CLINICAL REVIEW

Application Type	NDA 22-193
Submission Number	000
Submission Code	Original
Letter Date	September 21, 2007
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Reviewer Name	William M. Boyd, M.D.
Review Completion Date	June 30, 2008
Established Name	balanced salt ophthalmic solution with hypromellose, dextrose and glutathione
(Proposed) Trade Name	Navstel Intraocular Irrigating Solution
Therapeutic Class	balanced salt solution --------
Applicant	Alcon, Inc.
Priority Designation	S
Formulation	each mL of the reconstituted product contains: hypromellose 1.25 to 1.73 mg, sodium chloride 7.14 mg, potassium chloride 0.38 mg, calcium chloride 0.154 mg, magnesium chloride 0.2 mg,

	dibasic sodium phosphate 0.42 mg, sodium bicarbonate 2.1 mg, dextrose 0.92 mg, glutathione disulfide (oxidized glutathione) 0.184 mg, hydrochloric acid and/or sodium hydroxide (to adjust pH) in water for injection.
Dosing Regimen	solution should be used according to the standard technique employed by the operating surgeon
Indication	for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye
Intended Population	patients undergoing intraocular surgical procedures

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended that NDA 22-193 be approved with the labeling revisions listed in this review.

The application supports the safety and effectiveness of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye.

1.2 Risk Benefit Assessment

Results from three clinical studies in patients undergoing cataract surgery demonstrated that Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) is an effective irrigating solution for anterior segment surgical procedures. Results from an additional clinical study demonstrated that Navstel Solution is an effective irrigating solution for posterior segment surgical procedures.

There is support for the claim of significantly reduced turbulent flow in the anterior chamber: the primary variable for C-03-33 is significant, and a secondary variable in C-04-14 is significant even after correction for multiplicity.

During the course of the conduct of C-02-39 study, it was noted that subjects in the NGOIS 5 cps treatment group were presenting in the early post-operative period (6 hours) with a higher incidence of increased intraocular pressure (greater than or equal to 30 mmHg) compared to the BSS Plus treatment group. --- --- - --- -- ---

NGIOS 3 cps and NGIOS 4 cps were evaluated in C-03-33. Those results suggested that the risk for transient intraocular pressure elevations during the early postoperative period was lower in the NGOIS 3 cps treatment group compared to the NGOIS 4 cps treatment group.

NGIOS 3 cps alone was evaluated in C-04-14 and C-04-18 (and in C-04-64 for safety).

The addition of hypromellose to the irrigating solution results in a slight increase in viscosity from 1.0 cps for BSS Plus to approximately 3 cps for Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, corneal endothelium, and visual acuity. Patients in the anterior and posterior segment studies with exposure to NGOIS 3 cps reported a similar incidence of the most commonly reported adverse events versus patients with exposure to BSS Plus. This included reports of increased intraocular pressure (12% versus 11%), cataract (5% versus 3%), ocular discomfort (5% versus 3%), macular edema (4% versus 4%), conjunctival hyperemia (4% versus 3%), and dry eye (3% versus 5%).

1.3 Recommendations for Postmarketing Risk Management Activities

There are no recommended Phase 4 clinical study commitments.

1.4 Recommendations for other Post Marketing Study Commitments

There are no optional or recommended Phase 4 requests.

2 Introduction and Regulatory Background

2.1 Product Information

Navstel is a sterile intraocular irrigating solution for use during all surgical procedures, including those requiring a relatively long intraocular perfusion time (e.g. vitrectomy, extracapsular cataract extraction/lens aspiration, anterior segment reconstruction, etc.). The solution does not contain a preservative and should be prepared just prior to use in surgery.

Throughout this review, the drug product is primarily referred to as Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione), but it may also be referred to as Next Generation Ophthalmic Irrigation Solution (NGIOS), NGOIS 3 cps[1], Viscous Irrigating Solution, StablEyz™, or --- ------ ----- Intraocular Irrigating Solution (balanced salt intraocular irrigating solution enriched with bicarbonate, dextrose, glutathione and hypromellose).

Background
The majority of cataract surgeries are performed by phacoemulsification using a surgical hand-piece with a tip that vibrates at a very high frequency. This tip disintegrates or "emulsifies" the cataractous lens, a process which generates lens fragments or particles within the eye. Many

1 viscosity of 3.0 cps (cps = centipoise)

potential complications can occur during cataract surgery that results in damage to ocular tissues. During cataract removal, mobile lens fragments can cause damage to the surrounding ocular tissues (1), and fragments traveling to the anterior chamber may damage the corneal endothelium. In addition to tissue injury from lens fragments, damage may result directly from the turbulent flow of intraocular fluids, or from bubbles generated by the phacoemulsification hand-piece. Turbulent fluid flow also may cause lens fragments to collide with delicate corneal endothelial cells and other intraocular tissues, resulting in iatrogenic trauma. Endothelial cell protection is reduced or lost when too much viscoelastic is aspirated from the eye or exudes from the wound during the surgical procedure. Although most pediatric cataracts do not require phacoemulsification, loss of viscoelastic during surgery or damage to ocular tissues from air bubbles also represent potential risks during pediatric surgical procedures.

As with the anterior segment, turbulence in the posterior segment can lead to iatrogenic retinal movement. Minimizing this turbulence may facilitate posterior segment surgery by allowing the surgeon to work closer to the retina during membrane removal while minimizing the risk of incarceration of the retina into the vitrectomy-cutting instruments.

Contains:
Part I: Part I is a sterile 240 mL or 480 mL solution in a 250 mL or 500 mL single-dose glass bottle to which the Part II concentrate is added. Each mL of Part I contains: hypromellose, sodium chloride, potassium chloride, dibasic sodium phosphate, sodium bicarbonate, hydrochloric acid and/or sodium hydroxide (to adjust pH) in water for injection USP.

Part II: Part II is a sterile concentrate in a 10 mL or 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: calcium chloride, magnesium chloride, dextrose, gluthathione disulfide (oxidized glutathione), in water for injection USP.

After addition of Navstel Part II to the Part I bottle, each mL of the reconstituted product contains: hypromellose 1.25 to 1.73 mg, sodium chloride 7.14 mg, potassium chloride 0.38 mg, calcium chloride 0.154 mg, magnesium chloride 0.2 mg, dibasic sodium phosphate 0.42 mg, sodium bicarbonate 2.1 mg, dextrose 0.92 mg, glutathione disulfide (oxidized glutathione) 0.184 mg, hydrochloric acid and/or sodium hydroxide (to adjust pH) in water for injection.

See the Chemistry Review #1, page 10, for more detail.

Acceptance criteria for Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) Part I and Part II are shown in two tables below. They contain acceptance criteria for pH, hypromellose assay, viscosity, color and visible particles (for Part I) and for subvisible particles, bacterial endotoxins and visible particles (for Part II) that were not included in the specifications for BSS Plus Parts I and II.

Regulatory Acceptance Specifications for NGOIS Part I

Test	Regulatory Acceptance Specification
HPMC Assay	
Sodium Assay	
Potassium Assay	
Chloride Assay	
Bicarbonate Assay	
Phosphate Assay	
pH	
Osmolality	
Viscosity	
Color	
Clarity	
Visible Particles	
Subvisible Particles Stage 1 – Light Obscuration (HIAC) Stage 2 – Microscope [a]	
Sterility	
Bacterial Endotoxins [b]	

[a] As per USP <789>, Stage 2 testing is conducted only if Stage 1 results exceed the specification limits.
[b] Tested only at release.

Regulatory Acceptance Specifications for NGOIS Part II

Test	Regulatory Acceptance Specification
Glutathione Disulfide Assay	
Dextrose Assay	
Calcium Assay	
Magnesium Assay	
Chloride Assay	
pH	
Color	
Clarity	
Visible Particles	
Subvisible Particles Stage 1 – Light Obscuration (HIAC) Stage 2 – Microscope [a]	
Sterility	
Bacterial Endotoxins [b]	

[a] As per USP <789>, Stage 2 testing is conducted only if Stage 1 results exceed the specification limits.
[b] Tested only at release.

Acceptance criteria are given below for the reconstituted Navstel Intraocular Irrigating Solution. The acceptance criterion for pH has changed and several physical tests have been included that were not a part of the specification for reconstituted BSS Plus Parts I and II. The acceptance criterion for pH has changed and tests/acceptance criteria have been added for osmolality, viscosity, color, precipitate, visible and subvisible particles.

Regulatory Acceptance Specifications for Reconstituted NGOIS

Test [a]	Regulatory Acceptance Specification
pH	
Osmolality	
Viscosity	
Color	
Clarity	
Precipitate	
Visible Particles	
Subvisible Particles Stage 1 – Light Obscuration (HIAC) Stage 2 – Microscope [b]	

[a] During product development,

[b] As per USP <789>, Stage 2 testing is conducted only if Stage 1 results exceed the specification limits.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are three approved new drug applications for ophthalmic intraocular irrigating solutions:

- NDA 18-469: BSS PLUS Sterile Intraocular Irrigating Solution (balanced salt solution enriched with bicarbonate, dextrose, and glutathione)
- NDA 20-742: BSS Sterile Irrigating Solution (balanced salt solution)
- NDA 20-079: Endosol Extra Irrigating Solution (balanced salt solution enriched with bicarbonate, dextrose, and glutathione)

NDA 18-469 was approved in October 1981; NDA 20-742 was approved in December 1997; NDA 20-079 was approved in November 1991.

