CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-214

MEDICAL REVIEW

Medical Officer's Review of NDA 21-214

NDA 21-214
Medical Officer's Review #4

Submission: 2/14/00
Review Completed: 6/30/00

Proposed Tradename: Rescula

Generic Name: unoprostone isopropyl ophthalmic solution 0.15%

Sponsor: CIBA Vision
11460 Johns Creek Parkway
Duluth, GA 30097

Pharmacologic Category: prostaglandin analogue
(docosanoid analogue of a $PGF_{2\alpha}$ metabolite)

Proposed Indication: Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Investigator's Financial Disclosure Information: Submitted in Volume 2.5

Reviewer's Comments:

Recommendations:

NDA 21-214, Rescula (unoprostone isopropyl ophthalmic solution) 0.15%, is recommended for approval for lowering intraocular pressure in patients with chronic open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering medications or insufficiently responsive to another IOP-lowering medication.

NDA 21-214
HFD-550/Div Files
HFD-550/MO/Boyd
HFD-550/Dep Director/Chambers /S/ 7/11/00
HFD-550/Div Dir/Midthun
HFD-880/Biopharm/Tandon
HFD-725/Biostats/Li
HFD-550/Chem/Fenselau
HFD-550/PharmTox/Wilson
HFD-550/PM/Rodriguez
HFD-340/Carreras

/S/
William Boyd, M.D.
Medical Officer, Ophthalmology

Medical Officer's Review of NDA 21-214
Original

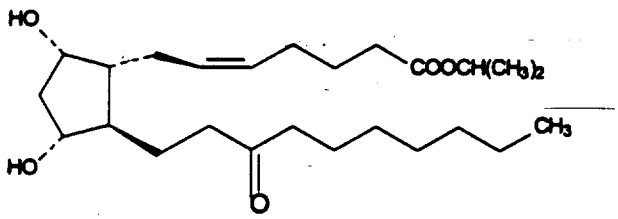
NDA 21-214
Medical Officer's Review

Submission: 2/14/00
Review Completed: 6/30/00

Proposed Tradename: Rescula

Generic Name: unoprostone isopropyl ophthalmic solution 0.15%

Chemical Name:



Rescula $C_{25}H_{44}O_5$

Isopropyl (+)-(Z)-7-[(1R, 2R, 3R, 5S)-3,5-dihydroxy-2-(3-oxodecyl)- cyclopentyl] hept-5-enoate

Sponsor: CIBA Vision
11460 Johns Creek Parkway
Duluth, GA 30097

Pharmacologic Category: prostaglandin analogue
(docosanoid analogue of a $PGF_{2\alpha}$ metabolite)

Proposed Indication: Lowering of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension

Dosage Form and Route of Administration: Ophthalmic solution for topical ocular administration

NDA Drug Classification: 1P

Related INDs: [redacted] unoprostone isopropyl ophthalmic solution

2 **Table of Contents** **Page**

3 Material Reviewed

NDA 21-214 Volumes 3.1-3.3, and Volumes 3.5-3.75.

4 Chemistry/Manufacturing Controls – See Chemistry Review.

Table 1 – Drug Product Formulation

RAW MATERIAL	FORMULA (mg/mL)
Unoprostone Isopropyl	1.5
Polysorbate 80, NF	[redacted]
Benzalkonium chloride, NF	0.15
Edetate disodium, USP	[redacted]
Mannitol, USP	[redacted]
Sodium hydroxide NF [redacted] and/or Hydrochloric acid NF [redacted]	as needed to adjust pH
Water for injection, USP	[redacted]

Reviewer's Comments:

Acceptable.

Table 2 – Original Proposed Finished Product Regulatory Acceptance Specifications

TEST	SPECIFICATIONS

Reviewer's Comments:

Modified acceptance specifications were submitted in an Amendment on 6/13/00. See below.

Related Substance	Release	Stability

5 **Animal PharmacologyToxicology** – No specific issues. See Pharmacology Review.

6 Clinical Background

Glaucoma is a life-long progressive disease. It is characterized by increased intraocular pressure (IOP), alterations of the optic disc, and damage to the retinal nerve fiber bundle with resultant visual-field loss. Glaucoma occurs in 0.5 to 1.5% of the population over age 40 and is responsible for 12% to 15% of the blindness in the United States and European Union. There continues to be a need for drugs that can safely lower the intraocular pressure.

Unoprostone isopropyl is an intraocular pressure (IOP)-lowering docosanoid analogue of a $PGF_{2\alpha}$ metabolite. It is one of several lipids known to lower intraocular pressure in several species including non-human primates and humans. Human and animal studies indicate that unoprostone isopropyl 0.15% lowers IOP by means other than suppressing production of aqueous humor (flow). It is believed to reduce IOP by increasing the outflow of aqueous humor; whether it increases outflow via conventional or uveoscleral outflow pathways is not clear.

The goal of the clinical development program for unoprostone isopropyl ophthalmic solution 0.15% was to demonstrate that it can safely and effectively lower intraocular pressure for extended periods of time in subjects with ocular hypertension or primary open-angle glaucoma.

The rationale for the proposed treatment regimen, unoprostone isopropyl ophthalmic solution 0.15%, b.i.d., is based upon two double-masked, controlled, Phase II studies. One study was a dose regimen study (C-06-96-001) and the other was a dose-response study (C97-UIOS-003).

Protocol C-06-96-001 was a double-masked, randomized, parallel-group comparison of the effects of different dosing frequencies of unoprostone isopropyl ophthalmic solution 0.12% on intraocular pressure in 146 subjects with primary open-angle glaucoma or ocular hypertension. The applicant considered the twice daily dosing similar in efficacy to three times a day dosing and more effective than once daily dosing.

Protocol C97-UIOS-003, a dose-response study, is reviewed at length in **Section 8.1.3.**

6.1 Relevant Human Experience

Since their introduction in the late 1970s and 1980s, topical β-adrenoceptor antagonists are used as first line pharmacotherapy due to their ocular hypotensive efficacy and fewer acute ocular side effects relative to the muscarinic agonists they replaced. The potential for systemic β-adrenoceptor blockade effects has become well known, and thus the use of these agents is cautioned or restricted in patients with chronic obstructive pulmonary disease, asthma, congestive heart failure, or severe heart block.

In the past two decades, several other topical therapies have been developed including α-adrenoceptor agonists, carbonic anhydrase inhibitors, and prostanoids. However, each of

these agents has its advantages and disadvantages with regard to ocular hypotensive efficacy, and ocular and systemic safety.

6.2 Foreign Experience

Unoprostone isopropyl ophthalmic solution 0.15% is not marketed in any foreign country.

Unoprostone isopropyl ophthalmic solution 0.12% was first approved on July 1, 1994, in Japan. It is currently marketed in Japan, South Korea, Argentina, Bolivia, Brazil, Chile, Columbia, Costa Rica, Ecuador, Egypt, El Salvador, Guatemala, Latvia, Lebanon, Maldives, Malta, Mexico, Pakistan, Panama, Paraguay, Peru, Philippines, Poland, Romania, Singapore, Sri Lanka, Thailand, and Uruguay.

6.4 Human Pharmacology, Pharmacokinetics, & Pharmacodynamics – See Pharmacology Review

7 Description of Clinical Data Sources

Included in this medical officer's review are five clinical trials conducted in the United States [redacted] or conducted in Europe, Canada, or Israel:

- Two, six-month trials to evaluate the safety and IOP-lowering efficacy of unoprostone isopropyl ophthalmic solution 0.15% BID compared to timolol maleate mg/mL BID or betaxolol hydrochloride ophthalmic solution 0.5% BID in patients with open angle glaucoma or ocular hypertension (USA and Canada, Europe and Israel)
- A 4-week dose-ranging study comparing three different concentrations of unoprostone isopropyl ophthalmic solution, placebo, and timolol maleate 0.5% BID in patients with open angle glaucoma or ocular hypertension (USA)
- A three-period, three-treatment, crossover study comparing the cardiovascular effects of 5 days of unoprostone isopropyl ophthalmic solution 0.15% BID with vehicle placebo and timolol maleate 0.5% BID in normal subjects (USA)
- A two-period cross-over comparison of a single dose of topical unoprostone isopropyl ophthalmic solution 0.15% versus vehicle placebo on pulmonary function in adults with mild-to-moderate reversible obstructive airway disease (United Kingdom).

See **Table 3** – Description of Clinical Data Sources, page 6.

Also included is a brief synopsis of the submitted Adjunctive Therapy Study, Aqueous Humor Dynamics Study, Ocular Hemodynamics Study, and a Post-Marketing Safety Update Report from Japan for UIOS 0.12%.

Table 3 – Description of Clinical Data Sources

Protocol #	Phase Design	Treatment	Subjects Entered Each Treatment	Age Range (Mean)	Regimen / Duration of Drug Treatment	Completion Status (Starting Date)	Patient Population
Efficacy/Safety C97-UIOS-004	Phase III Triple-masked Parallel-group Active drug-controlled Randomized 30 centers	0.15% UIOS 0.5% TMOS	379 192	20-88 (60.6)	b.i.d. 6 months[1]	Complete – 6 months (23 April 98)	open angle glaucoma and ocular hypertension
Efficacy/Safety C97-UIOS-005	Phase III Triple-masked Parallel-group Active drug-controlled Randomized 28 centers	0.15% UIOS 0.5% TMOS 0.5% BHOS	278 138 140	26-85 (63.2)	b.i.d. 6 months[2]	Complete – 6 months (13 May 98)	open angle glaucoma and ocular hypertension
Dose-Ranging C97-UIOS-003	Phase II Double masked Active drug- and Placebo-controlled Dose Ranging Parallel-group Randomized 7 centers	0.06% UIOS 0.12% UIOS 0.15% UIOS 0.5% TMOS PL	48 49 47 47 46	25-82 (54.7)	b.i.d. 4 weeks	Complete (29 May 97)	open angle glaucoma and ocular hypertension
Cardiovascular Safety C98-UIOS-012	Phase I Active and Placebo controlled Double-masked 2 period crossover Randomized 1 center	0.15% UIOS 0.5% TMOS PL	29	18-37 (24.1)	b.i.d. 5 days for each treatment	Complete (24 Feb. 99)	normal subjects
Pulmonary Safety C98-UIOS-013	Phase II Double-masked Placebo-controlled Crossover Randomized 1 center	0.15% UIOS PL	17	21-61 (43)	Single dose for each study medication	Complete (25 Jan 99)	mild-to-moderate reversible obstructive airway disease

Table 3 – Description of Clinical Data Sources – Continued

Abbreviations:		
	UIOS	unoprostone isopropyl ophthalmic solution
	TMOS	timolol maleate ophthalmic solution
	BHOS	betaxolol hydrochloride ophthalmic solution
	PL	placebo

[1] The primary analysis of 6-month efficacy data for Study C97-UIOS-004 is reported in the original NDA submission. The study is ongoing for 12 months at 30 centers and 24 months at 20 centers for additional safety data.

[2] The primary analysis of 6-month efficacy data for Study C97-UIOS-005 is reported in the original NDA submission. The study is ongoing for a total of 12 months safety and efficacy information.

8 Clinical Studies

8.1.1 Study #1 Protocol C97-UIOS-004

Title: Comparison of the IOP-Lowering Efficacy and Safety of Unoprostone Isopropyl 0.15% Ophthalmic Solution Versus Timolol Maleate 0.5% Ophthalmic Solution Dosed Twice Daily in Subjects Diagnosed with Primary Open Angle Glaucoma or Ocular Hypertension

Study Design: A prospective, randomized, double-masked, active-controlled, parallel-group study.

Test Drug Schedule: Subjects instilled one drop of masked medication into the eligible eye(s) twice daily, once between 0700-1000 hr and once between 1900-2200 hr, for six months.

Investigator Number	Investigator	Number Randomized
155	**Robert C. Allen, M.D.** Richmond, Virginia 23219 USA	14
156	**Howard S. Barnebey, M.D.** Seattle, Washington 98104 USA	20
129	**Gregg J. Berdy, M.D.** Creve Coeur, Missouri 63141 USA	22
133	**Louis B. Cantor, M.D.** Indianapolis, Indiana 46202 USA	23
157	**Alan S. Crandall, M.D.** Salt Lake City, Utah 84132 USA	4
158	**Douglas G. Day, M.D.** Atlanta, Georgia 30342 USA	42
159	**Robert T. Fechtner, M.D.** Louisville, Kentucky 40202 USA	28
178	**Mitchell Friedlaender, M.D.** La Jolla, California 92037 USA	4
161	**Ronald L. Gross, M.D.** Houston, Texas 77030 USA	21
163	**Andrew G. Iwach, M.D.** San Francisco, California 94102 USA	4
164	**L. Jay Katz, M.D.** Philadelphia, Pennsylvania 19107 USA	4

Investigator Number	Investigator	Number Randomized
165	**Allan E. Kolker, M.D.** Creve Coeur, Missouri 63141 USA	9
166	**Richard A. Lewis, M.D.** Sacramento, California 95819 USA	15
167	**Jeffrey M. Liebmann, M.D.** New York, NY 10003 USA	10
168	**Alan I. Mandell, M.D.** Memphis, Tennessee 38119	30
138	**Thomas K. Mundorf, M.D.** Charlotte, North Carolina 28204 USA	23
180	**Paul H, Murphy, M.D.** Saskatchewan, Canada S7K 0M7	28
169	**Michael H. Rotberg, M.D.** Charlotte, North Carolina 28204 USA	26
182	**Kenneth Sall, M.D.** Bellflower, California 90706 USA	23
170	**John R. Samples, M.D.** Portland, Oregon 97201-4179 USA	4
171	**Paul N. Schacknow, M.D.** Lake Worth, Florida 33461 USA	30
172	**Janet B. Serle, M.D.** New York, New York 10029 USA	10
140	**Elizabeth Sharpe, M.D.** Mount Pleasant, South Carolina 29464 USA	41
173	**Mark B. Sherwood, M.D.** Gainesville, Florida 32610 USA	25
174	**Steven T. Simmons, M.D.** Albany, New York 12204 USA	10
116	**William C. Stewart, M.D.** Atlanta, Georgia 30339 USA	23
149	**Thomas R. Walters, M.D.** Austin, Texas 78746 USA	12
175	**Martin B. Wax, M.D.** St. Louis, Missouri 63110 USA	8

Investigator Number	Investigator	Number Randomized
176	Mark J. Weiss, M.D. Tulsa, Oklahoma 74104 USA	14
177	Jeffrey C. Whitsett, M.D. Houston, Texas 77055 USA	44

Reviewer's Comments:

It is preferred to have at least 10 patients per arm per center.

