	23.55	24.05	22.02	22.00
Hour 12 (8PM)	21.45	23.00	22.74	21.39	22.31

Reviewer's Comments:

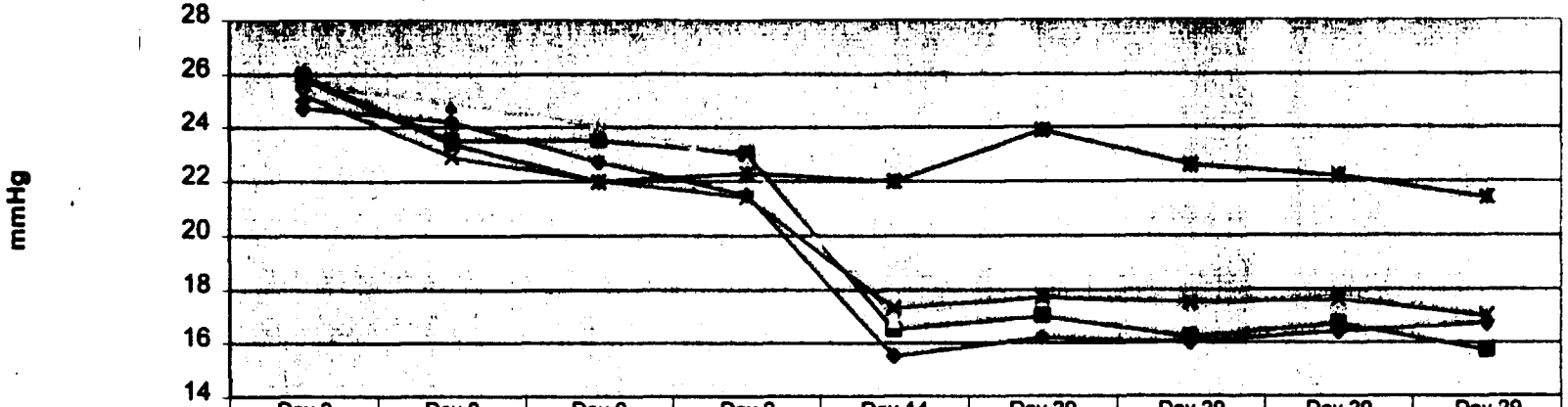
The among-group p-value (0.027) was statistically significant at the Baseline Hour 4 (Noon) Mean IOP measurement.

Pairwise comparisons between 0.06% NP and 0.03% P were significant at p = 0.019, and pairwise comparisons between latanoprost and 0.03% P were significant at p = 0.016.