2.3 Availability of Proposed Active Ingredient in the United States

Part I is composed of essential ions, buffer salts and hypromellose (a viscosity enhancing agent). The addition of hypromellose is the only difference between the compositions of Part I and Alcon's currently marketed BSS Plus Part I (NDA 18-469).

Part II contains essential ions, dextrose and glutathione disulfide ---------- ---------- ---------- ----------.
The composition of Part II is the same as that of Alcon's currentl- ---------- ---------- -- ---------- --

With the exception of hypromellose, all the ingredients of Parts I and II are physiologic.

2.4 Important Safety Issues with Consideration to Related Drugs

Adverse events reported during the use of ophthalmic irrigating solutions include postoperative inflammatory reactions, corneal edema, corneal clouding, corneal decompensation, and bullous keratopathy, and are listed in the package inserts for the approved products BSS and BSS Plus. The package inserts further indicate that studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

In 2006, balanced salt solutions marketed without New Drug Applications were found to have elevated levels of endotoxin; the FDA received numerous reports of Toxic Anterior Segment Syndrome (TASS), a serious and potentially irreversible eye injury. The balanced salt solutions subject to a February 13, 2006, recall order were manufactured by Cytosol Laboratories, Inc.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An End-of-Phase 2 Meeting was held with the U.S. Food and Drug Administration on May 17, 2004, during which Alcon presented a summary of completed clinical studies in order to obtain advice from the Agency for proceeding with the clinical development of Navstel Intraocular Irrigating Solution.

Alcon proposed 2 planned studies, including 1 anterior segment safety and efficacy study in patients undergoing cataract extraction (C-04-14), and 1 posterior segment safety and efficacy study in patients undergoing removal of epiretinal membrane during vitrectomy (C-04-18). Based on these discussions with the Agency, Alcon modified the primary statistical objective of C-04-14 to demonstrate non-inferiority of NGOIS to BSS Plus in the percent change from baseline in central endothelial cell density at Day 90, with tests of superiority for flow characteristics of the irrigating solution (turbulence and followability to the phacoemulsification tip). The study parameters for C-04-18 were acceptable; a special protocol assessment for C-04-18 was submitted in December 2004. The inclusion of pediatric patients in the clinical development plan was encouraged; this agency guidance resulted in the development of a pediatric safety study (C-04-64).

In April 2005, Alcon sought clarification of the Agency's responses to a Special Protocol Assessment for C-04-18. The meeting request also included the proposed study plan and questions for the pediatric study (C-04-64). The Agency's responses (received in January 2005) specified that at least 500 total patients needed exposure to Navstel Intraocular Irrigating Solution during the development plan with at least one-third of these subjects having posterior segment surgery.

The Agency also recommended that the primary endpoint(s) during any future clinical efficacy phases be clinically relevant and demonstrate a statistically significant difference between the

drug product and the control. Consequently, the primary statistical objective for C-04-18 was modified to demonstrate non-inferiority for the proportion of patients with maintenance or improvement of best-corrected logMAR visual acuity at the Day 90 visit, using a non-inferiority margin of 20%. The Agency indicated the Day 90 endpoint was acceptable, but specified 10% as the non-inferiority margin.

2.6 Other Relevant Background Information

By virtue of its increased viscosity compared to other irrigating solutions, Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) provides potential protection for patients during ophthalmic surgical procedures.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The major sources of clinical data utilized in this review include:

- Five clinical studies with 944 patients and 3 viscosities of NGOIS. These studies encompass 3 anterior segment safety and efficacy studies in adults (C-02-39, C-03-33, and C-04-14), 1 posterior segment safety and efficacy study in adults (C-04-18), and 1 anterior segment safety study in pediatric patients (C-04-64).
- Literature search conducted by Alcon to identify published clinical articles on the administration of balanced salt solution.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Alcon in this application for this indication.

3.2 Compliance with Good Clinical Practices

All studies were conducted in accordance with accepted clinical and ethical standards.

3.3 Financial Disclosures

Pursuant to 21 CFR§314.50(k), §312.53(c)(4), and §54.4, financial disclosure information has been provided by Alcon, Inc. for the covered clinical studies submitted in this application: C-02-39, C-03-33, C-04-14, C-04-18 and C-04-64.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Section 2.1 this review.

Per the Chemistry Review #1, page 8:

> The drug product is identical to that of the same sponsor in NDA 18-469 with one key difference. The present NDA includes enough hypromellose - - - --------- - - osmolality to 305 mOsm/kg and the viscosity to ---------- to make the solution more physiological and easier to handle during surgery. Other than the one component, the composition, processes, analytical methods, container/closure systems, etc. are identical to the earlier product (Balanced Salt Solution Plus Parts I and II). The sponsor has been diligent in showing the validity of the manufacturing process, the material and critical step controls, the sterility and stability of the product. From the prospective of chemistry and manufacturing controls, the product is safe.

Per the Product Quality Microbiology Review, page 13:

> The release criteria for the USP kinetic turbidimetric test for bacterial endotoxins remains unchanged as approved for NDA 18-469. The finished product Navstel Intraocular Irrigating Solution Part I will contain - ---------- and the Navstel Intraocular Irrigating Solution Part II will contain ------ --------- Both methods have been validated per Alcon technical documents TDOC-0002202 (Part I) and TDOC-0006071 (Part II).
>
> Part I: The test sensitivity λ ----------
> Part II: The test sensitivity λ ----------

4.2 Clinical Microbiology

Not applicable to this review.

4.3 Preclinical Pharmacology/Toxicology

Per the Pharmacology/Toxicology Review, page 12 - 13:

The composition of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) Part I is made up of various essential ions and buffer salts with hypromellose (also known as hydroxypropyl methylcellulose or HPMC) added as a viscosity enhancing agent. The composition of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) Part II consists of essential ions, dextrose and glutathione disulfide which is the same formula as Alcon's currently marketed BSS PLUS®A Part II, NDA 18-469.

Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) is intended for use as an intraocular irrigating solution during surgical procedures involving perfusion of the eye. HPMC is added to the formulation to impart improved physical characteristics to the product that facilitate surgeon convenience and control. HPMC is a chemically modified cellulose polymer that has no known receptor affinity, pharmacological action or side effect potential.

The specific HPMC ------ formulation ---------- ------ has been safely used intraocularly for over 10 years at a ten-fold higher concentration in the form of Ocucoat® (Bausch and Lomb) and Celoftal® (Alcon) viscoelastic products used during cataract surgery. Viscoelastic solutions help to push back the vitreous face, thus preventing formation of a flat chamber during surgery.

The carcinogenicity potential of Navstel Intraocular Irrigating Solution has not been investigated. The hypromellose in Navstel Intraocular Irrigating Solution has been demonstrated to be non-mutagenic in the *in vitro* Ames assay and the bacterial reverse mutation assay. A similar modified cellulose polymer (methyl cellulose) was also non-mutagenic at concentrations up to 5,000 mg/kg in the rat bone marrow cytogenic assay. Fertility studies have not been conducted with hypromellose; however, rats fed a diet of up to 5% methylcellulose had no significant adverse effects relative to reproductive function.

4.4 Clinical Pharmacology

Per the Clinical Pharmacology Review, page 13:

The applicant did not conduct any clinical pharmacology studies to assess the in vivo bioavailability of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione). All of the ingredients of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) Parts I and II are normally found in the aqueous humor with the exception of hypromellose. The specific hypromellose ------ formulation was chosen because ---------- --- ---------- ---------- -------- --- - ---------- -- - ------ ------ --- -- - ------- - ---------- --- ------- ----- - ------- ----- ----- -- - ---------- ---------- --------- --- ----- - ------ ------- -- - ------ -- - ---- - In addition, the systemic exposure of hypromellose will likely be less than that achieved by other currently marketed intraocular viscoelastic products (i.e., OCCUCOAT® [2% HPMC], CELOFTAL®

[2% HPMC], and CELLUGEL® [2% HPMC]) which have HPMC concentrations approximately 10× that of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).