8.1.1 Study Design

This was a prospective, randomized, triple-masked, active-controlled, parallel-group comparison of UIOS 0.15% and TMOS 0.5% (2:1 randomization) to evaluate their efficacy in lowering IOP in subjects with unilaterally or bilaterally elevated IOP associated with a clinical diagnosis of POAG or OH.

The study consisted of two periods. During the first period, each subject completed a screening evaluation at Visit 1 and a washout period during which previous ocular hypotensive medication was discontinued, if applicable. In the second period, qualified subjects were randomized to one of the two treatment groups and instilled one drop of masked study medication into each eligible eye(s) twice daily for six months.[1]

Table C97-UIOS-004-01 - Washout Periods for Prior Therapy

Type of Therapy	Duration of Washout Period
Topical ocular β-adrenergic blockers	At least 4 weeks
UIOS	At least 4 weeks
Topical ocular α-adrenoreceptor agonists	At least 2 weeks
Topical ocular epinephrine-related medications	At least 2 weeks
Carbonic anhydrase inhibitors	At least 3 days
Topical ocular pilocarpine	At least 3 days

Subjects qualified for randomization at Visit 2 (Day 0, Baseline) if they had a post-washout or untreated IOP ≥ 22 mm Hg and ≤ 30 mm Hg in the eligible eye(s) during the baseline 12-hour diurnal IOP evaluation. For subjects with bilateral IOP elevations, the difference in IOP measurements could not be > 5 mm Hg at any time point during the baseline 12-hour diurnal evaluation. At the conclusion of the baseline 12-hour diurnal IOP evaluation, study personnel instilled the first drop of masked medication into the

[1] The study is ongoing for 12 months at 30 centers and 24 months at 20 centers for additional safety and efficacy data. The primary analysis of 6-month efficacy data is reported in this submission.

eligible eye(s) to demonstrate the proper dosing technique. One bottle of masked medication was dispensed at Visit 2, and additional masked medication was dispensed at subsequent visits so the subject had enough masked medication for the interval between visits.

Follow-up evaluations were to be completed at Weeks 2 and 6 and at Months 3 and 6. Morning IOP was to be measured at each visit.

Reviewer's Comments:

The applicant should not have re-used subjects from earlier studies (*see* **Table C97-UIOS-004-01** - Washout Periods for Prior Therapy).

Study Medications

- Unoprostone isopropyl 0.15% ophthalmic solution
- Timolol maleate 0.5% ophthalmic solution

All study treatments were provided in polyethylene bottles containing

Subjects were instructed to refrain from instilling masked medication on the mornings of clinic visits. If a subject instilled masked medication on the morning of a clinic visit, the visit was to be re-scheduled, preferably within the acceptable visit window.

Study Population

Inclusion Criteria

The following requirements had to be met during Period I [at Screening (Visit 1) and Baseline (Visit 2; Day 0)] for a subject to be eligible to participate in this clinical study. Subjects of either gender and any race could be enrolled into the study if they:

- were able and willing to give written informed consent
- were at least 18 years of age,
- had clinical presentation of unilaterally or bilaterally elevated IOP associated with a diagnosis of either POAG (including pseudoexfoliation glaucoma) or OH. Subjects with a diagnosis of unilateral POAG or OH were required to exhibit IOP within the normal range in the fellow eye without the benefit of IOP-lowering medications,

- had a post washout or untreated IOP ≥ 22 mm Hg and ≤ 30 mm Hg in the eligible eye(s) at one or more time points during the baseline 12-hour diurnal IOP evaluation. In subjects with bilateral POAG or OH, both eyes had to meet IOP criteria at the same baseline 12-hour diurnal time point,
- had a best-corrected distance VA of better than 20/200 by Modified ETDRS in eligible eye(s) at screening and baseline,
- were willing to undergo multiple venipunctures for laboratory assessments throughout the clinical study (at sites performing laboratory assessments),
- were willing to undergo endothelial cell count assessments (by specular microscopy) throughout the clinical study (at sites performing specular microscopy).

Exclusion Criteria

A subject could not participate if any of the following criteria existed during Period 1 [at Screening (Visit 1) and/or Baseline (Visit 2; Day 0)] in the eligible eye(s) for ocular or systemic conditions:

OCULAR CONDITIONS

- Subject had a history of use of topical, ocular prostaglandin-type medication (except UIOS) for control of elevated IOP (e.g., latanoprost).
- Subject required the use of more than one medicinal therapy (topical or systemic) for control of elevated IOP, including combination products.
- Subject had undergone laser or any other intraocular surgery within three (3) months of beginning Period 1 in the eligible eye(s).
- Subject had undergone filtration surgery within six (6) months of beginning Period 1 in the eligible eye(s).
- The difference in IOP measurements at any one time point during the Baseline 12-hour diurnal IOP evaluation was greater than five (5) mm Hg between eyes in subjects diagnosed with bilateral POAG or OH. If the subject had undergone laser, intraocular, or filtration surgery for reduction of IOP in one eye that was not to be treated in this clinical study, this criterion did not apply.
- Subject had a history of or currently required chronic use of other ocular medications during the study. Intermittent use of artificial tear products, lid scrubs and topical, allergy medications was allowed.
- Subject presented with corneal or lid abnormalities that would prevent accurate assessments with an applanation tonometer or specular microscope.
- Subject had a history of or presented with any progressive retinal or optic nerve disease apart from POAG.

- Subject had a history of or presented with elevated IOP caused by any process other than POAG (including pseudoexfoliation) or OH (i.e., pigment dispersion, congenital, narrow angle, or glaucoma secondary to trauma or uveitis).
- Subject had a history within thirty (30) days prior to Screening or presented with any infectious or chronic noninfectious conjunctivitis, keratitis, or moderate to severe blepharitis.
- Subject had a history within five (5) years of Screening or presented with intraocular inflammation (uveitis, iritis, iridocyclitis, etc.).
- Subject had a history within thirty (30) days prior to Screening or presented with severe dry eye syndrome (i.e., moderately severe epithelial erosions of cornea).
- Subject had a history of or presented with advanced cupping (cup to disc ratio > 0.8) and/or severe VF loss which in the opinion of the Investigator was functionally significant.
- According to the Investigator's best judgment, there was a risk of worsening of VF, optic disc cupping or VA as a possible consequence of participation in the study.
- Subject presented with any condition that restricted adequate examination of the anterior chamber, lens, posterior chamber, vitreous or fundus.
- Subject had a history of or presented with clinically significant, serious or severe ocular conditions (e.g., recurrent disease).
- Subject had previously used or was currently using ocular and/or systemic medications that interfered with the subject's participation in the study.
- Subject was known to have a hypersensitivity to clinical study medications or any of their components or to any diagnostic agents to be used in the study.

SYSTEMIC CONDITIONS

- Subject was currently pregnant or lactating.
- Subject was a female of childbearing potential and had not been consistently using reliable mechanical or hormonal form of contraception during the three (3) months prior to Screening and who did not agree to continue use of such contraception throughout the study.
- Subject had a history of or presented with unstable systemic disease (i.e., cardiovascular, hepatic, renal, or metabolic) as defined by the disease not being controlled with consistent systemic therapy in the thirty (30) days prior to Screening.
- Subject presented with abnormally low or high heart rate or blood pressure, as defined by the following criteria (after a 5-minute resting period in a sitting position):
  (a) heart rate < 50 bpm or > 100 bpm,
  (b) systolic blood pressure < 70 or > 180 mm Hg,
  (c) diastolic blood pressure < 50 or > 100 mm Hg.

- Subject had a history of or presented with systemic conditions contraindicated with the use of topical, ocular β-adrenergic blocking agents, including but not limited to, uncontrolled bronchial asthma, moderate to severe chronic obstructive pulmonary disease, moderate to severe sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, and/or cardiogenic shock.
- Subject had a history of or presented with clinically significant, serious, or severe medical or psychiatric conditions. Subjects with serious but stable systemic diseases (e.g., hypertension, diabetes or thyroid disease) could have been included in the study.
- At sites performing clinical laboratory assessments, subject presented with clinically significant laboratory abnormalities that could have interfered with the assessment of safety and/or efficacy of the clinical study medications.
- Subject had experienced or was anticipated to experience an alteration in dose or regimen of existing chronic, systemic therapy or the initiation of new therapy with agents which could have had a substantial effect on IOP.
- Subject had a history of active substance abuse (including alcohol) within the past two (2) years.
- Subject demonstrated a potential for non-compliance with the study protocol (e.g., dosing schedule, visit schedule, or study procedures).
- Subject had received previous treatment with investigational medications or devices within four (4) weeks prior to Screening unless local regulatory guidelines mandated a longer period.
- Subject had previously been randomized for treatment in this study.

CIBA Vision also reserved the right to declare a subject ineligible or non-evaluable based on medical evidence that indicated the subject was unsuitable for the study.

Efficacy Variables

The protocol defined primary efficacy variable in this study was the change from baseline in 12-hour diurnal IOP. The 12-hour diurnal IOP was defined as the mean of four IOP measurements taken during the morning (0800 ± 1 hour), mid-morning (+2 hours after study medication instillation), afternoon (+8 hours after study medication instillation) and evening (+12 hours after study medication instillation). The 12-hour diurnal IOP was evaluated on Day 0 and Month 6.

An 8-hour diurnal IOP was also recorded at Week 2 and Month 3 and was defined as the mean of three IOP measurements taken during the morning, mid-morning, and afternoon.

A Morning Trough IOP (0800 ± 1 hour) only was evaluated at Week 6.

See **Table C97-UIOS-004-02** - Schedule of Assessments, page 16.

Reviewer's Comments:

The agency did not agree with the assessment of mean diurnal IOP as the primary efficacy variable as stated in the protocol. The primary efficacy variable utilized in the review of this NDA was the assessment of mean IOP at each individual 8 AM, 10 AM, 4 PM, and 8 PM time point.

Safety Variables

Ocular safety was determined from ophthalmic examinations, including:
1) IOP
2) best-corrected distance visual acuity
3) manifest refraction
4) dilated ophthalmoscopy
5) slit lamp biomicroscopy (for approximately 180 subjects: 120 UIOS, 60 TMOS)
6) specular microscopy
7) visual field evaluation.

Additional ocular safety assessments included iris and eyelid photography for evaluation of changes in iris color, eyelid skin color, and eyelid hair growth and ocular symptom queries to evaluate blurred vision, burning/stinging, foreign body sensation, itching, photophobia, and dryness.

Photographs of the iris and eyelids were taken using standard equipment, film, and settings. A central photographic laboratory developed the films. Slides were prepared for subjective assessments and also transferred to compact disc for archiving. **Note: The number of subjects assessed photographically varied based on the quality of photos taken, as compared to the actual number of subjects assessed for safety.**

Two independent observers who were masked to study treatment reviewed slides. A change was defined as any visually perceptible change in color of the iris that could not be attributed to variation in the photographic conditions between any two time points. If the two readers did not agree, a third observer made the final decision regarding the change. Photographs also were used to assess eyelash density and eyelash length changes. Slides were projected at 13X magnification, and the length of 5 upper and 5 lower eyelashes from each eye were measured using a tablet capable of digitizing the measurements. The density of eyelashes was determined in the central centimeter of both upper and lower lids. Skin pigmentation was expected to vary due to sun exposure and other factors. Photography of the skin also is subject to variability due to glare. As a result, slides were compared to baseline slides only if the investigational site observed changes in skin pigmentation.

Systemic safety was determined from vital signs (brachial artery blood pressure and radial pulse after sitting for 5 minutes), clinical laboratory tests (hematology, biochemistry), and adverse event reports. Clinical laboratory tests were to be completed for approximately 150 subjects (100 UIOS 0.15%, 50 TMOS 0.5%).

Table C97-UIOS-004-02 - Schedule of Assessments

Visit Number	1	2	3	4	5	6
Procedures	**Screening**	**Baseline**	**W2**	**W6**	**M3**	**M6**
Written Informed Consent	X					
Medical History/ Demographics	X	X				
Inclusion/Exclusion Criteria Review	X	X				
Vital Signs[1]	X	X	X	X	X	X
Screening IOP[2]	X					
Morning Trough IOP[3]		X	X	X	X	X
12-Hour Diurnal IOP[4]		X				X
8-Hour Diurnal IOP[5]			X		X	
Ocular Symptoms Query	X	X	X	X	X	X
Best-Corrected Distance VA[6]	X	X	X	X	X	X
Manifest Refraction[7]	X	X*				X
Dilated Ophthalmoscopy	X	X*			X	X
Slit Lamp Biomicroscopy	X	X	X	X	X	X
Visual Fields[8]	X	X*				X
Gonioscopy[9]	X					
Iris/Eyelid Photography		X			X	X
Specular Microscopy[10]		X				X
Laboratory Evaluations[11]	X	X*				X
Pregnancy Test[12]		X				X
Adverse Events[13]		X	X	X	X	X

[1] Brachial artery blood pressure and radial pulse taken after sitting 5 minutes.