8.1.6 Efficacy – Protocol 192024-004

Primary Efficacy Variable

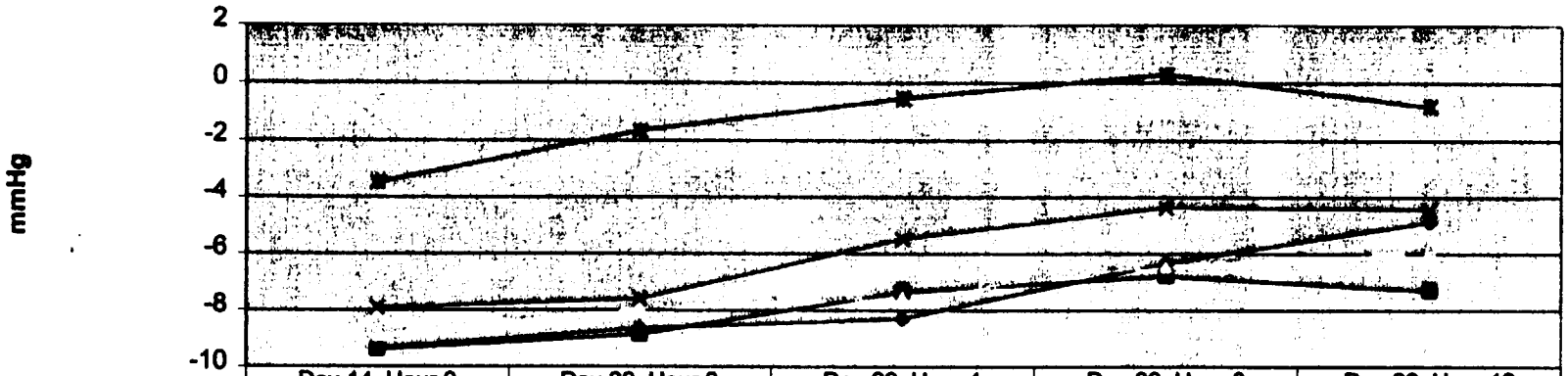
Mean IOP per Visit and Time



	Day 0 Hour 0	Day 0 Hour 4	Day 0 Hour 8	Day 0 Hour 12	Day 14 Hour 0	Day 29 Hour 0	Day 29 Hour 4	Day 29 Hour 8	Day 29 Hour 12
0.06% NP	24.7	24.2	22.7	21.5	15.5	16.2	16	16.4	16.7
0.03% NP	25.9	23.5	23.5	23	16.5	17	16.2	16.7	15.7
0.03% P	25.6	24.8	24	22.7	16.8	17.7	17.2	17.8	16.9
Latanoprost	25.2	22.9	22	21.4	17.3	17.7	17.5	17.6	17
Vehicle NP	25.8	23.4	22	22.3	22	23.9	22.6	22.2	21.4

Reviewer's Comments: *This study is limited by its short duration and limited number of patients. Latanoprost is not currently accepted by the Agency as an active control in IOP lowering trials. At all visits, all active treatment groups are more efficacious in reducing IOP than AGN 192024 vehicle.*

Mean IOP Change From Baseline at Each Timepoint



	Day 14 Hour 0	Day 29 Hour 0	Day 29 Hour 4	Day 29 Hour 8	Day 29 Hour 12
0.06% NP	-9.34	-8.63	-8.3	-6.35	-4.88
0.03% NP	-9.4	-8.86	-7.36	-6.81	-7.31
0.03% P	-8.89	-7.95	-7.53	-6.45	-5.92
Latanoprost	-7.93	-7.6	-5.5	-4.38	-4.45
Vehicle NP	-3.5	-1.66	-0.55	0.29	-0.82

Reviewer's Comments: *There is not a clear separation in IOPs between the active treatment groups until Day 29 Hour 12 when the greatest IOP lowering effect is demonstrated by 0.03% NP.*

8.1.6 Safety

Adverse Events

Four subjects discontinued due to adverse events: [subject #118, (024-preserved) had conjunctival hyperemia, swollen lids, and scratchy feeling in eyes; subject #409 (024-preserved) had ocular pain, conjunctival hyperemia, ocular heaviness and nausea; subject #205 (151 group) had allergic conjunctivitis; subject #116 (latanoprost) had body ache and stomach cramping]. See **Table 192024-004-02, page 81.**

Of greatest interest were reports of conjunctival hyperemia or ocular itching (pruritus). The incidence of conjunctival hyperemia was 14.3% (3/21), 28.6% (6/21), 14.3% (3/21), 13.6% (3/22), and 0% (0/21) in the AGN 192151 0.06%, AGN 192024 0.03% non-preserved, AGN 192024 0.03% preserved, latanoprost and vehicle treatment groups, respectively. The incidence of pruritus was 9.5% (2/21), 23.8% (5/21), 9.5% 2/21), 4.5% (1/22) and 4.8% (1/21) in the AGN 192151 0.06%, AGN 192024 0.03% non-preserved, AGN 192024 0.03% preserved, latanoprost and vehicle treatment groups, respectively.

Table 192024-004-05 - Number (%) of Patients with Adverse Events Regardless of Causality Reported by at Least 2 Patients in any AGN 192024 Group