Although Alcon Research, Ltd. did not request a waiver of evidence of in vivo bioavailability for Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione), a full waiver is hereby granted based on 21 CFR 320.22(e). The sponsor meets the requirements for granting a waiver of evidence of in vivo bioavailability for topical products based on the fact that Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) is an irrigating solution during surgical procedures, all the ingredients of Part I and Part II are normally found in the eye with the exception of hypromellose, hypromellose has no known receptor affinity, pharmacological action, or side effect potential, and distribution of hypromellose into ocular tissues is unlikely because of its molecular weight -- ---------- No further clinical pharmacology studies are necessary to support the in vivo bioavailability of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Summary of Completed Clinical Studies for Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione)

Protocol No. / Study Type	Study Design	Study Population	Treatment Group	N[a]	Dosing Regimen	Dosing Duration
Anterior Segment Studies						
C-02-39 Anterior Segment Safety and Efficacy	Multi-center, randomized, observer-masked, active-controlled, parallel group (NGOIS 5 cps & BSS Plus study arm was not randomized)	Patients, male or female, of any race, age 18 or older, who were expected to undergo surgical removal of the cataract by phacoemulsification with implantation of a posterior chamber intraocular lens	NGOIS 5 cps BSS Plus NGOIS 5 cps & BSS Plus	35 35 35	Volume sufficient to irrigate adequately during surgery	Single administration throughout surgery[b]
C-03-33 Anterior Segment Safety and Efficacy	Multi-center, randomized, double-masked, active-controlled, parallel group	Patients, male or female, of any race, age 18 or older, who were expected to undergo surgical removal of the cataract by phacoemulsification with implantation of a posterior chamber intraocular lens	NGOIS 3 cps NGOIS 4 cps BSS Plus	39 34 35	Volume sufficient to irrigate adequately during surgery	Single administration throughout surgery
C-04-14 Anterior Segment Safety and Efficacy	Multi-center, randomized, observer/ patient-masked, active-controlled, parallel group	Patients, male or female, of any race or age (all enrolled patients were age 18 or older), who were expected to undergo surgical removal of the cataract with implantation of a posterior chamber intraocular lens	NGOIS 3 cps BSS Plus	184 185	Volume sufficient to irrigate adequately during surgery	Single administration throughout surgery
Posterior Segment Study						
C-04-18 Posterior Segment Safety and Efficacy	Multi-center, randomized, observer/ patient-masked, active-controlled, parallel group	Adults 18 years of age or older with an epimacular membrane who would benefit from vitrectomy and membrane removal	NGOIS 3 cps BSS Plus	168 176	Volume sufficient to irrigate adequately during surgery	Single administration throughout surgery

Pediatric Safety Study						
C-04-64 Anterior Segment Pediatric Safety	Multi-center, randomized, observer/ patient-masked, active-controlled, parallel group	Patients from 1 week to less than 18 years of age at the baseline visit, of either sex, of any race, and who required cataract removal	NGOIS 3 cps BSS Plus	10 8	Volume sufficient to irrigate adequately during surgery	Single administration throughout surgery

Reviewer's Comments:

C-04-64 enrolled 18 pediatric patients, including 10 patients with exposure to NGOIS 3 cps and 8 patients with exposure to BSS Plus. Alcon did not include this study in the integrated analyses which follow, based on the small size of this study population and their younger age.

5.2 Review Strategy

The September 24, 2007, submission was submitted in paper. Subsequent amendments were submitted in paper. All study reports were reviewed. The included clinical study reports, literature review, and package insert formed the basis for the review of efficacy and safety for the proposed indications.

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Alcon in this application for this indication.

5.3 Discussion of Individual Studies

5.3.1 C-02-39

A Multi-Center, Randomized, Parallel Group Study to Evaluate the Safety and the Performance of Viscous Intraocular Irrigating Solution during Cataract Extraction and IOL Implantation Surgery

List of Investigators and Subinvestigators for Protocol C-02-39

Inv#	Investigator	Subinvestigator(s)
2902	Robert Cionni, MD Cincinnati Eye Institute 10494 Montgomery Rd Cincinnati, OH 45242 513-984-5133	
1346	Howard Gimbel, MD The Gimbel Eye Centre Suite 450, 4935 - 40 Avenue, NW Calgary, Alberta T3A 2N1 Canada 403-286-3022	None
970	Robert Lehmann, MD Lehmann Eye Center 5300 North St Nacogdoches, TX 75965 936-569-8278	None

Principal Investigator Name	Inv. #	Dates of Participation	Number of Patients on Test Article by Site
Robert Cionni, MD	2902	October 29, 2002 to October 23, 2003	NGOIS (N = 12) BSS Plus (N = 12) NGOIS / BSS Plus (N = 17)
Howard Gimbel, MD	1346	November 8, 2002 to May 6, 2003	NGOIS (N = 11) BSS Plus (N = 11) NGOIS / BSS Plus (N = 0)
Robert Lehmann, MD	970	October 16, 2002 to October 14, 2003	NGOIS (N = 12) BSS Plus (N = 12) NGOIS / BSS Plus (N = 18)

Study Plan for C-02-29

Study Activity	Activities to Be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	Day 0	6 ± 2h	Day 1 (24 ± 4 h)	Day 3 (± 1 d)	Day 7 (± 2 d)	Day 30 (± 7 d)	Day 90 (± 14 d)
Screening patients (includes potential acuity meter assessment of the fellow eye, if applicable [1])	X							
Informed consent	X							
Demographics	X							
Current (baseline) and postoperative change in medical condition(s) (systemic and ocular anterior and posterior segments)	X	X	X	X	X	X	X	
Central endothelial cell photographs (3 photos/visit)	X^B							X^B
Central corneal thickness (ultrasound pachymetry, 3 measurements/visit)	X^S		X^S	X^S		X^S	X^S	X^S
Best-corrected logMAR VA	X^B			X^S		X^S	X^S	X^B
Goldmann intraocular pressure	X^B		X^S	X^S	X^S	X^S	X^S	X^B
Slit-lamp examination [ocular signs: inflammation (cells and flare), corneal edema, ocular observations]	X^B			X^S		X^S	X^S	X^B
Estimate lens hardness	X							
Dilated fundus examination	X^B						X^S	X^S
Concurrent (non-surgically related) medications	X	X	X	X	X	X	X	X
Surgically-related medications		X	X	X	X	X	X	X
IOP-reducing therapy			X	X	X	X	X	X
Surgeon's evaluation of handling characteristics and viscoelastic retention		X						

Study Plan for C-02-29 (continued)

Study Activity	Activities to Be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	Day 0	6 ± 2 h	Day 1 (24 ± 4 h)	Day 3 (± 1 d)	Day 7 (± 2 d)	Day 30 (± 7 d)	Day 90 (± 14 d)
Videotaping of surgery (with subsequent assessment of handling characteristics by the masked video panel – minimum of 3 ophthalmic surgeons)		X						
Evaluation of lens hardness		X						
Surgical information (surgical techniques and procedures, viscoelastic and IOL data, phacoemulsification time, phacoemulsification time energy, phacoemulsification time duration, surgical complications, etc.)		X						
Irrigating solution data		X						
Record adverse events [2]		X	X	X	X	X	X	X
Complete exit form [3]							X	

[B] Both eyes.
[S] Study eye only.
[1] For patients with cataract and logMAR VA > 0.6 (<20/80) in the fellow eye (see Exclusion Criterion Number 15).
[2] An adverse event form was to be completed at the time an adverse event was first observed or reported to the investigator. If an adverse event did not coincide with a study examination visit, then an unscheduled visit form was to be completed and sent to the Sponsor, along with the adverse event form.
[3] An exit form was completed at the completion of the study (Day 90 Visit) or sooner if the patient discontinued from the study at an earlier date.

5.3.2 C-03-33

A Multi-Center, Double-Masked, Randomized, Parallel Group Study to Evaluate the Safety and the Performance of StablEyz™ Intraocular Irrigating Solution during Cataract Extraction and IOL Implantation Surgery

List of Investigators and Subinvestigators for Protocol C-03-33

Inv#	Investigator	Subinvestigator(s)
847	Stephen Brint, MD Brint Vision Centers 3900 Veterans Blvd, #203 Metairie, LA 70002 504-888-2020	
2902	Robert Cionni, MD Cincinnati Eye Institute 10494 Montgomery Rd Cincinnati, OH 45242 513-984-5133	
970	Robert Lehmann, MD Lehmann Eye Center 5300 North St Nacogdoches, TX 75965 936-569-8278	None
1434	W. Andrew Maxwell, MD California Eye Institute 1360 E. Herndon Ave, #401 Fresno, CA 93720 559-449-5010	None
3747	Harvey Reiser, MD Eye Care Specialists 703 Rutter Ave Kingston, PA 18704 570-288-7405	

Principal Investigator Name	Inv. #	Dates of Participation	Number of Patients on Test Article by Site
Stephen Brint, MD	847	August 13, 2003 to February 2, 2004	NGOIS 3 cps (N = 8) NGOIS 4 cps (N = 6) BSS Plus (N = 7)
Robert Cionni, MD	2902	September 16, 2003 to March 11, 2004	NGOIS 3 cps (N = 7) NGOIS 4 cps (N = 7) BSS Plus (N = 7)
Robert Lehmann, MD	970	September 9, 2003 to January 26, 2004	NGOIS 3 cps (N = 8) NGOIS 4 cps (N = 6) BSS Plus (N = 7)
W. Andrew Maxwell, MD	1434	September 11, 2003 to April 2, 2004	NGOIS 3 cps (N = 7) NGOIS 4 cps (N = 7) BSS Plus (N = 7)
Harvey Reiser, MD	3747	September 26, 2003 to March 12, 2004	NGOIS 3 cps (N = 9) NGOIS 4 cps (N = 8) BSS Plus (N = 7)

Study Plan for C-03-33

Study Activity	Activities to be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to −1 Day	(Day 0)	6 ±2 h	Day 1 (24 ±4 h)	Day 3 ±1	Day 7 ±2	Day 30 ±7	Day 90 ±14
Screening patients	X							
Informed consent	X							
Demographics	X							
Current (baseline) and postoperative change in medical condition(s) (systemic and ocular anterior and posterior segments)	X	X	X	X	X	X	X	X
Central endothelial cell photographs (2 photographs/visit)	X^B							X^B
Central corneal thickness (Ultrasound pachymetry, 3 measurements/visit)	X^S		X^S	X^S		X^S	X^S	X^S
Best-corrected logMAR VA	X^B			X^S		X^S	X^S	X^B
Goldmann intraocular pressure	X^B		X^S	X^S	X^S	X^S	X^S	X^B
Slit-lamp examination [ocular signs: inflammation (cells and flare), corneal edema, ocular observations]	X^B			X^S		X^S	X^S	X^B
Estimate lens hardness	X							
Dilated fundus examination	X^B						X^S	X^S
Concurrent (non-surgically related) medications	X	X	X	X	X	X	X	X
Surgically related medications		X	X	X	X	X	X	X
IOP-reducing therapy			X	X	X	X	X	X

Study Plan for C-03-33 (continued)

Study Activity	Activities to be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	(Day 0)	6 ±2 h	Day 1 (24 ±4 h)	Day 3 ±1	Day 7 ±2	Day 30 ±7	Day 90 ±14
Surgeon's evaluation of handling characteristics and viscoelastic retention		X						
Evaluation of lens hardness		X						
Surgical information (surgical techniques and procedures, viscoelastic and IOL data, phacoemulsification time, phacoemulsification energy, phacoemulsification duration, surgical complications, etc.)		X						
Irrigating solution data		X						
Record adverse events [1]		X	X	X	X	X	X	X
Complete exit form [2]								X

[B]Both eyes.
[S]Study eye only.
[1]An adverse event form is to be completed at the time an adverse event is first observed or reported to the investigator. If an adverse event does not coincide with a study examination visit, then an unscheduled visit form is to be completed and sent to the Sponsor along with the adverse event form.
[2]An exit form will be completed at the completion of the study (Day 90 Visit) or sooner if the patient discontinues from the study at an earlier date.