[2] Screening IOP could be measured at any time during the screening (SC) Visit.

[3] Morning Trough IOP was measured prior to morning dose of study medication at 0800 ± 1 hour.

[4] 12-Hour Diurnal IOP was obtained at BL and M6 and was defined as the mean of four (4) IOP measurements starting after and including the Morning Trough IOP measurement (0800 ± 1 hour). The BL 12-Hour Diurnal IOP measurements were taken at approximately +2, +8, and +12 hours after Morning Trough IOP (e.g., 1000, 1600, and 2000). The first instillation of study medication occurred after the +12 hour IOP measurement at the Baseline Visit. At M6, 12-Hour Diurnal IOP measurements were taken at approximately +2, +8 and +12 hours after study medication instillation (e.g., 1000, 1600 and 2000). All 12-hour Diurnal IOP measurements were to be performed within ± 30 minutes of the expected time.

[5] 8-hour Diurnal IOP was obtained at W2 and M3. 8-Hour Diurnal IOP was defined as the mean of three (3) IOP measurements starting after and including the Morning Trough IOP (0800 ± 1 hour) and approximately +2 and +8 hours after Morning Trough (e.g., 1000 and 1600). All 8-hour Diurnal IOP measurements were to be performed within ± 30 minutes of the expected time.

[6] Using modified ETDRS.

[7] Manifest refraction was repeated at W2, W6, and M3 if a change in VA of greater than 2 lines was noted on examination at any of these visits.

[8] If VF had been performed within 3 months of screening, results could be utilized to meet SC requirements, unless progression was suspected (Humphrey VF 24-2 or 30-2).

[9] If gonioscopy had been performed within 12 months of screening, results could be utilized to meet SC requirements unless a change in gonioscopy was suspected.

[10] Specular Microscopy (for endothelial cell count) was to be obtained on approximately 180 subjects at selected centers in the USA.

Table C97-UIOS-004-02 - Schedule of Assessments - Continued

[11] Standard hematology and biochemistry were to be obtained on approximately 150 subjects at selected centers in the USA. Clinically significant abnormalities were retested for final Investigator decision as to appropriateness of subject's participation in clinical study. For sites performing laboratory testing, SC and BL could not be the same day as results had to have been received and reviewed by the Investigator to determine subject eligibility.

[12] If the result of urine test was judged as inconclusive, the test was repeated using a test kit of a different lot number. If again the result was inconclusive, a serum pregnancy test result had to be negative before the female subject could be enrolled or continue to participate in clinical study.

[13] Treatment emergent AEs were reported after treatment was started at BL.

* These tests were repeated at BL ONLY if the SC and BL visits were more than 3 months apart.

Subject Disposition and Demographics

Of the 571 randomized subjects, 379 subjects were assigned to treatment with UIOS 0.15%, and 192 were assigned to treatment with TMOS 0.5%. Subject disposition is summarized in the table below.

Table C97-UIOS-004-03 - Subject Disposition

	Number of Subjects	
	UIOS 0.15%	TMOS 0.5%
Randomized	379	192
Discontinued prematurely	83	24
Completed Month 6	296	168
Included in intent-to-treat efficacy analysis	373	189
Included in per-protocol efficacy analysis	364	184
Included in safety evaluations	379	192

Table C97-UIOS-004-04 -Summary of Premature Discontinuations from the Study

	Number (%) of Subjects	
Primary reason for discontinuation	UIOS 0.15% (N=379)	TMOS 0.15% (N=192)
Adverse event	22 (5.8%)	11 (5.7%)
Treatment failure	29 (7.6%)	3 (1.6%)
Protocol violation	17 (4.5%)	7 (3.6%)
Lost to follow-up	5 (1.3%)	2 (1.0%)
Death	2 (0.5%)	0 (0.0%)
Withdrawal of consent	7 (1.8%)	0 (0.0%)
Other	1 (0.3%)	1 (0.5%)

There were no significant differences in baseline mean intraocular pressures between the treatment groups at any recorded IOP time (8 AM, 10 AM, 4 PM, or 8 PM) at Visit 2.

Table C97-UIOS-004-05 – Discontinued Patients and Reason

Investigator	Patient	Treatment	Reason
116	1002	UIOS 0.15%	Protocol Violation – did not qualify OU
	1005	UIOS 0.15%	Withdrawal of consent
	1006	UIOS 0.15%	Treatment failure – IOP not controlled
	1008	UIOS 0.15%	Treatment failure – IOP not controlled
	1022	UIOS 0.15%	Treatment failure – IOP not controlled
129	1103	UIOS 0.15%	Treatment failure – IOP not controlled
	1108	UIOS 0.15%	Death – cardiac arrest
	1112	UIOS 0.15%	Treatment failure – IOP not controlled
	1115	UIOS 0.15%	Withdrawal of consent
	1116	UIOS 0.15%	Withdrawal of consent
133	1209	UIOS 0.15%	Adverse Event – red eyes, headache
138	1302	UIOS 0.15%	Treatment failure – IOP not controlled
	1312	UIOS 0.15%	Protocol Violation – hx of Xalatan use
	1316	UIOS 0.15%	Protocol Violation – used excluded med
	1318	UIOS 0.15%	Protocol Violation – hx of Xalatan use
140	1418	UIOS 0.15%	Adverse Event – blurred vision, pain
	1419	UIOS 0.15%	Treatment failure – IOP not controlled
	1420	UIOS 0.15%	Treatment failure – IOP not controlled
	1431	UIOS 0.15%	Protocol Violation – hx of Xalatan use
	1435	UIOS 0.15%	Protocol Violation – baseline IOPs too high
	1436	UIOS 0.15%	Treatment failure – IOP not controlled
	1439	UIOS 0.15%	Treatment failure – IOP not controlled
149	4001	UIOS 0.15%	Withdrawal of Consent
	4003	UIOS 0.15%	Treatment failure – IOP not controlled
155	1501	UIOS 0.15%	Treatment failure – IOP not controlled
	1503	UIOS 0.15%	Adverse Event – penile rash
	1506	UIOS 0.15%	Withdrawal of Consent – blackouts, SOB
	1507	UIOS 0.15%	Treatment failure – IOP not controlled
	1509	UIOS 0.15%	Adverse Event – wheezing
	1514	UIOS 0.15%	Adverse Event – palpitations
156	1610	UIOS 0.15%	Adverse Event – burning
	1616	UIOS 0.15%	Adverse Event – Bell's Palsy
157	1702	UIOS 0.15%	Adverse Event – rash
158	1805	UIOS 0.15%	Adverse Event – Bell's Palsy
	1815	UIOS 0.15%	Protocol Violation – mis-scheduled drops
	1824	UIOS 0.15%	Treatment failure – IOP not controlled
	1826	UIOS 0.15%	Protocol Violation – noncompliant w/ sched
	1833	UIOS 0.15%	Adverse Event – palpitations
	1835	UIOS 0.15%	Treatment failure – IOP not controlled
159	1903	UIOS 0.15%	Adverse Event – burning/stinging
	1915	UIOS 0.15%	Adverse Event – pneumonia, PAT
161	2108	UIOS 0.15%	Treatment failure – IOP not controlled
	2115	UIOS 0.15%	Protocol Violation – dc treatment drug
	2116	UIOS 0.15%	Protocol Violation – pt started T1/2
163	2304	UIOS 0.15%	Withdrawal of Consent – nausea, sleepy
166	2609	UIOS 0.15%	Treatment failure – IOP not controlled
168	2805	UIOS 0.15%	Protocol Violation – histoplasmosis
	2828	UIOS 0.15%	Adverse Event – decreased HR

Table C97-UIOS-004-05 – Discontinued Patients and Reason - Continued

Investigator	Patient	Treatment	Reason
169	2909	UIOS 0.15%	Treatment failure – IOP not controlled
	2913	UIOS 0.15%	Treatment failure – IOP not controlled
	2914	UIOS 0.15%	Treatment failure – IOP not controlled
	2922	UIOS 0.15%	Adverse Event – headaches/brain lesions
	2924	UIOS 0.15%	Lost to Follow-up
171	3101	UIOS 0.15%	Protocol Violation – mis-scheduled drops
	3103	UIOS 0.15%	Protocol Violation – mis-scheduled drops
	3104	UIOS 0.15%	Protocol Violation – mis-scheduled drops
	3120	UIOS 0.15%	Adverse Event – ovarian cancer
172	3203	UIOS 0.15%	Adverse Event – SOB, tinnitus, anxiety
	3209	UIOS 0.15%	Lost to Follow-up
	3210	UIOS 0.15%	Adverse Event – indigestion, alopecia, rash
173	3305	UIOS 0.15%	Adverse Event – impotence, wt loss
	3307	UIOS 0.15%	Protocol Violation – used excluded med
	3316	UIOS 0.15%	Adverse Event – allergy to drop
	3318	UIOS 0.15%	Adverse Event – atopic keratitis
	3321	UIOS 0.15%	Lost to Follow-up
	3324	UIOS 0.15%	Other – sent to prison
	3325	UIOS 0.15%	Adverse Event – allergic conjunctivitis
174	3403	UIOS 0.15%	Treatment failure – IOP not controlled
	3408	UIOS 0.15%	Death – cardiac arrest
	3409	UIOS 0.15%	Lost to Follow-up
176	3607	UIOS 0.15%	Treatment failure – IOP not controlled
	3614	UIOS 0.15%	Treatment failure – IOP not controlled
177	3727	UIOS 0.15%	Lost to Follow-up
	3739	UIOS 0.15%	Treatment failure – IOP not controlled
	3742	UIOS 0.15%	Treatment failure – IOP not controlled
180	3908	UIOS 0.15%	Protocol Violation – baseline IOP too high
	3915	UIOS 0.15%	Protocol Violation – pigment dispersion
	3916	UIOS 0.15%	Withdrawal of Consent – keratitis, haze
182	4202	UIOS 0.15%	Treatment failure – IOP not controlled
	4209	UIOS 0.15%	Adverse Event – chest pain, SOB
	4211	UIOS 0.15%	Treatment failure – IOP not controlled
	4215	UIOS 0.15%	Treatment failure – IOP not controlled
	4219	UIOS 0.15%	Treatment failure – IOP not controlled
116	1001	TMOS 0.5%	Other – death of daughter
129	1120	TMOS 0.5%	Protocol Violation – incl/excl criteria
133	1214	TMOS 0.5%	Adverse Event – respiratory failure
140	1415	TMOS 0.5%	Protocol Violation – hx of Xalatan use
	1423	TMOS 0.5%	Treatment failure – IOP not controlled
149	4012	TMOS 0.5%	Adverse Event – loss of energy, blur
156	1619	TMOS 0.5%	Adverse Event – coronary artery dz
158	1834	TMOS 0.5%	Adverse Event – cataract
159	1905	TMOS 0.5%	Adverse Event – allergic rhinitis
	1910	TMOS 0.5%	Adverse Event – allergic reaction
	1927	TMOS 0.5%	Adverse Event – pt fell asleep at testing
164	2402	TMOS 0.5%	Protocol Violation – excluded meds

Table C97-UIOS-004-05 – Discontinued Patients and Reason - Continued

Investigator	Patient	Treatment	Reason
166	2601	TMOS 0.5%	Protocol Violation – poor birth control
	2614	TMOS 0.5%	Protocol Violation – excluded meds
169	2919	TMOS 0.5%	Adverse Event – dizziness, HA
171	3102	TMOS 0.5%	Protocol Violation – mis-scheduled meds
	3106	TMOS 0.5%	Adverse Event – narrow angle glaucoma
	3117	TMOS 0.5%	Adverse Event – chest pain, ↑HR, sweats
173	3311	TMOS 0.5%	Adverse Event – chest pain
	3314	TMOS 0.5%	Adverse event – flu-syndrome
176	3606	TMOS 0.5%	Treatment failure – IOP not controlled
177	3714	TMOS 0.5%	Lost to Follow-up
	3740	TMOS 0.5%	Protocol Violation – incl/excl criteria
	3741	TMOS 0.5%	Lost to Follow-up
178	2001	TMOS 0.5%	Treatment failure – IOP not controlled

Reviewer's Comments:

Two subjects receiving TMOS 0.5% had their treatment unmasked by CIBA Vision to determine if an expedited safety report was required (Patients 3311 and 3314).

Three subjects receiving UIOS 0.15% were categorized as "Withdrawal of Consent," but appeared to have significant adverse events associated with their withdrawal (Patients 1506, 2304, and 3916).

Only 78% of the UIOS 0.15% randomized subjects completed Month 6 of therapy (versus 88% of the TMOS 0.5% randomized subjects). This is a relatively low percentage of subjects.

Demographic characteristics for the intent-to-treat population are summarized in **Table C97-UIOS-004-06**. The treatment groups were comparable for age, gender, and race but significantly different for the frequency distribution of eye color (P=0.014).