BODY SYSTEM Preferred Term	AGN 192151 0.06%NP (N = 21)	AGN 192024 0.03% NP (N = 21)	AGN 192024 0.03% P (N = 21)	latanoprost (N = 22)	vehicle (N = 21)	Among-group P-value[a]
OVERALL	11 (52.4)	13 (61.9)	7 (33.3)	9 (40.9)	9 (42.9)	0.399
NERVOUS						
dizziness	1 (4.8)	1 (4.8)	0 (0.0)	0 (0.0)	2 (9.5)	0.439
RESPIRATORY						
upper respiratory infection	2 (9.5)	3 (14.3)	1 (4.8)	1 (4.5)	2 (9.5)	0.774
SPECIAL SENSES (OCULAR)						
conjunctival hyperemia	3 (14.3)	6 (28.6)	3 (14.3)	3 (13.6)	0 (0.0)	0.104
foreign body sensation	2 (9.5)	1 (4.8)	1 (4.8)	0 (0.0)	0 (0.0)	0.439
pruritus eye	2 (9.5)	5 (23.8)	2 (9.5)	1 (4.5)	1 (4.8)	0.351
visual disturbance	2 (9.5)	0 (0.0)	0 (0.0)	1 (4.5)	1 (4.8)	0.674

Note P = preserved, NP = nonpreserved
a Among-group p-value based on the Fisher's exact test.

Biomicroscopy

The only finding of significance was conjunctival hyperemia. Mean scores were not significantly different among the treatment groups at any timepoint.

Cup/disc Ratio and Visual Acuity

There were no significant mean changes from baseline for either cup/disc ratio or visual acuity in any treatment group.

Heart Rate and Blood Pressure

There were no clinically significant changes in heart rate or blood pressure.

Reviewer's Comments:

There are no clinically significant differences between treatment groups in visual acuity, laser flare meter measurements, heart rate, or blood pressure.

8.1.6 Reviewer's Summary of Efficacy and Safety

This study is limited by its short duration and limited number of patients.

Latanoprost is not currently accepted by the Agency as an active control in IOP lowering trials.

At all visits, all active treatment groups are more efficacious in reducing IOP than AGN 192024 vehicle.

There is not a clear separation in IOPs between the active treatment groups.

The incidence of conjunctival hyperemia is 14%, 28%, 14%, 13%, and 0% in the AGN 192151 0.06%, AGN 192024 0.03% non-preserved, AGN 192024 0.03% preserved, latanoprost and vehicle treatment groups, respectively.

9 Overview of Efficacy

Mean IOPs per visit and time are lower for bimatoprost ophthalmic solution 0.03% QD than for timolol 0.5% BID at all measured timepoints beginning at Week 2. Bimatoprost ophthalmic solution 0.03% administered QPM did not demonstrate equivalence to bimatoprost ophthalmic solution 0.03% administered BID in the ability to lower intraocular pressure.

Bimatoprost ophthalmic solution 0.03% QD lowered IOP between 7 and 9 mmHg from baseline.

Individually, the four phase 2 studies are limited by their short duration and small number of patients. When taken as a group, these studies adequately identify the proposed treatment concentration (bimatoprost ophthalmic solution 0.03%).

Analyses of efficacy data were performed on the pooled data from the phase 3 studies (192024-008 and 192024-009) for subgroups of patients defined by age, sex, race, and iris color. In each subgroup, mean IOP values during treatment with bimatoprost ophthalmic solution were statistically significantly less than with timolol at each follow-up visit for Hours 0, 2, and 8. The IOP lowering ability of bimatoprost ophthalmic solution 0.03% was not superior to timolol 0.5% BID by a clinically significant amount.

10 Overview of Safety

Iris color, blepharal pigmentation, and eyelash changes have been observed. The frequency of these changes cannot be accurately determined at this time.

The most frequent ocular adverse events (pooled) in bimatoprost ophthalmic solution 0.03% treated subjects were conjunctival hyperemia (40%), growth of eyelashes (22%), and eye pruritus (17%).

The most frequent non-ocular adverse events (pooled) in bimatoprost ophthalmic solution 0.03% treated subjects were infection [primarily colds and upper respiratory tract infections] (6%) and headache (4%). See the following table.