5.3.3 C-04-14

Clinical Evaluation of the Safety and Efficacy of Next Generation Ophthalmic Irrigating Solution Compared to BSS PLUS for Use during Cataract Extraction and IOL Implantation

List of Investigators and Subinvestigators for Protocol C-04-14

Inv. #	Principal Investigator Contact Information	Subinvestigator(s)
2666	Louis M. Alpern, MD The Cataract, Glaucoma and Refractive Surgery Center 4171 N. Mesa, Bldg D, Grnd Fl El Paso, TX 79902 (915) 545-2333	
3904	Mike Caplan, MD Berkeley Eye Center 3100 Weslayan, Suite 400 Houston, TX 77027 (713) 526-1600	
3900	Lisa Marie Cibik, MD Associates in Ophthalmology 500 Lewis Run Road West Mifflin, PA 15122 (412) 466-8011	
1723	James Davison, MD Wolfe Clinic, PC 309 E Church St Marshalltown, IA 50158 (641) 754-6262	
3899	Arthur M. Fishman, MD Eye Surgery Associates 603 N Flamingo Road Suite 250 Pembroke Pines, FL 33028 (954) 431-2777	
3903	Gary Foster, MD The Eye Center of Northern Colorado 1725 Prospect Road Fort Collins, CO 80525 (970) 221-2222	

List of Investigators and Subinvestigators for Protocol C-04-14 (continued)

Inv. #	Principal Investigator Contact Information	Subinvestigator(s)
1204	Stephen S. Lane, MD Associated Eye Physicians and Surgeons, Ltd 232 N Main Street Stillwater, MN 55082 (651) 275-3000	
3828	Satish S. Modi, MD 23 Davis Avenue Poughkeepsie, NY 12603 (845) 454-1025	
1806	Kenneth Sall, MD Sall Research Medical Center Kenlin Building 11423 187th Street Artesia, CA 90701-5653 (562)-804-1974	None
271	Robert Stewart, MD Houston Eye Associates 2855 Gramercy Dr Houston, TX 77025 (713)-668-6828	
3979	Patrick Sweeney, MD Sweeney Eye Associates 120 W Main St Mesquite, TX 75149 (972)-285-8966	
4065	Edward C. Wade, MD Eye Center of Texas 7505 Main St., Suite 370 Houston, TX 77030 (713)-797-1010	
1007	Thomas Walters, MD Texan Eye Care 1020 W 34th St Austin, TX 78705 (512)-314-1653	

Principal Investigator Name	Inv. #	Dates of Participation	Number of Patients on Test Article by Site
Louis M. Alpern, MD	2666	November 1, 2004 to May 31, 2005	NGOIS (N = 20) BSS Plus (N = 21)
Mike Caplan, MD	3904	September 30, 2004 to June 28, 2005	NGOIS (N = 13) BSS Plus (N = 13)
Lisa Marie Cibik, MD	3900	October 12, 2004 to April 29, 2005	NGOIS (N = 13) BSS Plus (N = 15)
James Davison, MD	1723	October 1, 2004 to May 9, 2005	NGOIS (N = 7) BSS Plus (N = 7)
Arthur M. Fishman, MD	3899	September 27, 2004 to July 18, 2005	NGOIS (N = 22) BSS Plus (N = 22)
Gary Foster, MD	3903	October 15, 2004 to June 22, 2005	NGOIS (N = 18) BSS Plus (N = 18)
Stephen S. Lane, MD	1204	October 14, 2004 to July 19, 2005	NGOIS (N = 12) BSS Plus (N = 13)
Satish S. Modi, MD	3828	September 28, 2004 to July 1, 2005	NGOIS (N = 21) BSS Plus (N = 21)
Kenneth Sall, MD	1806	October 14, 2004 to July 13, 2005	NGOIS (N = 10) BSS Plus (N = 9)
Robert Stewart, MD	271	October 8, 2004 to May 16, 2005	NGOIS (N = 12) BSS Plus (N = 12)
Patrick Sweeney, MD	3979	October 12, 2004 to March 21, 2005	NGOIS (N = 12) BSS Plus (N = 12)
Edward C. Wade, MD	4065	December 22, 2004 to June 7, 2005	NGOIS (N = 5) BSS Plus (N = 5)
Thomas Walters, MD	1007	October 7, 2004 to May 23, 2005	NGOIS (N = 19) BSS Plus (N = 17)

Principal Investigator Name	Inv. #	Dates of Participation	Number of Patients on Test Article by Site
Louis M. Alpern, MD	2666	November 1, 2004 to May 31, 2005	NGOIS (N = 20) BSS Plus (N = 21)
Mike Caplan, MD	3904	September 30, 2004 to June 28, 2005	NGOIS (N = 13) BSS Plus (N = 13)
Lisa Marie Cibik, MD	3900	October 12, 2004 to April 29, 2005	NGOIS (N = 13) BSS Plus (N = 15)
James Davison, MD	1723	October 1, 2004 to May 9, 2005	NGOIS (N = 7) BSS Plus (N = 7)
Arthur M. Fishman, MD	3899	September 27, 2004 to July 18, 2005	NGOIS (N = 22) BSS Plus (N = 22)
Gary Foster, MD	3903	October 15, 2004 to June 22, 2005	NGOIS (N = 18) BSS Plus (N = 18)
Stephen S. Lane, MD	1204	October 14, 2004 to July 19, 2005	NGOIS (N = 12) BSS Plus (N = 13)
Satish S. Modi, MD	3828	September 28, 2004 to July 1, 2005	NGOIS (N = 21) BSS Plus (N = 21)
Kenneth Sall, MD	1806	October 14, 2004 to July 13, 2005	NGOIS (N = 10) BSS Plus (N = 9)
Robert Stewart, MD	271	October 8, 2004 to May 16, 2005	NGOIS (N = 12) BSS Plus (N = 12)
Patrick Sweeney, MD	3979	October 12, 2004 to March 21, 2005	NGOIS (N = 12) BSS Plus (N = 12)
Edward C. Wade, MD	4065	December 22, 2004 to June 7, 2005	NGOIS (N = 5) BSS Plus (N = 5)
Thomas Walters, MD	1007	October 7, 2004 to May 23, 2005	NGOIS (N = 19) BSS Plus (N = 17)

Study Plan for C-04-14

Study Activity	Activities to be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	Day 0	6 ± 2 h	24 ± 4 h	Day 3 ± 1	Day 7 ± 2	Day 30 ± 7	Day 90 ± 14
Screening subjects	X							
Informed consent	X							
Demographics	X							
Current (baseline) and postoperative change in medical condition(s) (systemic and ocular anterior and posterior segments)	X	X	X	X	X	X	X	X
Central endothelial cell photographs (2 photos/visit)	X^S							X^S
Central ultrasound pachymetry (3 measurements/visit)	X^S		X^S	X^S	X^S	X^S	X^S	X^S
Record surgically related ocular conditions				X		X	X	X
Record surgically related ocular symptoms			X		X			
Best-corrected logMAR VA	X^B			X^S		X^S	X^S	X^B
Intraocular pressure	X^B		X^S	X^S	X^S	X^S	X^S	X^B
Slit-lamp examination (ocular signs: inflammation [cells and flare], corneal edema)	X^B			X^S		X^S	X^S	X^B
Dilated fundus examination	X^B							X^S
Concurrent (non-surgically related) medications	X	X	X	X	X	X	X	X
Cataract Lens Hardness Assessment	X^S	X^S						
Surgically related medications		X	X	X	X	X	X	X
IOP-reducing therapy			X	X	X	X	X	X
Surgeon's evaluation of handling characteristics and viscoelastic retention		X						
Surgical information (surgical techniques and procedures, viscoelastic and IOL data, surgical complications, etc.)		X						

Study Plan for C-04-14 (continued)

Study Activity	Activities to be Performed by Study Visit							
	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	Day 0	6 ± 2 h	24 ± 4 h	Day 3 ± 1	Day 7 ± 2	Day 30 ± 7	Day 90 ± 14
Irrigating solution data		X						
Record adverse events [1]		X	X	X	X	X	X	X
Complete Exit Form [2]								X

[B] Both eyes
[S] Study eye only
[1] An adverse event form was to be completed at the time an adverse event was first observed or reported to the investigator. If an adverse event did not coincide with a study examination visit, then an Unscheduled Visit Form was to be completed and sent to the Sponsor along with the adverse event form.
[2] An exit form was to be completed at the completion of the study (Day 90 Visit) or sooner if the patient discontinued from the study at an earlier date.