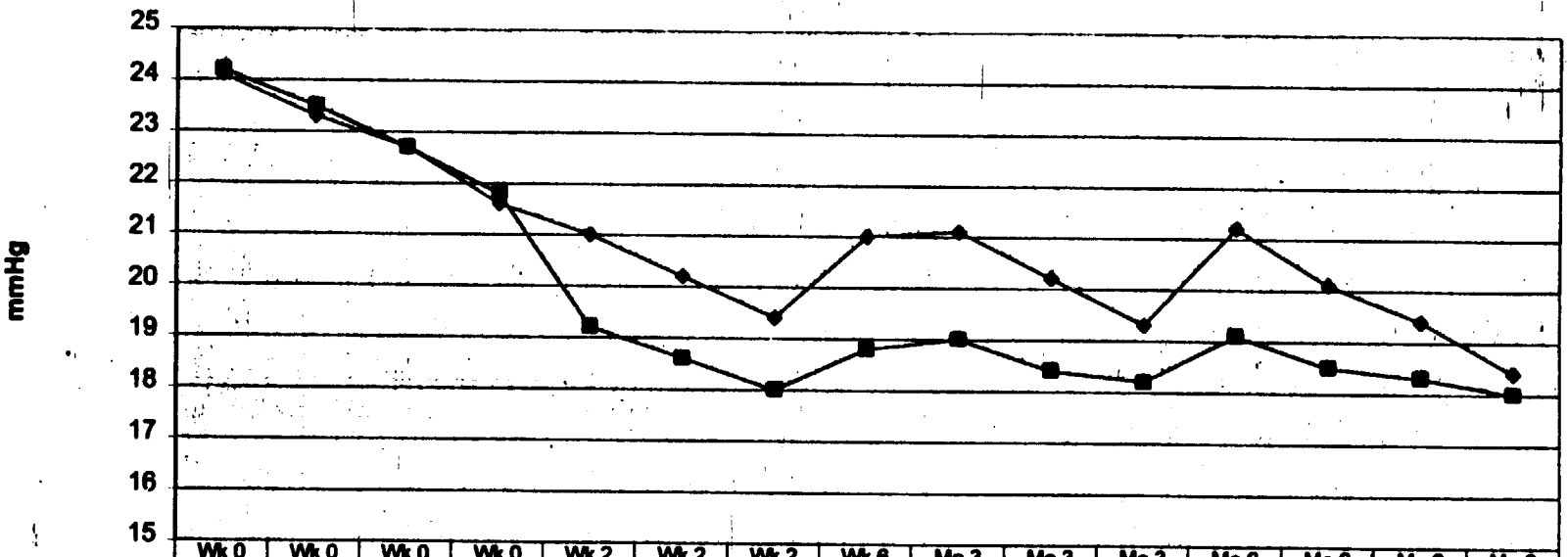
Table C97-UIOS-004-06 - Summary of Demographic Characteristics (Intent-to-Treat)

		UIOS 0.15%	TMOS 0.5%	P-value
Number randomized		N = 379	N = 192	
Gender (%)	Female	55%	57%	0.722
	Male	45%	43%	
Race (%)	Caucasian	74%	73%	0.994
	Black	21%	21%	
	Hispanic	4%	5%	
	Other	<1%	1%	
Age (years)	20-29	1%	2%	0.132
	30-39	6%	4%	
	40-49	15%	14%	
	50-59	24%	25%	
	60-69	30%	24%	
	70-79	22%	28%	
	Mean (S.D.)	60.1 (12.4)	61.6 (12.9)	
Iris Color (%)	Black	0%	1%	0.014
	Brown	46%	43%	
	Hazel	16%	24%	
	Green	4%	7%	
	Blue	30%	21%	
	Gray	2%	1%	
	Other	2%	3%	
Diagnosis OD (%)	Ocular HTN	47%	46%	0.917
	POAG	51%	52%	
	Pseudoexfoliation	1%	1%	
Diagnosis OS (%)	Ocular HTN	47%	47%	0.944
	POAG	50%	52%	
	Pseudoexfoliation	1%	1%	

8.1.1 Efficacy – Protocol C97-UIOS-004 Intent-to-Treat Population

Primary Efficacy Variable

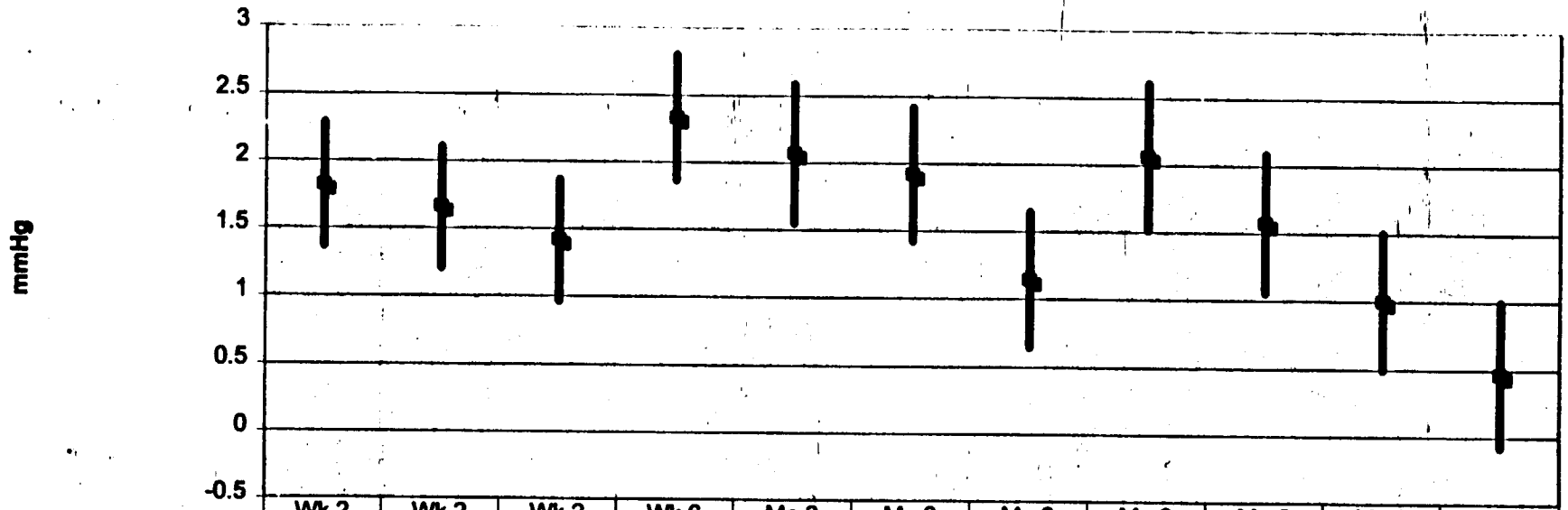
Mean IOP per Visit and Time



	Wk 0 (8 AM)	Wk 0 (10 AM)	Wk 0 (4 PM)	Wk 0 (8 PM)	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
UIOS	24.1	23.3	22.7	21.6	21	20.2	19.4	21	21.1	20.2	19.3	21.2	20.1	19.4	18.4
TMOS	24.2	23.5	22.7	21.8	19.2	18.6	18	18.8	19	18.4	18.2	19.1	18.5	18.3	18

Reviewer's Comments: *Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%. There is also greater variation in the IOP during the day with UIOS 0.15%.*

Mean Difference (UIOS - TMOS) with 95% Confidence Intervals

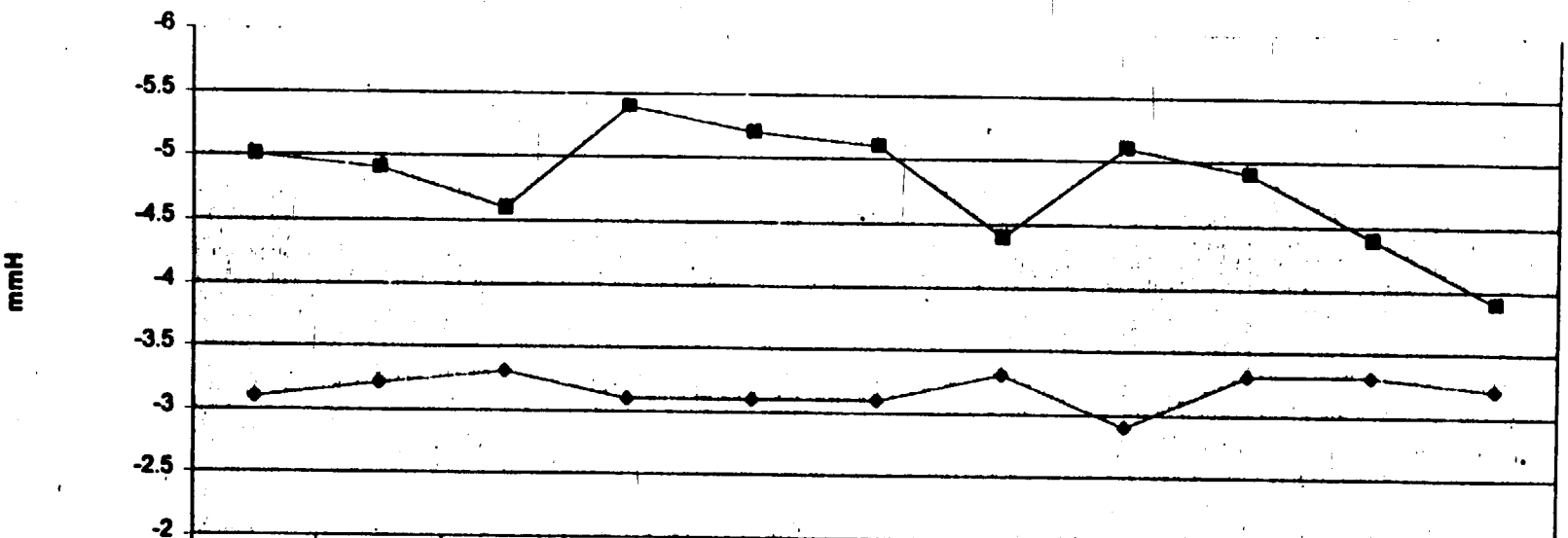


	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
Lower CI	1.36	1.2	0.96	1.86	1.55	1.42	0.64	1.51	1.05	0.49	-0.08
Upper CI	2.29	2.11	1.87	2.8	2.59	2.42	1.65	2.61	2.09	1.51	1
Mean Difference	1.82	1.66	1.42	2.33	2.07	1.92	1.14	2.06	1.57	1	0.46

Reviewer's Comments:

The mean difference between UIOS and TMOS is statistically significant at almost all time points. The 95% confidence interval crosses zero at Month 6 (8:00 PM).

Change in IOP from Baseline per Visit and Time



	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
UIOS	-3.1	-3.2	-3.3	-3.1	-3.1	-3.1	-3.3	-2.9	-3.3	-3.3	-3.2
TMOS	-5	-4.9	-4.6	-5.4	-5.2	-5.1	-4.4	-5.1	-4.9	-4.4	-3.9

Reviewer's Comments: *The mean change-from-baseline ranged from –2.9 mmHg to –3.3 mmHg for UIOS 0.15% and from –3.9 mmHg to –5.5 mmHg for TMOS 0.5%. Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%.*

8.1.1 Safety

Adverse Events

Serious adverse events other than death were reported for 17/379 (4.5%) subjects treated with UIOS 0.15% and for 16/192 (8.3%) subjects treated with TMOS 0.5%. These other serious AEs resulted in premature discontinuation from the study for six subjects treated with UIOS 0.15% and four subjects treated with TMOS 0.5%.

Table C97-UIOS-004-07– Serious Adverse Events

Treatment	Investigator	Patient	AE Code	Final Outcome	D/C from Study
Double-masked Period					
UIOS	129	1108	Myocardial infarct	Death	N/A
		1111	Pancreatitis	Complete recovery	No
	140	1427	Arteriosclerosis CVA	Present & unchanged Complete recovery	No
		1428	Coronary occlusion	Complete recovery	No
	155	1513	Granuloma	Complete recovery	No
	156	1616	Facial paralysis	Present & unchanged	Yes
	158	1805	Facial paralysis	Condition improving	Yes
	159	1915	Pneumonia Atrial fibrillation	Complete recovery Complete recovery	Yes
	161	2112	Tenosynovitis	Incomplete recovery	No
	167	2707	Pneumonia	Complete recovery	No
	168	2828	Arrhythmia	Incomplete recovery	Yes
	169	2907	Lung disorder	Complete recovery	No
		2917	Bladder Ca Prostatic Ca	Complete recovery Complete recovery	No
		2922	Headache	Present & unchanged	Yes
	171	3120	Carcinoma Abdominal pain	Condition worsening Incomplete recovery	Yes
	173	3322	Arthritis	Incomplete recovery	No
	174	3408	Cardiac arrest	Death	N/A
	175	3505	Hematuria	Condition improving	No
	177	3742	DVT	Complete recovery	No
TMOS	116	1001	CHF	Complete recovery	No
		1023	Carcinoma	Complete recovery	No
	129	1102	Arthritis	Complete recovery	No
	133	1214	Pharyngitis Acidosis Overdosage Perforated ulcer Kidney failure Respiratory failure Shock	Condition improving Present & unchanged Present & unchanged Condition improving Present & unchanged Present & unchanged Present & unchanged	Yes
	138	1313	Back pain	Condition improving	No
	140	1424	Neoplasm	Complete recovery	No
	156	1619	Coronary artery dz	Condition improving	Yes
	158	1831	Prostatic ca	Present & unchanged	No
	159	1906	Flu syndrome	Complete recovery	No

Table C97-UIOS-004-07– Serious Adverse Events – Continued

Treatment	Investigator	Patient	AE Code	Final Outcome	D/C from Study
Double-masked Period					
TMOS	169	2901	Back pain	Complete recovery	No
		2905	Accidental injury	Incomplete recovery	No
	173	3311	Chest pain	Condition improving	Yes
		3314	Asthma Flu syndrome	Complete recovery Complete recovery	Yes
	177	3714	Cerebral ischemia	Complete recovery	No
	180	3920	Prostatic ca	Present & unchanged	No
	182	4214	Venereal warts	Incomplete recovery	No

Two deaths occurred during the study:

1) Subject 1108 (UIOS 0.15%) was a 68-year-old male who entered the study with a history of hypertension. On the day of his Month 3 clinic visit, the subject presented with a 1.5 to 2 hour history of chest pain associated with diaphoresis and a syncopal episode. When the subject returned for the afternoon IOP check, he presented with increasing chest pain and experienced cardiac arrest. Full cardiopulmonary resuscitation and electrocardioversion were administered by emergency medical technicians at the site. The subject stabilized and was transferred to the hospital where he experienced another myocardial infarction, developed asystole, and died.