Table 4 – Number (%) of Patients in the Phase 3 Monotherapy Studies with Adverse Events Regardless of Causality Reported by at Least 10 Patients (≥ 2%) in Either AGN 192024 Group

Body System Preferred Term	AGN 192024 QD (N = 474)	AGN 192024 BID (N = 483)	timolol (N = 241)	Among-group P-value[a]
BODY AS A WHOLE				
infection	26 (5.5%)[b]	18 (3.7%)	3 (1.2%)	0.021
headache	17 (3.6%)	18 (3.7%)	8 (3.3%)	0.962
accidental injury	10 (2.1%)	5 (1.0%)	1 (0.4%)	0.153[d]
CARDIOVASCULAR				
hypertension	11 (2.3%)	8 (1.7%)	3 (1.2%)	0.617[d]
SPECIAL SENSES (OCULAR)				
conjunctival hyperemia	189 (39.9%)[b,c]	246 (50.9%)[b]	23 (9.5%)	<0.001
growth of eyelashes	103 (21.7%)[b,c]	156 (32.3%)[b]	4 (1.7%)	<0.001
eye pruritus	54 (11.4%)[b,c]	81 (16.8%)[b]	9 (3.7%)	<0.001
eye dryness	26 (5.5%)[b]	39 (8.1%)[b]	5 (2.1%)	0.005
burning sensation in eye	24 (5.1%)	26 (5.4%)	22 (9.1%)	0.073
foreign body sensation	21 (4.4%)[c]	41 (8.5%)[b]	4 (1.7%)	< 0.001
eye pain	19 (4.0%)[c]	45 (9.3%)[b]	7 (2.9%)	< 0.001
visual disturbance	18 (3.8%)	24 (5.0%)	8 (3.3%)	0.504
erythema eyelid	12 (2.5%)	11 (2.3%)	1 (0.4%)	0.110[d]
blepharal pigmentation	10 (2.1%)[c]	25 (5.2%)[b]	1 (0.4%)	< 0.001
irritation eye	9 (1.9%)	12 (2.5%)	3 (1.2%)	0.594[d]
asthenopia	7 (1.5%)	10 (2.1%)	1 (0.4%)	0.237[d]
eye discharge	7 (1.5%)	14 (2.9%)[b]	1 (0.4%)	0.048[d]
epiphora	6 (1.3%)	10 (2.1%)	3 (1.2%)	0.573[d]
photophobia	6 (1.3%)[c]	30 (6.2%)[b]	1 (0.4%)	< 0.001
eyelash discoloration	4 (0.8%)	10 (2.1%)[b]	0 (0.0%)	0.036[d]
eyelid pruritus	1 (0.2%)[c]	17 (3.5%)[b]	1 (0.4%)	< 0.001[d]

a Among-group p-value based on Pearson's chi-square test, unless indicated otherwise.
b $P \leq 0.05$ for pairwise comparison of AGN 192024 QD or AGN 192024 BID to timolol.
c $P \leq 0.05$ for pairwise comparison of AGN 192024 QD to AGN 192024 BID.
d P-value based on Fisher's exact test.

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11 **Labeling Review**

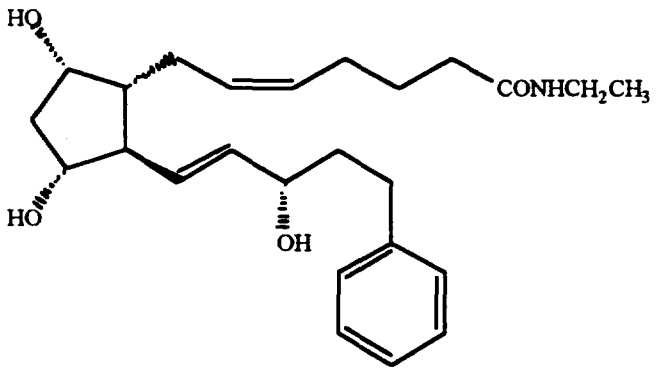
Reviewer's Comments:

Recommended additions are shown by underlining: recommended deletions are shown by strikethrough lines.

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03%

DESCRIPTION

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is a prostamide with ocular hypotensive activity. Its chemical name is (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl]cyclopentyl]-5-N-ethylheptenamide, and its molecular weight ~~of~~ is 415.58. Its molecular formula is $C_{25}H_{37}NO_4$. Its chemical structure is:



Bimatoprost is a powder, which is very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water. **LUMIGAN™** is a clear, isotonic, colorless, sterile ophthalmic solution with an osmolality of approximately 290 mOsmol/kg.