5.3.4 C-04-18

Clinical Evaluation of the Safety of Next Generation Ophthalmic Irrigating Solution Compared to BSS Plus for Use during Surgery for Removal of Epimacular Membrane and Vitrectomy

List of Principal Investigators and Subinvestigators for Protocol C-04-18

Principal Investigator (No.)	Contact Information	Subinvestigator(s)
Prema Abraham, MD (3913)	Black Hills Regional Eye Institute 2800 3rd St Rapid City, SD 57701 605-341-2000	
Brian B. Berger, MD (4839)	Retina Research Center 3705 Medical Parkway, Suite 440 Austin, TX 78705 512-454-0138	
George A. Bertolucci, MD (3235)	Eye Medical Center 1360 East Herndon Ave Suite 301 Fresno, CA 93720 559-449-5078	
Thomas Bochow, MD (3239)	EyeCare Associates of East Texas 2440 East 5th St Tyler, Texas 75701 903-595-0500	None
Michael Borne, MD (4793)	Mississippi Retina Associates, PA 1190 North State Street, Ste 500 Jackson, MS 39202 601-981-4091	
David Callanan, MD (4047)	Texas Retina 1001 N Waldrop Suite 512 Arlington, TX 76012 817-261-9625	
Stanley Chang, MD (4063)	Columbia University Department of Ophthalmology Edward Harkness Eye Institute 635 W 165th St, Room 231 New York, NY 10032 212-305-2725	

List of Principal Investigators and Subinvestigators for Protocol C-04-18 (continued)

Principal Investigator (No.)	Contact Information	Subinvestigator(s)
Steven Charles, MD (2667)	Charles Retina Institute 6401 Popular Ave Suite 190 Memphis, TN 38119 901-683-0399	
Tom Ciulla, MD (2338)	Midwest Eye Institute 201 Pennsylvania Pkwy Indianapolis, IN 46280 317-817-1822	None
W. Lloyd Clark, MD (4771)	Palmetto Retina Center 2750 Laurel St Suite 101 Columbia, SC 29204 803-931-0077	
Tim Cleland, MD (4772)	Retina Associates of South Texas, PA 7940 Floyd Curl Suite 120 San Antonio, TX 78229 210-615-7600	
David Dyer, MD (4792)	Retina Associates, PA 9119 W 74th St Suite 268 Shawnee Mission, KS 66204 913-831-7400	
Jeffrey Gross, MD (4770)	Carolina Retina Center, PA 7620 Trenholm Rd, Extension Columbia, SC 29223 803-736-7200	
Sunil Gupta, MD (4070)	Retina Specialists 5150 N Davis Hwy Pensacola, FL 32503 850-476-6759	
Darin Haivala, MD (4444)	Dean A. McGee Eye Institute 608 Stanton L. Young Oklahoma City, OK 73104 405-271-6307	
Leo S. Harf, MD (3663)	Intermountain Eye Centers 4400 E Flamingo Ave Suite 300 Nampa, ID 83687 208-466-2222	None
Clio A. Harper, MD (3251)	Austin Retina Associates 801 W 38th St Suite 200 Austin, TX 78705 512-451-0103	

List of Principal Investigators and Subinvestigators for Protocol C-04-18 (continued)

Principal Investigator (No.)	Contact Information	Subinvestigator(s)
Henry Hudson, MD (2855)	Retina Center, PC 6585 N Oracle Rd Tucson, AZ 85704 520-742-0236	
Ray Iezzi, MD (4064)	Kresge Eye Institute 4717 Saint Antoine Blvd. Detroit, MI 48201-1423 313-577-0871	
H. Michael Lambert, MD (2675)	Retina and Vitreous of Texas 2727 Gramercy Suite 200 Houston, TX 77025 713-799-9975	
S. Young Lee, MD (4712)	Retina Research Institute of Texas 5441 Health Center Dr Abilene, TX 79606 325-673-9806	
Jeffrey Marx, MD (3256)	Lahey Clinic Northshore The Eye Institute One Essex Center Drive Peabody, MA 01960 978-538-4412	
Roger L. Novack, MD (4441)	Retina-Vitreous Associates Medical Group 8641 Wilshire Blvd Suite 210 Beverly Hills, CA 90211 310-854-6201	
Jeffrey L. Olson, MD (4325)	Rocky Mountain Lions Institute 1675 N Ursula St P.O. Box 6510, Mail Stop F731 Aurora, CO 80045-0510 720-848-5051	
Arun C.Patel, MD (4442)	Retina Consultants Medical Group 3939 J St Suite 106 Sacramento, CA 95819 916-454-6191	
Michael Petersen, MD, PhD (3523)	Cincinnati Eye Institute 1945 CEI Drive Cincinnati, OH 45242 513-984-5133	

List of Principal Investigators and Subinvestigators for Protocol C-04-18 (continued)

Principal Investigator (No.)	Contact Information	Subinvestigator(s)
Richard J. Rothman, MD (4814)	Retina and Vitreous Consultants, PC 1625 University Club Tower 1034 S Brentwood Blvd St Louis, MO 63117 314-727-6711	
Todd Schneiderman, MD (4075)	Retina Center Northwest 9800 NW Levin Road, Suite 203 Silverdale, WA 98383 360-307-0300	
Cameron Stone, MD (4101)	Western Carolina Retinal Associates 21 Medical Park Dr Asheville, NC 28803 828-255-8978	
Joseph Walker, MD (4794)	National Ophthalmic Research Institute 6901 International Center Blvd Fort Myers, FL 33912 239-938-1284	
George Williams, MD (3266)	Associated Retinal Consultants, PC 3535 W 13 Mile Rd Suite 632 Royal Oak, MI 48073 248-288-2280	

Principal Investigator Name	Invest. No.	Dates of Participation	Number of Patients on Test article by site
Prema Abraham, MD	3913	June 9, 2006 - March 19, 2007	NGIOS (N = 7) BSS PLUS (N = 7)
Brian B. Berger, MD	4839	August 2, 2006 – February 9, 2007	NGIOS (N = 3) BSS PLUS (N = 2)
George Bertolucci, MD	3235	November 8, 2005 - March 9, 2007	NGIOS (N = 10) BSS PLUS (N = 9)
Thomas Bochow, MD	3239	April 14, 2006 - March 15, 2007	NGIOS (N = 13) BSS PLUS (N = 13)
Michael Borne, MD	4793	July 13, 2006 - February 13, 2007	NGIOS (N = 3) BSS PLUS (N = 4)
David Callanan, MD	4047	March 2, 2006 - March 20, 2007	NGIOS (N = 7) BSS PLUS (N = 8)

Stanley Chang, MD	4063	October 28, 2005 - January 24, 2007	NGIOS (N = 4) BSS PLUS (N = 4)
Steven Charles, MD	2667	February 27, 2006 - January 15, 2007	NGIOS (N = 5) BSS PLUS (N = 4)
Tom Ciulla, MD	2338	June 8, 2006 - February 1, 2007	NGIOS (N = 5) BSS PLUS (N = 4)
W. Lloyd Clark, MD	4771	August 1, 2006 - March 19, 2007	NGIOS (N = 4) BSS PLUS (N = 5)
Tim Cleland, MD	4772	July 31, 2006 - March 21, 2007	NGIOS (N = 5) BSS PLUS (N = 5)
David Dyer, MD	4792	July 26, 2006 - January 24, 2007	NGIOS (N = 2) BSS PLUS (N = 1)
Jeffrey Gross, MD	4770	October 3, 2006 - March 8, 2007	NGIOS (N = 2) BSS PLUS (N = 3)
Sunil Gupta, MD	4070	July 14, 2006 - March 8, 2007	NGIOS (N = 13) BSS PLUS (N = 13)
Darin Haivala, MD	4444	March 9, 2006 - October 10, 2006	NGIOS (N = 3) BSS PLUS (N = 3)
Leo S. Harf, MD	3663	August 9, 2006 - February 26, 2007	NGIOS (N = 1) BSS PLUS (N = 1)
Clio Arme Harper, MD	3251	August 7, 2006 - January 12, 2007	NGIOS (N = 1) BSS PLUS (N = 2)
Henry Hudson, MD	2855	August 31, 2006 - January 22, 2007	NGIOS (N = 3) BSS PLUS (N = 3)
Ray Iezzi, MD	4064	November 7, 2005 - February 6, 2007	NGIOS (N = 5) BSS PLUS (N = 4)
Michael Lambert, MD	2675	May 4, 2006 - November 20, 2006	NGIOS (N = 1) BSS PLUS (N = 2)
S. Young Lee, MD	4712	February 14, 2006 - January 3, 2007	NGIOS (N = 12) BSS PLUS (N = 12)
Jeffrey Marx MD	3256	December 15, 2005 - January 11, 2007	NGIOS (N = 2) BSS PLUS (N = 3)
Roger L. Novack, MD	4441	January 17, 2006 - January 23, 2007	NGIOS (N = 5) BSS PLUS (N = 5)
Jeffrey L. Olson, MD	4325	November 22, 2005 - January 5, 2007	NGIOS (N = 3) BSS PLUS (N = 3)
Arun C.Patel, MD	4442	February 20, 2006 - March 14, 2007	NGIOS (N = 9) BSS PLUS (N = 9)
Michael Petersen, MD	3523	October 19, 2005 - December 19, 2006	NGIOS (N = 5) BSS PLUS (N = 6)
Richard Rothman, MD	4814	August 21, 2006 - December 8, 2006	NGIOS (N = 1) BSS PLUS (N = 0)
Todd Schneiderman, MD	4075	April 17, 2006 - February 6, 2007	NGIOS (N = 11) BSS PLUS (N = 10)
Cameron Stone, MD	4101	July 6, 2006 - December 1, 2006	NGIOS (N = 3) BSS PLUS (N = 4)
Joseph Walker, MD	4794	June 14, 2006 - February 9, 2007	NGIOS (N = 9) BSS PLUS (N = 10)
George Williams, MD	3266	November 30, 2005 - January 29, 2007	NGIOS (N = 12) BSS PLUS (N = 12)