2) Subject 3408 (UIOS 0.15%) was a 59-year-old male who experienced cardiac arrest and died approximately six months after starting masked study medication. The subject had a history of hypertension.

Twenty-two subjects (5.8%) receiving UIOS 0.15% discontinued from the study due to adverse events. Eleven subjects (5.7%) receiving TMOS discontinued from the study due to adverse events.

The most frequent ocular adverse events in subjects treated with UIOS 0.15% were burning and stinging upon instillation (27%), burning and stinging (25%), itching (16%), and dry eyes (16%).

The most frequent non-ocular adverse events in subjects treated with UIOS 0.15% were flu syndrome (7%), pharyngitis (5%), headache (5%) and sinusitis (4%).

Table C97-UIOS-004-08 – Non-ocular and ocular treatment-emergent adverse events with an incidence ≥ 2% regardless of relationship to study treatment

	UIOS 0.15% Subjects		TMOS 0.5% Subjects	
	N	%	N	%
Total with at least one AE	323	85.2	157	81.8
Body as a whole:	***78***	***20.6***	***44***	***22.9***
Accidental injury	7	1.8	4	2.1
Asthenia	3	0.8	5	2.6
Back pain	6	1.6	4	2.1
Flu syndrome	27	7.1	10	5.2
Headache	17	4.5	11	5.7
Pain	12	3.2	5	2.6
Cardiovascular system:	***32***	***8.4***	***14***	***7.3***
Hypertension	15	4.0	9	4.7
Metabolic and nutritional disorders	***14***	***3.7***	***11***	***5.7***
Hypercholesteremia	5	1.3	6	3.1
Respiratory system:	***59***	***15.6***	***31***	***16.1***
Bronchitis	6	1.6	4	2.1
Cough increased	7	1.8	5	2.6
Pharyngitis	18	4.7	6	3.1
Rhinitis	10	2.6	2	1.0
Sinusitis	15	4.0	14	7.3
Special senses:	***278***	***73.4***	***124***	***64.6***
Abnormal vision	40	10.6	20	10.4
Blepharitis	8	2.1	3	1.6
Burning/stinging	96	25.3	28	14.6
Burning/stinging upon drug instillation	103	27.2	38	19.8
Cataract specified	10	2.6	6	3.1
Conjunctivitis	11	2.9	3	1.6
Corneal lesion	5	1.3	6	3.1
Discharge	12	3.2	5	2.6
Dry eyes	61	16.1	23	12.0
Eye hemorrhage	2	0.5	5	2.6
Eye pain	9	2.4	4	2.1
Eyelid disorder	19	5.0	8	4.2
Foreign body sensation	48	12.7	28	14.6
Injection	41	10.8	28	14.6
Irritation	9	2.4	5	2.6
Itching	62	16.4	26	13.5
Keratitis	13	3.4	4	2.1
Lacrimation disorder	34	9.0	19	9.9
Photophobia	21	5.5	8	4.2

Iris Color Change

282 subjects treated with UIOS 0.15% and 159 subjects treated with TMOS 0.5% were assessed for potential iris color changes. Iris/Eyelid photography was performed at Baseline, Month 3, and Month 6 (and planned at Month 9 and Month 12).

No evaluated subjects were considered to have had a change in iris color between the baseline and Month 6 visits. The two primary independent readers agreed in their subjective assessments of iris color change for all but four subjects, two treated with UIOS 0.15% and two treated with TMOS 0.5%. For these four subjects, the third independent determined that no changes in iris color occurred.

Reviewer's Comments:

Subject #1613 was reported to have bilateral mild iris pigmentation change at Month 3, and subject #1611 was reported to have mild bilateral hyperpigmentation of the eyelashes at Month 3. However, neither of the changes was confirmed photographically by three independent observers who were masked to the treatment.

This reviewer agrees that changes in iris pigmentation and lash pigmentation cannot be identified photographically for these subjects.

Eyelashes

EYELASH DENSITY

The mean change from baseline in eyelash density was small and similar for the two treatment groups. At Month 6, the mean change from baseline was statistically significant for lower-lid lashes on both eyes for subjects treated with UIOS 0.15%. At Month 3, the mean change from baseline was statistically significant for upper-lid lashes for right eyes of subjects treated with TMOS 0.5%.

At Months 3 and 6, no statistically significant differences between the treatment groups were observed for the mean change from baseline in density of eyelashes on either the lower or the upper lid.

Table C97-UIOS-004-09 – Eyelash Density (Lashes/0.5 cm) – Intent to Treat

Visit		UIOS 0.15%		TMOS 0.5%	
		OD	OS	OD	OS
Lower Lid					
Month 3	N	265	264	144	144
	Baseline	14.8	14.7	14.4	14.7
	Mean	15.0	14.9	14.4	14.6
	Mean Change	0.2	0.2	0.0	-0.1
	P- value[1]	0.160	0.172	0.915	0.684
Month 6	N	244	244	139	139
	Baseline	14.8	14.6	14.3	14.6
	Mean	15.2	14.9	14.6	14.5
	Mean Change	0.4	0.3	0.3	-0.1
	P- value[1]	**0.003**	**0.016**	0.218	0.732
Upper Lid					
Month 3	N	265	263	144	144
	Baseline	27.8	27.8	28.3	27.8
	Mean	27.7	27.6	27.8	27.8
	Mean Change	-0.2	-0.2	-0.5	0.0
	P- value[1]	0.314	0.348	**0.025**	0.853
Month 6	N	244	244	139	139
	Baseline	27.8	27.7	28.1	27.7
	Mean	27.7	27.5	28.0	27.7
	Mean Change	-0.1	-0.2	-0.1	-0.1
	P- value[1]	0.706	0.237	0.763	0.845

[1] *P*-value for the within-treatment change from baseline based from the paired t-test.

Reviewer's Comments:

Changes in eyelash density as assessed by the photographic evaluation do not appear clinically relevant.

EYELASH LENGTH

Table C97-UIOS-004-10 – Eyelash Length (mm) – Intent to Treat

Visit		UIOS 0.15%		TMOS 0.5%	
		OD	OS	OD	OS
Lower Lid					
Month 3	N	261	259	142	142
	Baseline	4.73	4.75	4.51	4.65
	Mean	4.92	4.95	4.68	4.73
	Mean Change	0.19	0.20	0.17	0.08
	P- value[1]	<0.001	<0.001	0.001	0.142
Month 6	N	243	241	137	135
	Baseline	4.71	4.72	4.52	4.67
	Mean	5.04	5.02	4.71	4.70
	Mean Change	0.33	0.30*	0.19	0.02*
	P- value[1]	<0.001	<0.001	<0.001	0.665
Upper Lid					
Month 3	N	262	263	143	142
	Baseline	6.57	6.46	6.50	6.45
	Mean	6.65	6.54	6.56	6.44
	Mean Change	0.08	0.08	0.06	-0.01
	P- value[1]	0.143	0.117	0.373	0.908
Month 6	N	243	240	139	137
	Baseline	6.57	6.47	6.56	6.49
	Mean	6.70	6.51	6.44	6.27
	Mean Change	0.13*	0.04*	-0.12*	-0.22*
	P- value[1]	0.013	0.494	0.066	0.003

[1] *P*-value for the within-treatment change from baseline based from the paired t-test.

* Between-treatment difference for mean change from baseline is statistically significant; *P*-value ≤ 0.050 from analysis of variance with factors for treatment, center, and treatment-by-center interaction.

Reviewer's Comments:

Changes in eyelash length as assessed by the photographic evaluation are consistent with an ocularly administered prostaglandin-type effect. Note the mean change in lower lid eyelash length at Month 6 in the UIOS 0.15% randomized subjects.

Visual Acuity

Table C97-UIOS-004-11 – Visual Acuity Tabulated by Changes in Line Number (Six-Months Versus Baseline)

		Treatment Group			
		UIOS 0.15%		TMOS 0.5%	
	Line Changes	N	%	N	%
OD	N	358	100	179	100
	≥ -2	6	1.7	4	2.2
	> -2 to ≤ -1	36	10.1	18	10.1
	> -1 to < 0	88	24.6	35	19.6
	0	69	19.3	41	22.9
	> 0 to < +1	104	29.1	50	27.9
	≥ +1 to < +2	50	14.0	24	13.4
	≥ +2	5	1.4	7	3.9
OS	N	348	100	180	100
	≥ -2	1	0.3	3	1.7
	> -2 to ≤ -1	39	11.2	19	10.6
	> -1 to < 0	89	25.6	46	25.6
	0	80	23.0	35	19.4
	> 0 to < +1	96	27.6	46	25.6
	≥ +1 to < +2	35	10.1	21	11.7
	≥ +2	8	2.3	10	5.6

Reviewer's Comments:

There are no clinically significant differences in visual acuity tabulated by changes in line number.

Manifest Refraction

There are no substantial changes from the screening examination to Month 6 observed for either treatment group. Differences between treatments are not statistically or clinically significant.

Endothelial Cell Counts

Table C97-UIOS-004-12 – Endothelial Cell Counts – Intent to Treat

Visit		UIOS 0.15%		TMOS 0.5%	
		OD	OS	OD	OS
Endpoint*	N	100	98	54	48
	Baseline	2562.5	2547.4	2435.9	2452.4
	Mean	2590.5	2557.1	2425.9	2450.1
	Mean Change	28.0**	9.7	-9.9**	-2.3
	P- value[1]	0.013	0.411	0.598	0.885
Month 6	N	79	77	48	48
	Baseline	2536.9	2529.9	2440.4	2463.4
	Mean	2575.4	2546.5	2421.8	2458.3
	Mean Change	38.5**	16.5	-18.6**	-5.1
	P- value[1]	0.002	0.205	0.355	0.144

[1] *P*-value for the within-treatment change from baseline from the paired t-test.

* Endpoint = a subject's last observation after baseline.

** Between-treatment difference for mean change from baseline is statistically significant; *P*-value ≤ 0.050 from analysis of variance with factors for treatment, center, and treatment-by-center interaction.

Reviewer's Comments:

Mean endothelial cell count at Month 6 is statistically significantly greater in the right eye (OD) for UIOS 0.15%. This increase is not clinically relevant.

Slit Lamp Examinations

The percentage of subjects who experienced a change from baseline in slit lamp examinations was similar for the two treatment groups at each follow-up examination.

The percentages of subjects having any worsening in slit lamp examinations from baseline to any follow-up visit were comparable between treatments.

Dilated Ophthalmoscopy

The percentage of subjects who experienced a change from screening was small and similar for the two treatment groups at each follow-up examination.

The percentage of subjects with any worsening from screening to any follow-up visit was similar for the two treatment groups.

Cup-to-Disc Ratio

The mean change from screening to Month 6 in cup-to-disc ratio is small and comparable for the two treatment groups at both Month 3 and Month 6. Neither the within-treatment change from baseline nor the difference between treatments is statistically significant.

Visual Field Examination

The percentage of subjects with changes [mean defect (dB) and investigator's evaluation of glaucomatous versus non-glaucomatous progression] from baseline to Month 6 in Humphrey visual field examinations was small and comparable for the two treatment groups.

Vital Signs

No clinically or statistically significant changes from baseline were observed for systolic blood pressure or diastolic blood pressure at any of the follow-up visits for either treatment group. No clinically or statistically significant changes from baseline in mean heart rate were observed at any follow-up visit for subjects treated with UIOS 0.15%.

For subjects treated with TMOS 0.5%, mean heart rate decreased from baseline at each visit. The mean decrease from baseline was -1.41, -0.91, -1.22, and -1.50 beats per minute at Week 2, Week 6, Month 3, and Month 6, respectively.

Clinical Laboratory Evaluation

The percentages of subjects with a normal value at screening and an abnormal value at Month 6 were low and comparable for the two treatment groups (for the subset of measured subjects). Laboratory test results that required special notification to the investigator were reported for three subjects treated with UIOS 0.15% and for no subjects treated with TMOS 0.5%.

Reviewer's Comments:

There does not appear to be a clinically significant difference between the treatment groups in the Clinical Laboratory Evaluations performed.

8.1.1 Reviewer's Summary of Efficacy and Safety

Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%. There is also greater variation in the IOP during the day with UIOS 0.15%.

The mean change-from-baseline IOP ranged from –2.9 mmHg to –3.3 mmHg for UIOS 0.15% and from –3.9 mmHg to –5.5 mmHg for TMOS 0.5%. Efficacy in IOP reduction has been demonstrated because IOP reduction from placebo would not have been expected to exceed 2 mmHg.

The iris/eyelid photographs read by masked independent observers did not reveal clinically relevant changes in iris color through Month 6 of treatment. Changes in lower lid eyelash length are consistent with an ocularly administered prostaglandin-type effect.

There were an unusually high percentage of subjects that did not complete the six-month study period.

8.1.2 Study #2 Protocol C97-UIOS-005

Title: Comparison of the IOP-lowering Efficacy and Safety of Unoprostone Isopropyl 0.15% Ophthalmic Solution versus Timolol Maleate 0.5% Ophthalmic Solution versus Betaxolol Hydrochloride 0.5% Ophthalmic Solution Dosed Twice Daily in Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension.

Test Drug Schedule: Subjects instilled one drop of masked medication into the eligible eye(s) twice daily, once between 0700-1000 hr and once between 1900-2200 hr, for six months.