Each mL contains: Active: bimatoprost 0.3 mg; Preservative: Benzalkonium chloride 0.05 mg; Inactives: Sodium chloride; sodium phosphate, dibasic; citric acid; and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. The pH during its shelf life ranges from 6.8-7.8.

CLINICAL PHARMACOLOGY

Mechanism of Action

Bimatoprost is a prostamide, a synthetic analog of prostaglandin with ocular hypotensive activity. It selectively mimics the effects of a naturally occurring substance, prostamide

Bimatoprost is believed to lowers intraocular pressure (IOP) in humans by increasing outflow of aqueous

humor through both the trabecular meshwork and uveoscleral routes. Elevated IOP presents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

Pharmacokinetics

Absorption:

After one drop of bimatoprost ophthalmic solution 0.03% was administered once daily to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing, and were below the lower limit of detection (0.025 ng/mL) in most subjects within 1.5 hours after dosing. Mean C_{max} and $AUC_{0\text{-}24hr}$ values were similar on days 7 and 14 at approximately 0.08 ng/mL and 0.09 ng•hr/mL, respectively, indicating that steady state was reached during the first week of ocular dosing.

There was no significant systemic drug accumulation over time

Distribution

Bimatoprost is moderately distributed into body tissues with a steady-state volume of distribution of 0.67 L/kg. In human blood, bimatoprost resides mainly in the plasma. Approximately 12% of bimatoprost remains unbound in human plasma.

Metabolism

Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes N-deethylation and deamidation to form a diverse variety of metabolites.

Elimination

Following an intravenous dose of radiolabeled bimatoprost (3.12 µg/kg) to six healthy subjects, the maximum blood concentration of unchanged drug was 12.2 ng/mL and decreased rapidly with an elimination half-life of approximately 45 minutes. The total blood clearance of bimatoprost was 1.5 L/hr/kg. Up to 67% of the administered dose was excreted in the urine while 25% of the dose was recovered in the feces.

Clinical Studies:

In clinical studies of patients with glaucoma or ocular hypertension with a mean baseline IOP of 26 mm Hg, the IOP-lowering effect of **LUMIGAN** (bimatoprost ophthalmic solution) 0.03% once daily (in the evening) was 7-8 mm Hg.

INDICATIONS AND USAGE

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication..

CONTRAINDICATIONS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is contraindicated in patients with hypersensitivity to bimatoprost or any other ingredient in this product.

WARNINGS

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% has been reported to cause changes to pigmented tissues. increased pigmentation and growth of eyelashes and increased pigmentation of the iris and periorbital tissue (eyelid). These changes may be permanent.

LUMIGAN™ may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of **LUMIGAN™**.

LUMIGAN™ may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also

be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. [redacted]

PRECAUTIONS

General:

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see Information for Patients).

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% should be used with caution in patients with active intraocular inflammation (e.g., uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with bimatoprost ophthalmic solution. **LUMIGAN™** should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

LUMIGAN™ has not been evaluated for the treatment of angle closure, inflammatory or neovascular glaucoma.

LUMIGAN™ should not be administered while wearing contact lenses.

LUMIGAN™ [redacted] has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

Information for Patients:

Patients should be informed that **LUMIGAN™** has been reported to cause increased growth and darkening of eyelashes and darkening of the skin around the eye in some patients. These changes may be permanent.

Some patients may slowly develop darkening of the iris, which may be permanent.

When only one eye is treated, patients should be informed of the potential for a cosmetic difference between the eyes in eyelash length, darkness or thickness, and/or color changes of the eyelid skin or iris.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to avoid contamination of the solution by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice.

Contact lenses should be removed prior to instillation of **LUMIGAN™** and may be reinserted 15 minutes following its administration. Patients should be advised that **LUMIGAN™** contains benzalkonium chloride, which may be absorbed by soft contact lenses.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes between applications.

Drug Interactions:
No drug-drug interactions are anticipated in humans since systemic drug concentrations of bimatoprost are extremely low (less than 0.2 ng/mL) following multiple ocular dosing.