Study Plan for C-04-18

Study Activity	Preop. Screening/ Baseline	Surgery	Post-surgery					
	-6 Weeks to -1 Day	Day 0	24 Hour ± 4 hours	Day 7 ± 2 days	Day 14 ± 2 days	Day 30 ± 5 days	Day 60 ± 7 days	Day 90 (-7 to +14 days)/ Early Exit[2]
Screening subjects	X							
Informed consent	X							
Demographics	X							
Current (baseline) and postoperative change in medical condition(s) (systemic and ocular anterior and posterior segments)	X	X	X	X	X	X	X	X
Electroretinogram (ERG) (at selected study sites only)	X[B]							X[B,3]
Best-corrected logMAR VA	X[B]			X[S]	X[S]	X[S]	X[S]	X[B]
Goldmann intraocular pressure	X[B]		X[S]	X[S]	X[S]	X[S]	X[S]	X[B]
Slit-lamp examination: ocular inflammation (cells, flare, corneal edema)	X[B]		X[S]	X[S]	X[S]	X[S]	X[S]	X[B]
Slit-lamp examination: lens status (LOCS II)	X[B]					X[S]	X[S]	X[B]
Dilated fundus examination (vitreous haze, retina, macula, choroid, optic nerve)	X[B]		X[S]	X[S]	X[S]	X[S]	X[S]	X[B]
Concurrent (non-surgically related) medications	X	X	X	X	X	X	X	X
Surgically related ocular conditions			X[S]	X[S]	X[S]	X[S]	X[S]	X[S]
Surgically related medications		X	X	X	X	X	X	X
Irrigating solution/surgical information		X						
IOP-lowering therapy			X	X	X	X	X	X
Record adverse events [1]		X	X	X	X	X	X	X
Complete exit form								X

[B] Both eyes.
[S] Study eye only.
[1] An adverse event form was to be completed at the time an adverse event was first observed or reported to the investigator. If an adverse event did not coincide with a study examination visit, then an unscheduled visit form was to be completed and sent to the Sponsor along with the adverse event form.
[2] Exit procedures were to be completed at the Day-90 visit or sooner if the patient discontinued early from the study.
[3] ERG had to be performed if the patient discontinued at Day 30 (± 5 days) or later post-operatively.

5.3.5 C-04-64

See also Section 7.3.5.2 in this review.

Clinical Evaluation of the Safety of Next Generation Ophthalmic Irrigating Solution Compared to BSS Plus for Use During Cataract Extraction in Pediatric Patients

List of Principal Investigators and Subinvestigators for Protocol C-04-64

Principal Investigator No.	Contact Information	Subinvestigator(s)
4927	Patrick Arnold, MD Eye Center of Northern Colorado, P.C. 1725 East Prospect Road Fort Collins, CO 80525 970-221-2222	None
4039	Scott Lambert, MD Emory Eye Center 1365-B Clifton Rd, N.E. Atlanta, GA 30322 404-778-5134	None
3292	David A. Plager, MD Indiana University School of Medicine Department of Ophthalmology Section of Pediatrics Riley Outpatient Center 702 Barnhill Dr, , Room 3340 Indianapolis, IN 46202 317-274-3630	
3296	M. Edward Wilson, MD Medical University of South Carolina Storm Eye Institute 167 Ashley Ave Charleston, SC 29425 843-792-6301	

Principal Investigator Name (Inv. No.)	Total Patients Enrolled	Treatment Groups	
		NGOIS	BSS Plus
Patrick Arnold, MD (4927)	2	2	0
Scott Lambert, MD (4039)	5	2	3
David Plager, MD (3292)	6	3	3
M. Edward Wilson, MD (3296)	5	3	2
Total:	**18**	**10**	**8**

Study Plan for C-04-64

Study Activity	Preoperative Screening/ Baseline -6 weeks to -1 day	Surgery	Post-surgery					
		Day 0	6 ± 2 hrs	24 hrs ± 6 hrs	Day 3 ± 1 day	Day 7 ± 2 days	Day 30 ± 7 days	Day 90 ± 14 days/ Exit[5]
Informed consent	X							
Record demographics	X							
Record systemic and ocular medical conditions	X							
Record patient's current (baseline) medications	X							
Record changes in systemic and ocular conditions		X	X	X	X	X	X	X
Record change in non-surgically related medications		X	X	X	X	X	X	X
Central endothelial cell photographs[1] (2 photos)	X[B]							X[B]
Visual acuity assessment[2]	X[B]			X[S]		X[S]	X[S]	X[B]
Applanation tonometry	X[B]		X[S]	X[S]	X[S]	X[S]	X[S]	X[B]
Assess ocular signs[2]	X[B]			X[S]		X[S]	X[S]	X[B]
Perform fundus examination[2]	X[B]							X[B]
Record surgically related medications		X						
Record changes in surgically related medications			X	X	X	X	X	X
Record adverse events[3]		X	X	X	X	X	X	X
Complete exit form[4]								X

[B] Both eyes.
[S] Study eye only.
[1] To be obtained if feasible (as age and mental competency permitted).
[2] Developmentally appropriate.
[3] Adverse events were to be reported after the administration of test article.
[4] An exit form was to be completed at the completion of the study (Day-90 Visit) or sooner if the patient discontinued from the study at an earlier date.
[5] Exit procedures were to be completed at the Day 90 visit or sooner if the patient discontinued early from the study.

6 Review of Efficacy

Efficacy Summary

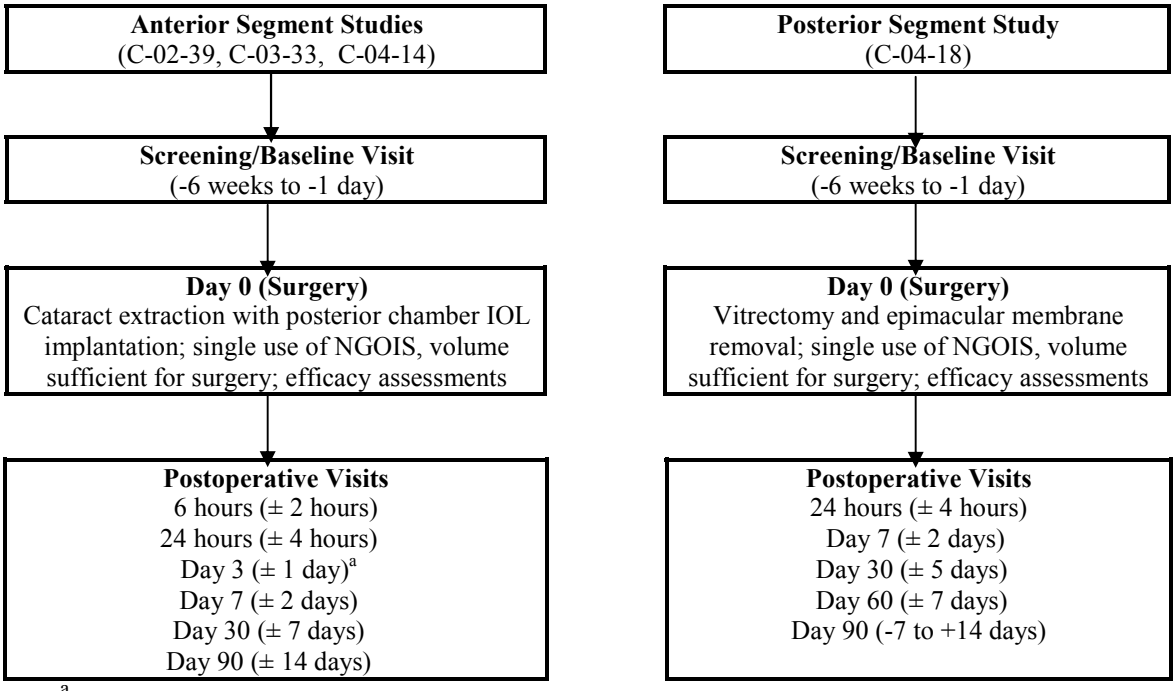
6.1 Indication

All five cited studies support the use of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) as an intraocular irrigating solution during surgical procedures involving perfusion of the eye.