Investigator	Investigator	Completed Subjects
Dr. Mark Batterbury St. Paul's Eye Unit Royal Liverpool University Hospital Liverpool L7 8XP U.K.	**Invest. No. 25**	20
Dr. Michael Birch Royal Victoria Hospital Department of Ophthalmology Queen Victoria Road Newcastle upon Tyne NE4 1 LP U.K.	**Invest. No. 24**	22
Dr. Anita Blixt-Wojechowski Ogonkliniken Universitetssjukhuset S-221 85 Lund Sweden	**Invest. No. 20**	20
Prof. Massimo Gilberto Bucci F. Cocco Clinica Oculistica Columbus Università Tor Vergata Via G. Moscati, 31/33 00168 Roma Italy	**Invest. No. 27**	14
Prof. Bertil Calel Ögonklinken St. Eriks Jukhus S-112 82 Stockholm Sweden	**Invest. No. 19**	17

Investigator	Investigator	Completed Subjects
Dr. Catherine Elisabeth Paulina de Graaf-Kret Oogheelkundig Medisch Centrum Amsterdamsevaart 26 B NL-2032 EK Hartem Netherlands	**Invest. No. 13**	35
Dr. Veva de Groot Universiteits Ziekenhuis Antwerpen Wilrijkstraat 10 2650 Edegem Belgium	**Invest. No. 01**	11
Mr. Jeremy Diamond Bristol Eye Hospital Lower Maudlin Street Bristol BS1 2LX U.K.	**Invest. No. 26**	12
Dr. Marc Goethals Universiteits Ziekenhuis St. Raphael Kapucijnenvoer 33 Leuven Belgium	**Invest. No. 02**	16
Dr. Chris Lohmann Universitätsaugenklinik Regensburg Franz Josef Strauss-Allee 11 D-93053 Rgensburg Germany	**Invest. No. 07**	4
Prof. Shlomo Melamed The Sam Rothberg Glaucoma Center Golschlager Eye Institute Sackler School of Medicine Tel-Aviv University Israel	**Invest. No. 12**	40
Dr. Andre Mermoud Hôpital Ophtalmologique Universitaire Jules Gonin 15, Avenue de France 1004 Lausanne Switzerland	**Invest. No. 21**	15
Dr. Peter Meurs Phacovision, Tongelrestraat 20 NL-5613 DG Eindhoven Netherlands	**Invest. No. 15**	16

Investigator	Investigator	Completed Subjects
Dr. Ron Neumann 28 Yehuda Hammacabi St. Tel-Aviv, 62005 Israel	**Invest. No. 11**	36
Pr. Jean-Philippe Nordmann Hospital Tenon Service d'Ophtalmologie 4, rue de la Chine F-75020 PARIS, France	**Invest. No. 04**	32
Prof. Nicola Orzalesi Clinica Oculistica dell'Università di Milano Ospedale S. Paolo Via A. Di Rudinì, 8 I-20142 Milano, Italy	**Invest. No. 28**	17
Dr. Peter Otto Anzengruber Strasse 7 D-12043 Berlin Germany	**Invest. No. 10**	39
Dr. Jordano Perez Hospital U. de Puerto Real Ctra. Nacional IV, Km. 665 E-11510 Puerto Real (Cadíz) Spain	**Invest. No. 17**	8
Pr. Jean-Paul Renard Hôpital d'Instruction des Armées du Val de Grace Service d'Ophtalmologie 74, bld Port Royal 75230 PARIS CEDEX 05 France	**Invest. No. 05**	6
Jean-Pr. François Rouland Hôpital Claude Huriez Service d'Ophtalmologie Aile Ouest, Place de Verdun Mail: 2, Av. Oscar Lambert 59037 LILLE CEDEX France	**Invest. No. 03**	0

Investigator	Investigator	Completed Subjects
Dr. Garcia Sanchez Hospital Universitario San Carlos Catedra de Oftalmologia Universidad Complutense Doctor Martin Lagos, S/N Spain	**Invest. No. 18**	20
Dr. Sonja Schölzel Britzer Damm 55 D-12347 Berlin Germany	**Invest. No. 08**	40
Mr. Sanjay Shah St Bart's Hospital West Smithfield London EC1A 7BE U.K.	**Invest. No. 23**	2
Dr. Reinhard Smettan Johannesstrasse 31 1. Floor D-70806 Kornwestheim Germany	**Invest. No. 09**	44
Dr. Gordana Sunaric Hôpital Universitaire de Geneve Service d'ophthalmologie 22 Rue Alcide Jentzer CH-1205 Geneve Switzerland	**Invest. No. 22**	8
Dr.Henk Veraart Oogheelkunde Rijswijk Madame Cutie laan 8 NL-2289 CA Rijswijk Netherlands	**Invest. No. 14**	32
Dr. Fernández Vila Instituto Galego de Oftalmoloxia Hospital Xetal de Galicia C/Galcras s/n Santiago dc Compostela Espana Spain	**Invest. No. 16**	30

Reviewer's Comments:

It is preferred to have at least 10 patients per arm per center.

8.1.2 Study Design

The study was conducted in 28 centers in Europe or Israel.

The major difference between Protocol C97-UIOS-005 and Protocol C97-UIOS-004 was the inclusion of a betaxolol hydrochloride 0.5% ophthalmic solution treatment arm (BHOS). BHOS 0.5% was selected as an additional active control because it is commonly prescribed as an ocular hypertensive medication.

An additional evening IOP measurement (8 PM) was taken at Week 2 and at Month 3.

As in C97-UIOS-004, the protocol defined primary efficacy variable was the change from baseline in 12-hour diurnal IOP.

The study is ongoing for a total of 12 months safety and efficacy information. The primary analysis of 6-month efficacy data for Study C97-UIOS-005 is reported in this original NDA submission.

Reviewer's Comments:

As in C97-UIOS-004, the agency did not agree with the assessment of mean diurnal IOP as the primary efficacy variable as stated in the protocol. The primary efficacy variable utilized in the review of this NDA was the assessment of mean IOP at each individual 8 AM, 10 AM, 4 PM, and 8 PM time point.

Other minor variations in Study Design are noted below in **Table C97-UIOS-005-01** - Schedule of Assessments.

Table C97-UIOS-005-01 - Schedule of Assessments

Procedures	Period I	Period II				
	Visit 1 Screening	Visit 2 Baseline	Visit 3 W2	Visit 4 W6	Visit 5 M3	Visit 6 M6
Urine pregnancy test		✓				
Vital signs	✓	✓	✓	✓	✓	✓
Screening IOP	✓					
Morning IOP				✓		
12-hour diurnal IOP		✓	✓		✓	✓
Best-corrected distance VA	✓	✓	✓	✓	✓	✓
Manifest refraction	✓	✓*				✓
Dilated ophthalmoscopy	✓	✓*			✓	✓
Slit lamp biomicroscopy	✓	✓	✓	✓	✓	✓
Visual fields (Humphrey)	✓	✓*				✓
Gonioscopy	✓					
Iris / Eyelid photography		✓			✓	✓
Ocular symptoms	✓	✓	✓	✓	✓	✓
Adverse events		✓	✓	✓	✓	✓

* Only performed if the screening and baseline measurements were more than 3 months apart

Study Medications

All study treatments provided were presented as 7.5 ml [redacted] polyethylene bottles, with 5 ml of liquid volume [redacted]
These bottles were filled with one of the following solutions listed in the following table

Table C97-UIOS-005-02 - Composition and Batch Numbers of the Study Treatments

Ingredients	Composition
UIOS 0.15% Batch No:	unoprostone isopropyl 0.15% = 1.5 mg/ml polysorbate 80, mannitol, edetate disodium, sodium hydroxide, hydrochloric acid, [redacted] water and benzalkonium chloride (0.015%) [redacted]
TMOS 0.5% Batch No:	timolol maleate 0.5% = 5.0 mg/ml [redacted]
BHOS 0.5% Batch No:	betaxolol hydrochloride 0.5% = 5.0 mg/ml [redacted]

Subject Disposition and Demographics

Of the 556 subjects enrolled into the study, 278 were randomized to UIOS 0.15%, 138 were randomized to TMOS 0.5% and 140 were randomized to BHOS 0.5%. Four hundred ninety (490) subjects completed the study up to the end of the six month triple-masked treatment period and 66 subjects discontinued the study in that period.

Table C97-UIOS-005-03 - Subject Disposition

	Number of Subjects		
	UIOS 0.15%	TMOS 0.5%	BHOS 0.5%
Randomized	278	138	140
Discontinued prematurely	40	12	14
Completed Month 6	238	126	126
Included in intent-to-treat efficacy analysis	276	137	139
Included in per-protocol efficacy analysis	213	111	115
Included in safety evaluations	278	138	140

Reviewer's Comments:

Four patients were not included in the ITT analysis because they discontinued before having the Week 2 visit.

Table C97-UIOS-005-04 -Summary of Premature Discontinuations from the Study

Number of subjects	UIOS 0.15%	TMOS 0.5%	BHOS 0.5%	Total
Randomized	278	138	140	556
Discontinued:	40	12	14	66
due to AE	9	5	2	16
therapy failure	19	1	5	25
protocol violation	2	3	1	6
lost to follow-up	1	2	1	4
death	1	0	0	1
withdrawal of consent	4	0	3	7
other	4	1	2	7
Completed Month 6	238	126	126	490

There were no significant differences in baseline mean intraocular pressures between the treatment groups at any recorded IOP time (8 AM, 10 AM, 4 PM, or 8 PM) at Visit 2.

Table C97-UIOS-005-05 – Discontinued Patients and Reason

Investigator	Patient	Treatment	Reason
2	210	UIOS 0.15%	Treatment failure – IOP not controlled
7	702	UIOS 0.15%	Withdrawal of Consent
8	838	UIOS 0.15%	Lost to Follow-up
9	901	UIOS 0.15%	Treatment failure – IOP not controlled
	906	UIOS 0.15%	Treatment failure – IOP not controlled
	909	UIOS 0.15%	Treatment failure – IOP not controlled
	927	UIOS 0.15%	Treatment failure – IOP not controlled
	939	UIOS 0.15%	Withdrawal of Consent
10	1012	UIOS 0.15%	Adverse Event – conjunctival injection
	1021	UIOS 0.15%	Adverse Event – abnormal VA
	1027	UIOS 0.15%	Adverse Event – tachycardia
	1032	UIOS 0.15%	Adverse Event – abnormal VA
11	1102	UIOS 0.15%	Adverse Event – itching, burning, FBS
	1104	UIOS 0.15%	Treatment failure – IOP not controlled
	1124	UIOS 0.15%	Treatment failure – IOP not controlled
12	1214	UIOS 0.15%	Protocol Violation – hx of Xalatan use
	1218	UIOS 0.15%	Treatment failure – IOP not controlled
	1227	UIOS 0.15%	Treatment failure – IOP not controlled
	1236	UIOS 0.15%	Treatment failure – IOP not controlled
13	1333	UIOS 0.15%	Withdrawal of Consent
14	1425	UIOS 0.15%	Adverse Event – insomnia, depression
15	1508	UIOS 0.15%	Adverse Event – V-tach
16	1622	UIOS 0.15%	Other – IOP not controlled, VF loss
	1623	UIOS 0.15%	Treatment failure – IOP not controlled
	1629	UIOS 0.15%	Other – IOP not controlled

Table C97-UIOS-005-05 – Discontinued Patients and Reason - Continued

Investigator	Patient	Treatment	Reason
19	1906	UIOS 0.15%	Treatment Failure – IOP not controlled
	1907	UIOS 0.15%	Treatment Failure – IOP not controlled
	1909	UIOS 0.15%	Treatment Failure – IOP not controlled
	1910	UIOS 0.15%	Treatment Failure – IOP not controlled
	1915	UIOS 0.15%	Other – IOP not controlled
20	2002	UIOS 0.15%	Treatment Failure – IOP not controlled
21	2110	UIOS 0.15%	Death – bladder cancer
22	2201	UIOS 0.15%	Protocol Violation – IOP too low at baseline
24	2407	UIOS 0.15%	Adverse Event – HA, eyelid edema
	2417	UIOS 0.15%	Treatment Failure – IOP not controlled
25	2507	UIOS 0.15%	Treatment Failure – IOP not controlled
	2509	UIOS 0.15%	Adverse Event – irritation
26	2606	UIOS 0.15%	Treatment Failure – IOP not controlled
27	2706	UIOS 0.15%	Withdrawal of Consent – FBS
28	2805	UIOS 0.15%	Other – cataract surgery performed
1	108	TMOS 0.5%	Adverse Event – AV block
8	816	TMOS 0.5%	Adverse Event – CVA
	822	TMOS 0.5%	Lost to Follow-up
10	1001	TMOS 0.5%	Lost to Follow-up
12	1217	TMOS 0.5%	Treatment Failure – IOP not controlled
	1235	TMOS 0.5%	Adverse Event – eye pain
16	1608	TMOS 0.5%	Other – patient wanted cataract surgery
	1613	TMOS 0.5%	Protocol Violation – mis-scheduled meds
22	2203	TMOS 0.5%	Protocol Violation – IOP too low at baseline
	2206	TMOS 0.5%	Protocol Violation – IOP too low at baseline
24	2409	TMOS 0.5%	Adverse Event – rhinitis
25	2520	TMOS 0.5%	Adverse Event – breathless, wheezy
2	203	BHOS 0.5%	Treatment Failure – IOP not controlled
	206	BHOS 0.5%	Other – non-compliance
9	907	BHOS 0.5%	Withdrawal of Consent
	942	BHOS 0.5%	Withdrawal of Consent
10	1019	BHOS 0.5%	Protocol Violation – hx of Latanoprost use
	1033	BHOS 0.5%	Adverse Event – burning
12	1204	BHOS 0.5%	Treatment Failure – IOP not controlled
	1216	BHOS 0.5%	Adverse Event – uveitis, RD
16	1602	BHOS 0.5%	Treatment Failure – IOP not controlled
19	1912	BHOS 0.5%	Treatment Failure – IOP not controlled
20	2020	BHOS 0.5%	Other – IOP not controlled
21	2104	BHOS 0.5%	Treatment Failure – IOP not controlled
	2109	BHOS 0.5%	Withdrawal of Consent – can't keep appts
22	2202	BHOS 0.5%	Lost to Follow-up

Reviewer's Comments:

Based on the narrative summary in the data listing, the number of patients discontinued for adverse events may have been under-reported (i.e. they were coded as "other" or "withdrawal of consent").