Carcinogenesis, Mutagenesis, Impairment of fertility:
Carcinogenicity studies were not performed with bimatoprost.

Bimatoprost was not mutagenic or clastogenic in the Ames test, in the mouse lymphoma test, or in the *in vivo* mouse micronucleus tests.

Bimatoprost did not impair fertility in male or female rats up to doses of 0.6 mg/kg/day (approximately 103 times the recommended human exposure).

Pregnancy: Teratogenic effects: ***Pregnancy Category C:***
In embryo/fetal developmental studies in pregnant mice and rats, abortion [redacted] was observed at oral doses of bimatoprost which achieved at least 33 or 97 times, respectively, the intended human exposure [redacted] based on blood AUC levels.

[redacted]

There are no adequate and well-controlled studies of **LUMIGAN™** administration in pregnant women. Because animal reproductive studies are not always predictive of human response, **LUMIGAN™** should be administered during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers:
It is not known whether **LUMIGAN™** is excreted in human milk, although in animal studies, bimatoprost has been shown to be excreted in breast milk. Because many drugs are excreted in human milk, caution should be exercised when **LUMIGAN™** is administered to a nursing woman.

Pediatric use:
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use:
No overall clinical differences in safety or effectiveness have been observed between elderly and other adult patients.

ADVERSE REACTIONS

In clinical trials, the most frequent event associated with the use of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% Growth of eyelashes and ocular pruritus

Ocular adverse events occurring in approximately 3 to 10% of patients, in descending order of incidence, included ocular dryness, ocular burning, foreign body sensation, eye pain, The following ocular adverse events reported in approximately 1 to 3% of patients:

Systemic adverse events reported in approximately

OVERDOSAGE

No information is available on overdosage in humans. If overdose with **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% occurs, treatment should be symptomatic.

In oral (by gavage) mouse and rat studies, doses up to mg/kg/day did not produce any toxicity. This dose expressed as mg times higher than the accidental dose of one bottle of **LUMIGAN™** for a 10 kg child.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of **LUMIGAN™** (bimatoprost ophthalmic solution) 0.03% should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

LUMIGAN™ may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

LUMIGAN™ (bimatoprost ophthalmic solution) 0.03% is supplied sterile in opaque white [redacted] NDC 0023-XXXX-07.

Rx only

Storage: LUMIGAN™ should be stored in the original container at [redacted] 15° to 25°C (59°F to 77°F). [redacted]

® and ™ Marks owned by Allergan, Inc. This product covered under US Pat. No. 5,688,819. Additional patents pending.

Revised [redacted]

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12 Conclusions

Lumigan (bimatoprost ophthalmic solution) 0.03% lowers intraocular pressure by 7-[redacted] mmHg in patients with baseline IOP ≥ 22 mm Hg. The amount of IOP reduction is greater than that observed with timolol maleate 0.5% at all measured timepoints, but the IOP reduction is not greater by a clinically significant amount.

A significant change in iris color may signal the ability of the bimatoprost to increase the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or disposition of pigment granules to other areas of the eye are currently unknown.

The potential benefit outweighs the potential risks in this application only if safety information and efficacy information are properly labeled. Indications and usage in the labeling should specify the use of bimatoprost ophthalmic solution 0.03% as second line therapy for the reduction of intraocular pressure.

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13 Recommendations

1) *Following resolution of any chemistry/manufacturing issues and labeling issues, NDA 21-275 is recommended for approval for lowering intraocular pressure in patients with glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.*

2) *The applicant should submit revised labeling consistent with the recommendations in this review.*

3) *The applicant should also propose a post-marketing plan to adequately address concerns raised by the report of increased iris pigmentation and the potential for changes in eyelash length and density over time.*

4) *The applicant should commit to conduct a study to evaluate pigmentation in the trabecular meshwork after patients have been treated with bimatoprost ophthalmic solution 0.03% for over two years.*

William M. Boyd, M.D.
Medical Officer

NDA 21-275
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers
HFD-880/Biopharm/Tandon
HFD-550/Chem/Tso
HFD-550/PharmTox/Chen, Z
HFD- 800/Micro/Langille
HFD-550/PM/Puglisi
HFD-340/Carreras