6.1.1 Methods

General Study Design
The general study design for the 3 anterior segment studies (C-02-39, C-03-33, and C-04-14) and 1 posterior segment study (C-04-18) is shown below:

General Study Design for the Efficacy Trials



[a] This visit was not included in C-02-39

Patient Inclusion/Exclusion Criteria

The inclusion and exclusion criteria that were specific to each study are shown below. Exclusion criteria common to all 4 studies included the following: any abnormality that prevented reliable tonometry in either eye; a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis); participation in any other clinical study within 30 days before the baseline visit or at any time during study participation; and, the second (fellow) eye of a patient currently or previously enrolled into the study (each patient was allowed to have only 1 eye enrolled into the study).

Inclusion/Exclusion Criteria for NGOIS Efficacy Studies

Anterior Segment (C-02-39, C-03-33, and C-04-14)	**Posterior Segment (C-04-18)**
Inclusion Criteria	
Patients (male or female) of any race or age (age 18 or older for C-02-39 and C-03-33) with a cataract.	Patients (male or female), of any race at least 18 years of age or lens status (phakic, aphakic, or pseudophakic) with an epimacular membrane. Patients were permitted to have had a previous retinal detachment surgery (pneumoretinopexy, scleral buckle, vitrectomy with scleral buckle, or primary vitrectomy) in the operative eye if the retina had been completely attached for a minimum of 90 days prior to the preoperative screening/baseline visit.
Patients who were expected to undergo surgical removal of the cataract (by phacoemulsification for C-02-39 and C-03-33) with implantation of a posterior chamber intraocular lens.	Patients who were expected to undergo membrane peeling and complete or partial 20-gauge to 25-gauge vitrectomy.
Exclusion Criteria	
Patients with glaucoma or who were suspected of having glaucoma in either eye. For C-04-14, patients with glaucoma (including pseudoexfoliation or pigmentary) or any causes of compromised outflow in the operative eye.	Patients with any previous glaucoma filtration surgery, or a history of an attack of acute narrow angle-closure glaucoma or chronic angle-closure glaucoma in the operative eye. Glaucoma patients with a cup-to-disc ratio > 0.8 in the operative eye, or a baseline IOP ≥ 21 mm Hg in the operative eye while on IOP lowering medication.
Ocular hypertension (IOP > 21 mm Hg in C-02-39 and C-03-33 or IOP ≥ 21 mm Hg in C-04-14) in the operative eye at the baseline examination.	Ocular hypertension (IOP ≥ 21 mm Hg) in the operative eye at the baseline examination.
Any abnormality that prevented reliable tonometry in either eye.	Any abnormality that prevented reliable tonometry in either eye.
Planned multiple procedures during cataract/IOL implantation surgery (e.g., trabeculoplasty, corneal transplant). NOTE: A planned relaxing keratotomy was permitted for the correction of astigmatism (and these patients were not excluded from the per protocol analyses).	Other planned surgical procedures (e.g., lensectomy)

Inclusion/Exclusion Criteria for NGOIS Efficacy Studies (continued)

Anterior Segment (C-02-39, C-03-33, and C-04-14)	**Posterior Segment (C-04-18)**
Exclusion Criteria	
Previous ocular trauma to the operative eye, including previous intraocular surgery and traumatic cataract. For C-04-14, also included previous corneal transplant.	Previous ocular trauma to the operative eye, or previous intraocular posterior segment surgery in the operative eye within 90 days of the preoperative screening/baseline visit;
Proliferative diabetic retinopathy (C-02-39 and C-03-33) or diabetic retinopathy (C-04-14) in the operative eye.	Patients with proliferative diabetic retinopathy in the operative eye (only patients that could be included were those with mild, non-proliferative diabetic retinopathy, in the operative eye, defined as microaneurysms only)
For C-04-14, previous retinal detachment in the operative eye	Retinal detachment in the operative eye within 90 days of the preoperative screening/baseline visit
For C-04-14, clinically significant RPE/macular changes (e.g. macular degeneration), in the operative eye	RPE/macular changes (including age related macular degeneration) in the operative eye associated with a best-corrected Snellen visual acuity worse than 20/40 (equivalent to logMAR visual acuity worse than 0.3)
Baseline endothelial cell density less than 1500 cells/mm2 in the operative eye. For C-04-14, any patient at increased risk of corneal decompensation (based upon the investigator's assessment of the preoperative baseline endothelial cell image). A corneal abnormality (or any condition for C-04-14) that resulted in a poor quality endothelial cell photograph and prevented a reliable endothelial cell density measurement in either eye. For C-04-14, endothelial cell density measurements were collected only for the operative eye.	
Lens pseudoexfoliation syndrome where glaucoma or zonular compromise was present in the operative eye.	
History of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iritis)	
Uncontrolled diabetes mellitus	

Inclusion/Exclusion Criteria for NGOIS Efficacy Studies (continued)

Anterior Segment (C-02-39, C-03-33, and C-04-14)	Posterior Segment (C-04-18)
Exclusion Criteria	
Congenital ocular anomaly (e.g., aniridia). For C-02-39 and C-03-33, also excluded congenital cataract. Congenital cataract was permitted in C-04-14.	
Iris atrophy in the operative eye	
	Silicone oil currently present in the operative eye
	Myopes with a spherical equivalent ≥ 8.00 D
	Significant proliferative vitreoretinopathy other than epimacular membrane in the operative eye
	A history of or current branch or central retinal vein or artery occlusion (BRVO, CRVO, BRAO, CRAO) in the operative eye
	History of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis)
A visually non-functional fellow eye (to be assessed by the investigator). In C-02-39, visually nonfunctional was defined as non-study eye visual acuity worse than 0.6 logMAR [20/80 Snellen equivalent]). An exception to this exclusion was when the patient's visual acuity reduction was due to a cataract and it had been demonstrated with the use of a Potential Acuity Meter (or similar instrument) that the patient would have functional vision following removal of the cataract	A visually non-functional fellow eye with best-correct Snellen visual acuity worse than 20/200 (equivalent to logMAR visual acuity worse than 1.0)
Use of an investigational intraocular lens	Use of any investigational product during the surgical procedure. Approximately 0.1 mL of intraocular triamcinolone was permitted for visualization during the surgical procedure. All triamcinolone was to be removed as completely as possible before the close of the case. Periocular injection of triamcinolone at the close of the case or thereafter was permitted.
The Alcon Medical Monitor could declare any patient ineligible for per protocol evaluability based upon sound medical reason (e.g., where there were significant surgical complication(s) unrelated to the use of the irrigating solution; i.e., difficult lens placement, zonular dehiscence, vitreous in the anterior chamber, etc)	The Alcon Medical Monitor was permitted to declare any patient ineligible for per protocol evaluability based upon sound medical reason.
Participation in any other clinical study within 30 days before the baseline visit or at any time during study participation	Participation in any other clinical study within 30 days before the baseline visit or at any time during study participation
The second (fellow) eye of a patient currently or previously enrolled into this study (each patient was allowed to have only 1 eye enrolled into the study)	The second (fellow) eye of a patient currently or previously enrolled into this study (each patient was allowed to have only 1 eye enrolled into the study)

Assessment of Efficacy
The primary and secondary variables for the 4 efficacy studies are shown below.

In the 3 anterior segment studies (C-02-39, C-03-33, and C-04-14), multiple variables were measured to establish the efficacy of NGOIS based on maintenance of the corneal endothelium and improvement of irrigating flow characteristics during cataract surgery with phacoemulsification.

In C-02-39, the primary efficacy endpoint was phacoemulsification time (actual time phacoemulsification energy was applied), with turbulence, lens fragment followability, and viscoelastic retention as secondary efficacy variables.

Turbulence (lens fragment or fluid) was the primary endpoint in C-03-33, with lens fragment followability and viscoelastic retention as secondary efficacy variables.

The percent change in endothelial cell density was the primary endpoint in C-04-14, with turbulence, lens fragment followability, and viscoelastic retention as secondary efficacy variables.

In the posterior segment study (C-04-18), maintenance or improvement of best-corrected logMAR visual acuity was selected as a primary efficacy outcome for establishing efficacy of NGOIS based on use during surgery for removal of epimacular membrane during vitrectomy.

Reviewer's Comments:

C-04-64 is a safety study. See Section 7.3.5.2 in this review.

Although listed in the following table from the Alcon submission (source Table 2.5.4.2.-2), Percent change in endothelial cell density was not a pre-specified efficacy variable in C-03-33.

Alcon states in the CSR for C-03-33, page 6, "Mean endothelial cell density, although based upon a variable collected primarily for safety, is presented in the efficacy section to support use of this study as a Phase 3 clinical trial."