At least four subjects listed as "other" were actually withdrawn for treatment failure (Subjects #1622, 1629, 1915, 2020).

There was no significant difference between treatment groups for any of the subject demographic characteristics.

There was no significant difference between treatment groups for previous or concurrent medical or surgical conditions or injuries, whether general or ophthalmic.

There was no significant difference between treatment groups for the number of subjects presenting each diagnosis.

Table C97-UIOS-005-06 - Summary of Demographic Characteristics (Intent-to-Treat)

	UIOS 0.15%	TMOS 0.5%	BHOS 0.5%	*P*-value
Number of Subjects	278	138	140	
Gender:				
Female	137 (49%)	62 (45%)	66 (47%)	0.696[1]
Male	141 (51%)	76 (55%)	74 (53%)	
Ethnic origin:				
Caucasian	274 (99%)	137 (99%)	137 (98%)	0.731[2]
Black	2 (1%)	1 (1%)	2 (1%)	
Afro-Caribbean	1 (0%)	0 (1%)	1 (1%)	
Other	1 (0%)	0 (0%)	0 (0%)	
Age (years):				
Mean (SD)	63.6 (10.9)	61.8 (10.3)	63.9 (11.2)	0.092[3]
Iris Color:				
Black	1 (0%)	0 (0%)	1 (1%)	0.186[4]
Brown	94 (34%)	35 (25%)	42 (30%)	
Hazel	40 (14%)	19 (14%)	16 (11%)	
Green	13 (5%)	7 (5%)	7 (5%)	
Blue	67 (24%)	43 (31%)	45 (32%)	
Grey	20 (7%)	9 (7%)	6 (4%)	
Other/mixed	43 (15%)	25 (18%)	22 (16%)	
Missing[5]	0 (0%)	0 (0%)	1 (1%)	

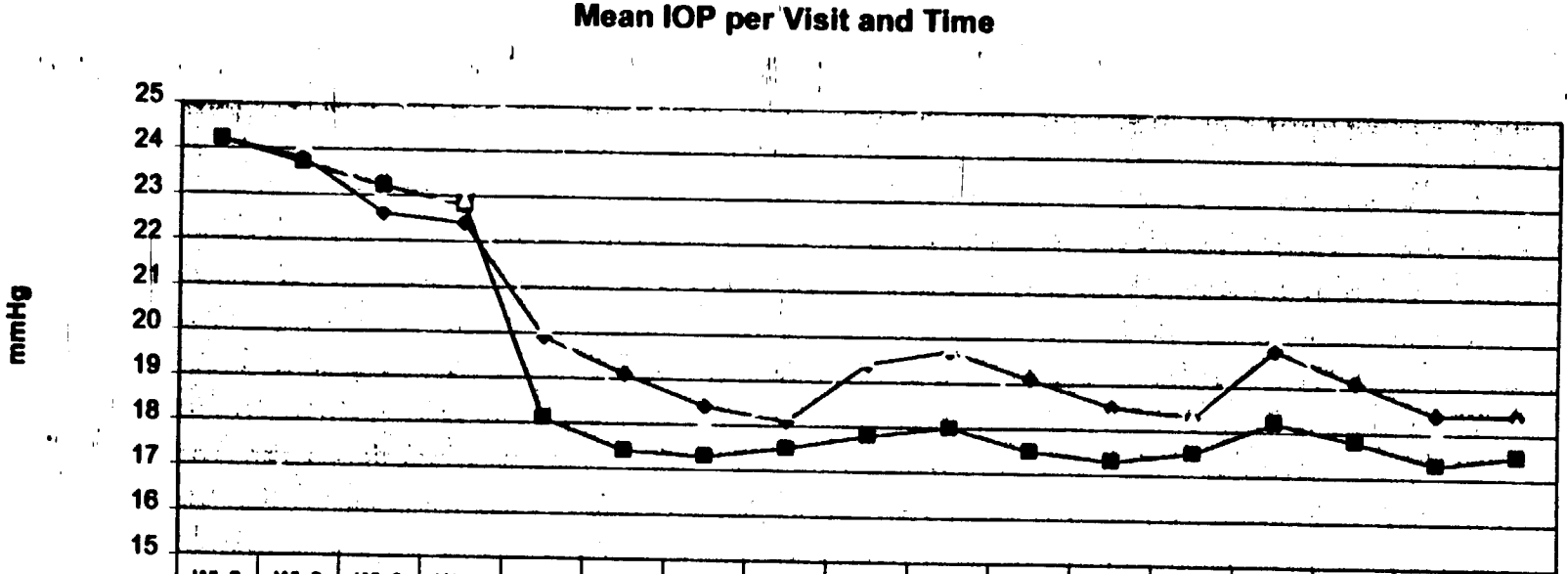
1 Fisher's exact test
2 Caucasians vs. others, Fisher's exact test
3 Kruskal Wallis test
4 Fisher's exact test (dark vs. light irides)
5 subject not assessed

Reviewer's Comments:

The ethnic origin is not consistent with the U.S. population.

8.1.2 Efficacy – Protocol C97-UIOS-005 Intent-to-Treat Population

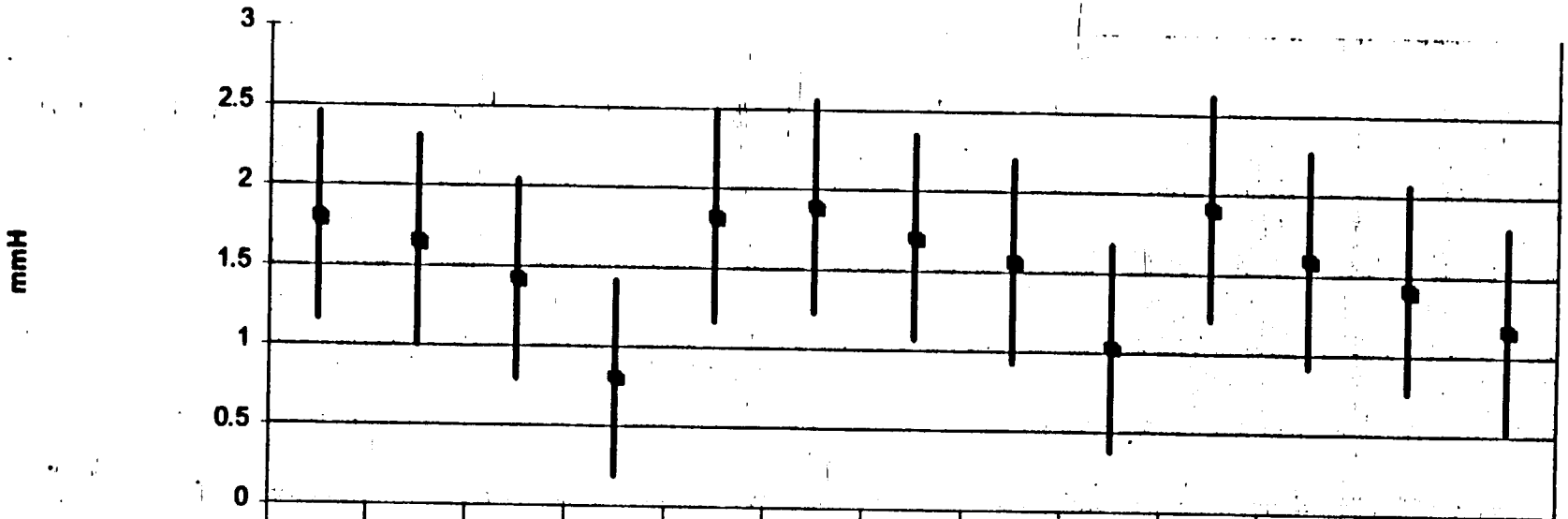
Primary Efficacy Variable



	Wk 0 (8 AM)	Wk 0 (10 AM)	Wk 0 (4 PM)	Wk 0 (8 PM)	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 2 (8 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 3 (8 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
UIOS	24.2	23.8	22.6	22.4	19.9	19.1	18.4	18.1	19.4	19.7	19.1	18.5	18.3	19.6	19.1	18.4	18.4
TMOS	24.2	23.7	23.2	22.8	18.1	17.4	17.3	17.5	17.8	18	17.5	17.3	17.5	18.2	17.8	17.3	17.5
BHOS	24.6	24.1	22.9	22.9	20.1	18.7	18.1	18.3	19.5	19.8	18.6	18.3	18.3	20.1	18.7	18	18.3

Reviewer's Comments: *Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%. There is also greater variation in the IOP during the day with UIOS 0.15% (similar to BHOS).*

Mean Difference (UIOS - TMOS) with 95% Confidence Intervals

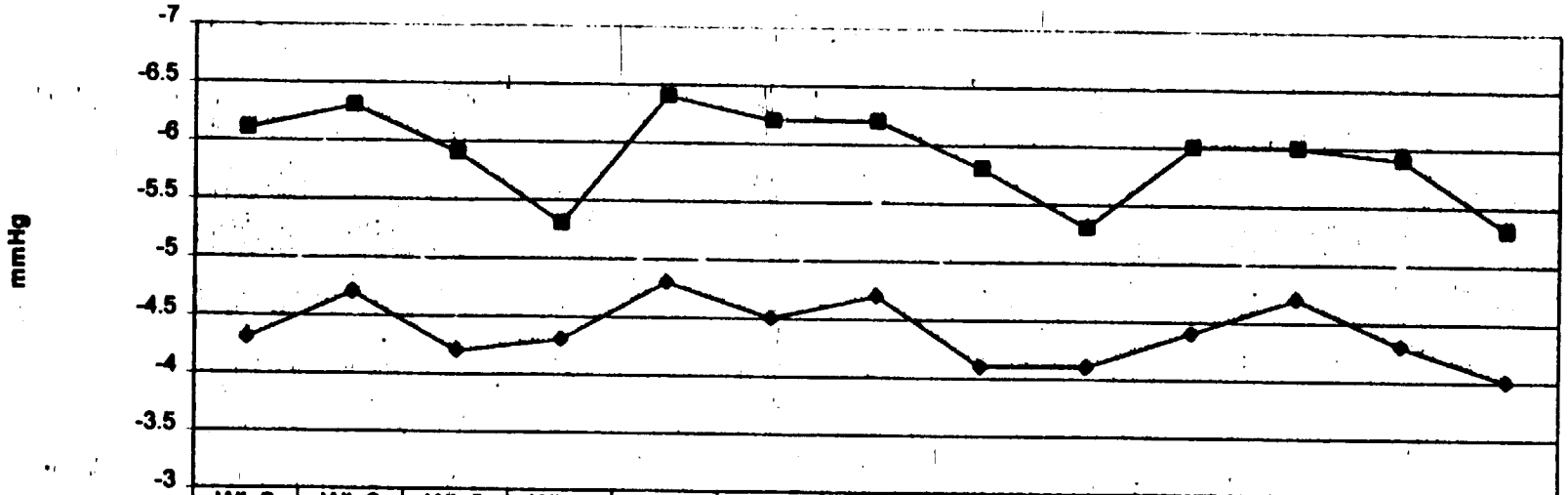


	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 2 (8 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 3 (8 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
Lower CI	1.16	1	0.79	0.19	1.16	1.22	1.06	0.92	0.38	1.2	0.91	0.76	0.52
Upper CI	2.45	2.31	2.04	1.41	2.49	2.56	2.35	2.2	1.67	2.61	2.27	2.07	1.8
■ Mean Difference	1.808	1.653	1.416	0.799	1.822	1.887	1.701	1.557	1.025	1.905	1.594	1.415	1.157

Reviewer's Comments:

The mean difference between UIOS and TMOS is statistically significant at all time points. None of the 95% confidence intervals cross zero.

Change in IOP from Baseline per Visit and Time



	Wk 2 (8 AM)	Wk 2 (10 AM)	Wk 2 (4 PM)	Wk 2 (8 PM)	Wk 6 (8 AM)	Mo 3 (8 AM)	Mo 3 (10 AM)	Mo 3 (4 PM)	Mo 3 (8 PM)	Mo 6 (8 AM)	Mo 6 (10 AM)	Mo 6 (4 PM)	Mo 6 (8 PM)
UIOS	-4.3	-4.7	-4.2	-4.3	-4.8	-4.5	-4.7	-4.1	-4.1	-4.4	-4.7	-4.3	-4
TMOS	-6.1	-6.3	-5.9	-5.3	-6.4	-6.2	-6.2	-5.8	-5.3	-6	-6	-5.9	-5.3
BHOS	-4.6	-5.4	-4.8	-4.7	-5.1	-4.8	-5.5	-4.7	-4.6	-4.6	-5.4	-5	-4.6

Reviewer's Comments: *The mean change-from-baseline ranged from –4.1 mmHg to –4.7 mmHg for UIOS 0.15%, –4.6 mmHg to –5.5 mmHg for BHOS 0.5%, and from –5.3 mmHg to –6.4 mmHg for TMOS 0.5%. Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%.*

8.1.2 Safety

Adverse Events

Serious adverse events other than death were reported for 10/278 (2.8%) subjects treated with UIOS 0.15%, for 2/138 (1.5%) subjects treated with TMOS 0.5% and for 6140 (4.3%) subjects treated with BHOS 0.5%. These other SAEs resulted in premature discontinuation from the study for two subjects treated with UIOS 0.15%, two subjects treated with TMOS 0.5%, and no subjects treated with BHOS 0.5%.

Table C97-UIOS-005-07– Serious Adverse Events

Treatment	Investigator	Patient	AE Code	Final Outcome	D/C from Study
Double-masked Period					
UIOS	1	101	Atherosclerosis	Complete recovery	No
		105	Sinusitis	Complete recovery	No
	4	411	Neuralgia	Condition improving	No
	10	1009	Infection left leg	Complete recovery	No
		1018	Thrombophlebitis	Present & unchanged	No
	12	1229	Dizziness	Condition improving	No
	14	1410	Depression	Present & unchanged	No
		1423	Cholelithiasis	Incomplete recovery	No
	15	1508	Ventricular tachycardia	Incomplete recovery	Yes
	21	2110	Bladder carcinoma	Death	N/A
	24	2407	Lung carcinoma	Condition worsening	No
TMOS	1	108	AV block	Lost to follow-up	Yes
	8	816	CVA	Incomplete recovery	Yes
BHOS	11	1120	EKG abnl	Complete recovery	No
	12	1216	Retinal detachment	Complete recovery	Yes
	13	1303	CVA	Complete recovery	No
		1323	Prostatic disorder	Complete recovery	No
	20	2004	Colitis	Complete recovery	No
	25	2510	A-fib Heart failure	Condition improving Condition improving	No

The most frequent ocular adverse events in subjects treated with UIOS 0.15% were burning and stinging (18%), injection (13%), and burning/stinging upon instillation (7%). The most frequent non-ocular adverse events in subjects treated with UIOS 0.15% were rhinitis (7%), headache (5%), and flu syndrome (4%).

Table C97-UIOS-005-08 – Non-ocular and ocular treatment-emergent adverse events with an incidence ≥ 2% regardless of relationship to study treatment

	UIOS 0.15% Subjects		TMOS 0.5% Subjects		BHOS 0.5% Subjects	
	N	%	N	%	N	%
Total with at least one AE	161	57.9	75	54.3	96	68.6
Body as a whole:	***37***	***13.3***	***15***	***10.9***	***25***	***17.9***
Accidental injury	4	1.4	1	0.7	4	2.9
Back pain	4	1.4	-	-	3	2.1
Flu syndrome	11	4.0	6	4.3	6	4.3
Headache	13	4.7	8	5.8	8	5.7
Pain	4	1.4	1	0.7	3	2.1
Cardiovascular system:	***12***	***4.3***	***3***	***2.2***	***9***	***6.4***
Hypertension	7	2.5	2	1.4	5	3.6
Digestive system:	***9***	***3.2***	***5***	***3.6***	***10***	***7.1***
Tooth disorder	1	0.4	3	2.2	6	4.3
Nervous system:	***13***	***4.7***	***9***	***6.5***	***10***	***7.1***
Dizziness	5	1.8	4	2.9	2	1.4
Insomnia	3	1.1	1	0.7	3	2.1
Respiratory system:	***28***	***10.1***	***22***	***15.9***	***18***	***12.9***
Pharyngitis	3	1.1	4	2.9	2	1.4
Rhinitis	19	6.8	13	9.4	10	7.1
Skin and appendages:	***7***	***2.5***	***7***	***5.1***	***3***	***2.1***
Pruritus	2	0.7	3	2.2	2	1.4
Special senses:	***136***	***48.9***	***53***	***38.4***	***83***	***59.3***
Abnormal vision	14	5.0	10	7.2	5	3.6
Blepharitis	9	3.2	1	0.7	3	2.1
Burning/stinging	51	18.3	17	12.3	32	22.9
Burning/stinging on drug instillation	19	6.8	4	2.9	18	12.9
Cataract specified	6	2.2	2	1.4	2	1.4
Conjunctivitis	10	3.6	9	6.5	8	5.7
Corneal lesion	10	3.6	4	2.9	4	2.9
Dry eyes	9	3.2	1	0.7	6	4.3
Eye disorder	4	1.4	2	1.4	4	2.9
Eye pain	-	-	3	2.2	1	0.7
Eyelid disorder	20	7.2	7	5.1	10	7.1
Foreign body sensation	11	4.0	4	2.9	14	10.0
Injection	35	12.6	8	5.8	8	5.7
Itching	25	9.0	4	2.9	11	7.9
Lacrimation disorder	7	2.5	3	2.2	11	7.9
Photophobia	10	3.6	4	2.9	2	1.4

Iris Color Change

242 subjects treated with UIOS 0.15%, 127 subjects treated with TMOS 0.5%, and 128 subjects treated with BHOS 0.5% were assessed for potential iris color changes. Iris/Eyelid photography was performed at Baseline, Month 3, and Month 6 (and planned at Month 9 and Month 12).

No evaluated subjects were considered to have had a change in iris color between the baseline and Month 6 visits.

Reviewer's Comments:

At the Month 9 visit in this study, subject #1414 (UIOS 0.15%) was found by the judges at the independent reading center to have a significant change of iris color. Neither the investigator nor the subject had noted the change.

At baseline (Visit 2), the subject had brown pigment located in a diffuse pattern centrally with several brown spots (nevi) tending to cluster at the edges of the brown pigmentation. The brown pigment appeared to be over-layered on a base color of blue-gray, which predominated peripherally.

The color change was not evident to the naked eye at Visit 5 (Month 3) or Visit 6 (Month 6), but became quite noticeable at Visits 7 (Month 9) and 8 (Month 12). The color change was an increase in surface area of the diffuse brown pigmentation; the nevi appear to remain the same approximate size and color.

Eyelashes

EYELASH DENSITY

There were statistically significant mean changes from baseline in eyelash density noted at Months 3 and 6 for the upper lid in TMOS 0.5%-treated subjects (a decrease) and at Month 6 for the lower lid in UIOS 0.15%-treated subjects (an increase).

At Months 3 and 6, a statistical difference between treatment groups was observed in density of eyelashes of the lower lid.

Table C97-UIOS-005-09 – Eyelash Density (Lashes/0.5 cm) – Intent to Treat

Visit		UIOS 0.15%	TMOS 0.5%	BHOS 0.5%
Lower Lid				
Month 3	N	208	108	112
	Baseline	15.3	15.0	14.6
	Mean	15.48	14.07	14.67
	Mean Change	0.20	-0.88	0.08
	P- value[1]	0.123	0.224	0.706
Month 6	N	196	108	100
	Baseline	15.1	15.1	14.7
	Mean	15.58	14.44	14.66
	Mean Change	0.46	-0.64	-0.05
	P- value[1]	0.001	0.376	0.810
Upper Lid				
Month 3	N	208	107	112
	Baseline	28.1	27.6	27.4
	Mean	27.78	27.13	27.07
	Mean Change	-0.27	-0.46	-0.36
	P- value[1]	0.071	0.024	0.091
Month 6	N	194	107	102
	Baseline	28.0	27.6	27.4
	Mean	27.75	27.27	26.98
	Mean Change	-0.26	-0.36	-0.41
	P- value[1]	0.106	0.046	0.053

[1] *P*-value for the within-treatment change from baseline based from the paired t-test.

Reviewer's Comments:

Changes in eyelash density as assessed by the photographic evaluation do not appear clinically relevant.

Unlike C97-UIOS-004, eyelash density was not broken down into OD and OS. A single value was given for treated eyes.

EYELASH LENGTH

Table C97-UIOS-005-10 – Eyelash Length (mm) – Intent to Treat

Visit		UIOS 0.15%	TMOS 0.5%	BHOS 0.5%
Lower Lid				
Month 3	N	208	106	108
	Baseline	4.56	4.56	4.50
	Mean	4.93	4.83	4.71
	Mean Change	0.37	0.27	0.20
	P- value[1]	<0.001	0.015	0.061
Month 6	N	195	105	100
	Baseline	4.54	4.59	4.52
	Mean	5.07	4.86	4.76
	Mean Change	0.53	0.27	0.24
	P- value[1]	<0.001	<0.001	0.037
Upper Lid				
Month 3	N	206	106	112
	Baseline	6.50	6.37	6.33
	Mean	6.52	6.62	6.33
	Mean Change	0.02	0.25	0
	P- value[1]	0.751	0.311	0.961
Month 6	N	193	107	102
	Baseline	6.44	6.37	6.33
	Mean	6.56	6.49	6.24
	Mean Change	0.12	0.12	-0.09
	P- value[1]	0.018	0.075	0.338

[1] *P*-value for the within-treatment change from baseline based from the paired t-test.

Reviewer's Comments:

Changes in eyelash length as assessed by the photographic evaluation are consistent with an ocularly administered prostaglandin-type effect. Note the mean change in lower lid eyelash length at Month 6 in the UIOS 0.15% randomized subjects.

Visual Acuity

Table C97-UIOS-005-11 –Visual Acuity Tabulated by Changes in Line Number (Six-Months Versus Baseline)

		Treatment Group					
		UIOS 0.15%		TMOS 0.5%		BHOS 0.5%	
OD	Line Changes	N	%	N	%	N	%
	N	242	100	115	100	121	100
	≥ 2 lines loss	8	3.3	4	3.5	1	0.8
	1 line loss	28	11.6	6	5.2	14	11.6
	No change	169	69.8	85	73.9	90	74.4
	1 line gain	28	11.6	17	14.8	14	11.6
	≥ 2 lines gain	9	3.7	3	2.6	2	1.7
OS	Line Changes	N	%	N	%	N	%
	N	245	100	119	100	120	100
	≥ 2 lines loss	9	3.7	4	3.4	4	3.3
	1 line loss	38	15.5	9	7.6	11	9.2
	No change	177	72.2	88	73.9	83	69.2
	1 line gain	17	6.9	10	8.4	17	14.2
	≥ 2 lines gain	4	1.6	8	6.7	5	4.2

Reviewer's Comments:

There are no clinically significant differences in visual acuity tabulated by changes in line number.

Manifest Refraction

There are no substantial changes from the screening examination to Month 6 observed for either treatment group. Differences between treatments are not statistically or clinically significant.

Slit Lamp Examinations

The percentage of subjects who experienced a change from baseline in slit lamp examinations was similar for the two treatment groups at each follow-up examination. A difference was observed in conjunctival hyperemia where the UIOS 0.15% group had a slightly higher incidence than the other 2 treatment groups (23% versus 17% for other treatments).

Dilated Ophthalmoscopy

The percentage of subjects who experienced a change from screening was small and similar for the two treatment groups at each follow-up examination.

The percentage of subjects with any worsening from screening to any follow-up visit was similar for the two treatment groups.

Cup-to-Disc Ratio

The changes from baseline within each treatment group were not clinically significant at each follow-up assessment. In addition, differences between treatment groups in the change from baseline were neither clinically nor statistically significant at any visit.

Visual Field Examination

The percentage of subjects with changes (mean defect (dB) and investigator's evaluation of glaucomatous versus non-glaucomatous progression) from baseline to Month 6 in Humphrey visual field examinations was small and comparable for the two treatment groups.

Vital Signs

There were no significant changes in the vital signs (systolic blood pressure, diastolic blood pressure, and heart rate) between baseline and at any timepoint for the UIOS 0.15% treatment group.

For the TMOS 0.5% and BHOS 0.5% treatment groups there was a significant decrease in both systolic blood pressure and diastolic blood pressure at Month 3 and 6. The change in heart rate was significant for the BHOS 0.5% treatment group from Week 2 to Month 6 visit and was significant for TMOS 0.5% treatment group only at Week 2.

8.1.2 Reviewer's Summary of Efficacy and Safety

Twice-daily-dosed UIOS 0.15% does not demonstrate equivalence in the ability to lower IOP compared to twice-daily-dosed TMOS 0.5%. There is also greater variation in the IOP during the day with UIOS 0.15%.

The mean change-from-baseline IOP ranged from –4.1 mmHg to –4.7 mmHg for UIOS 0.15%, –4.6 mmHg to –5.5 mmHg for BHOS 0.5%, and from –5.3 mmHg to –6.4 mmHg for TMOS 0.5%. Efficacy in IOP reduction has been demonstrated because IOP reduction from placebo would not have been expected to exceed 2 mmHg.

The judges at the independent reading found iris color changes; neither the investigator nor the UIOS treated subject had noted the change. This change in iris color may signal the ability of UIOS 0.15% to increase the number of melanosomes (pigment granules) in melanocytes. Changes in lower lid eyelash length are also consistent with an ocularly administered prostaglandin-type effect.

The percentage of subjects in the UIOS group completing the six-month study period was notably lower than the percentage of subjects in either of the other treatment groups.

8.1.3 Study #3 Protocol C97-UIOS-003

Title: Comparison of the Effects of Different Concentrations of Unoprostone Isopropylate Ophthalmic Solution on Intraocular Pressure in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension

Test Drug Schedule: Subjects instilled one drop of masked medication into the eligible eye(s) twice daily for four weeks.

Investigator Number	Investigator	Number Randomized
146	**John R. Campagna, M.D.** San Antonio, TX 78205 USA	53
148	**Robert C. Davidson, M.D.** Chandler, AZ 85224 USA	25
145	**Steven Dell, M.D.** Austin, TX 78746 USA	39
140	**Elizabeth Sharpe, M.D.** Mt. Pleasant, SC 29484 USA	23
147	**David G. Shulman, M.D.** San Antonio, TX 78229 USA	48
116	**William C. Stewart, M.D.** Charleston, SC 29412 USA	25
144	**Frances J. Wapner, M.D.** Salt Lake City, UT 84124	22

8.1.3 Study Design

This was a randomized, double-masked, parallel-group, placebo- and active-controlled, multi-center comparison of UIOS 0.06%, 0.12%, and 0.15%, its vehicle placebo, and TMOS 0.5% in controlling IOP in subjects with POAG or OH. Both investigator and subject were masked in the evaluation of the five study treatments.

All study treatments were topical ophthalmic eye drops. Masked study medication was administered twice daily (8 a.m., 8 p.m.) for 4 weeks.