Efficacy Variables in the NGOIS Clinical Studies

Anterior Segment			Posterior Segment
C-02-39	**C-03-33**	**C-04-14**	**C-04-18**
PRIMARY EFFICACY VARIABLE(S)			
• Phacoemulsification time (actual time phacoemulsification energy is applied)	• Turbulence (lens fragment or fluid) • Percent change in endothelial cell density	• Percent change in endothelial cell density	• Maintenance or improvement in best-corrected logMAR visual acuity
SECONDARY EFFICACY VARIABLE(S)			
• Surgeon's evaluation of lens fragment followability to the phacoemulsification tip • Video panel's evaluation of lens fragment followability to the phacoemulsification tip (observer-masked) • Surgeon's evaluation of lens fragment/fluid turbulence during phacoemulsification • Video panel's evaluation of lens fragment/fluid turbulence during phacoemulsification (observer-masked) • Surgeon's evaluation of viscoelastic retention immediately following phacoemulsification • Central corneal thickness • Average phacoemulsification energy • Phacoemulsification duration (elapsed time)	• Surgeon's evaluation of lens fragment followability to the phacoemulsification tip • Surgeon's evaluation of viscoelastic retention immediately following phacoemulsification • Central corneal thickness (measured by ultrasound pachymetry) • Average phacoemulsification energy • Average phacoemulsification time • Average phacoemulsification duration (elapsed time)	• Best-corrected logMAR visual acuity • Central corneal thickness • Surgeon questionnaire regarding flow characteristics of the irrigating solution (turbulence and followability to the phacoemulsification tip) • Retention of the viscoelastic	

Reviewer's Comments:

The C-04-18 efficacy variable maintenance or improvement of BCVA, defined as a change from baseline in BCVA of < 0.1 logMAR units, is <u>not acceptable</u>. The agency believes that a 3-line change in visual acuity (i.e. 15 ETDRS letters) is clinically significant. The agency would accept

a statistically significant difference in the proportion of subjects who have 3 lines or more improvement from baseline based on the ETDRS evaluation. See Section 6.1.4.4.

Grading Scales for Turbulence and Followability

Turbulence	Overall turbulence during phacoemulsification	
	N/A	Unable to visualize
	0	None
	1	Mild
	2	Moderate
	3	Pronounced
Followability	Attraction of lens material to the phacoemulsification tip	
	1	Poor
	2	Fair
	3	Good
	4	Excellent

N/A = not applicable

Data Analysis

The original statistical objective for C-02-39 was to [redacted] the statistical objective was amended to provide a descriptive comparison between treatment groups.

The statistical objective for C-03-33 was to demonstrate superiority of NGOIS (3 and 4 cps) to BSS Plus for surgeon rated turbulence.

In C-04-14, the statistical objective was to demonstrate the non-inferiority of NGOIS to BSS Plus in the percent change from baseline in central endothelial cell density at Day 90. The FDA-established criterion for non-inferiority was based upon two factors. An observed absolute endothelial cell loss within the NGOIS treatment group less than or equal to 10% from baseline was required. Additionally, to demonstrate the non-inferiority of NGOIS to BSS Plus, the non-inferiority margin was established at 7.5%. All hypothesis testing was conducted with a 0.05 probability of a Type I error.

For C-04-18, the primary statistical objective was to demonstrate non-inferiority of NGOIS relative to BSS Plus when used during surgery for removal of epimacular membrane and vitrectomy. The primary efficacy endpoint was the percentage of patients with maintenance or improvement in best-corrected visual acuity (<1 line loss from baseline) at the postoperative Day 90 visit. A two-sided 95% confidence interval for the difference in proportions between the two treatment groups for the primary variable was constructed; the FDA-established non-inferiority criterion was 15%. Primary inference for non-inferiority was based on the per protocol data set and confirmed with the intent-to-treat data set.

Per protocol data and intent-to-treat results are provided for all safety/efficacy studies. Studies C-04-14 and C-04-18 were designed to demonstrate the non-inferiority of NGOIS relative to BSS Plus; per protocol data were considered primary. Studies C-02-39 and C-03-33 were designed to demonstrate superiority of NGOIS relative to BSS Plus; the intent-to-treat data were considered primary. All patients who were exposed to the test article were considered evaluable for the safety analyses. All patients who were exposed to the test article and attended at least one postoperative visit were considered evaluable for the intent-to-treat analyses. Last observation carried forward was used to impute values for incomplete data in the intent-to-treat data set. All patients who were exposed to the test article, satisfied the inclusion/exclusion criteria, attended at least one postoperative visit and adhered to protocol guidelines were considered evaluable for per protocol (PP) analyses. All evaluable data were used in the per protocol analysis and no imputation was carried out for missing data.

6.1.2 Demographics

Patient Demographics
(All Studies, Safety Data Set)

	Anterior Segment				Sub-Total	Posterior Segment	Grand Total
	C-02-39	C-03-33	C-04-14	C-04-64		C-04-18	
	105	**108**	**369**	**18**	**599**	**344**	**944**
Race							
Caucasian	96	105	275	14	489	316	805
Black	4	2	25	3	34	13	47
Asian	4	1	4	1	10	6	16
Other	1	0	65	0	66	9	75
Ethnicity							
Hispanic, Latino, or Spanish	-- [a]	-- [a]	-- [a]	2	2	-- [a]	2
Not Hispanic, Latino, or Spanish	-- [a]	-- [a]	-- [a]	16	16	-- [a]	16
Age							
1 to 23 mo.	0	0	0	4	4	0	4
2 to 11 yrs	0	0	0	11	11	0	11
12 to 17 yrs	0	0	0	3	3	0	3
18 to 65 yrs	26	22	78	0	126	63	189
≥ 65 yrs	79	86	291	0	455	281	736
Sex							
Male	48	42	172	12	274	158	432
Female	57	66	197	6	325	186	511
Eye Color							
Brown	43	34	176	9	262	131	393
Hazel	12	21	40	2	75	53	128
Green	7	10	30	1	48	23	71
Blue	41	42	119	6	207	122	329
Grey	2	1	4	0	7	15	22

A summary of the patient demographics for each of the clinical studies (C-02-39, C-03-33, C-04-14, C-04-64 and C-04-18) is shown above.

Reviewer's Comments:

Patients are predominately elderly and Caucasian. There is a slight predominance of female patients, which is typical of an elderly population. No clinically relevant differences are observed between the treatment groups comparing the demographic characteristics (i.e., age, race, sex, and iris color) of the population when integrated across studies, as well as within each individual clinical study.

6.1.3 Patient Disposition

Disposition of Patients Enrolled in C-02-39
One hundred eight patients were enrolled in the study. Three of the 108 patients discontinued the study prior to surgery and did not receive a test article; therefore, they were excluded from all analyses leaving 105 patients who were evaluable for safety analyses. One of the remaining 105 patients discontinued from the study on the day of surgery after exposure to test article and was excluded from the ITT and PP analyses because the patient was implanted with an anterior chamber intraocular lens rather then a posterior chamber intraocular lens. The remaining 104 patients were present for at least one post-operative visit. Of the patients evaluable for the ITT analysis, 99 were also evaluable for per protocol analyses. Five patients were excluded from the PP data set due to: phacoemulsification not used to remove lens (2), unreadable baseline endothelial photographs (1), detached Descemet's membrane and excessive phacoemulsification duration (1) and zonular laxity and excessive phacoemulsification duration (1).

Patients Discontinued from Study C-02-39

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days
970	203	VIIS	74	Male	07NOV2002	4
1346	402	BSS PLUS	80	Male	27JAN2003	1
	405	BSS PLUS	87	Female	31JAN2003	5

Reviewer's Comments:

The subject receiving the anterior chamber lens should not have been excluded from the ITT population.

Disposition of Patients Enrolled in C-03-33
One hundred-eight (108) patients were enrolled in the study. All 108 patients received a test article and were present for at least one post-operative visit hence all of these patients were evaluable for the safety and ITT analyses. Of the patients evaluable for the ITT analysis, 104 were also evaluable for per protocol analyses. The remaining 4 patients were excluded from the PP data set due to: History of glaucoma suspect (2), changes in Inifiniti Custom setting causing

poor fluidics (1) and posterior capsule rupture/major vitreous loss, pars plana vitrectomy and lens placement not bag-bag (1).

Patients Discontinued from Study C-03-33

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days
847	1201	NGOIS 3	73	Male	29SEP2003	35
1434	4210	BSS PLUS	85	Male	09JAN2004	37
3747	5205	NGOIS 3	54	Male	04NOV2003	23

Disposition of Patients Enrolled in C-04-14
Three hundred sixty-nine (369) patients were enrolled in the study. All 369 patients received a test article and were present for at least one post-operative visit; hence, all of these patients were evaluable for the safety and ITT analyses. Of the patients evaluable for the ITT analysis, 344 were also evaluable for per protocol analyses. The remaining 25 patients were excluded from the PP data set.

Reviewers' Comments:

In the following table, Subject 3903 2606 developed congestive heart failure and eventually died. See Section 7.3.1 this review.

Subject 3904 2205 was lost to follow-up after Day 30. No additional information is available on the subject's case report form. This subject did not appear to discontinue for an adverse event.

Patients Discontinued from Study C-04-14

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Concomitant Medication	Dose	Reason
3904	2205	BSS PLUS	82	Female	14JAN2005	30	REFRESH PLUS	1 GTT	Lost to Follow-Up
							ACULAR	1 GTT	Lost to Follow-Up
							VIGAMOX	1 GTT	Lost to Follow-Up
							ACTONEL	35 MG	Lost to Follow-Up
							METROPRONLOL	25 MG	Lost to Follow-Up
							PREDNISONE	10 MG	Lost to Follow-Up
							POTASSIUM CHLORIDE	10 MG	Lost to Follow-Up
							ROBAXIN	750 MG	Lost to Follow-Up
							LESCOL XL	80 MG	Lost to Follow-Up
							NEXIUM	40 MG	Lost to Follow-Up
							ASPRIN	81 MG	Lost to Follow-Up
							FUROSEMIDE	40 MG	Lost to Follow-Up
							LIDOCAINE 2% PF	1 GTT	Lost to Follow-Up
							SENSORCAINE 0.75%	1 GTT	Lost to Follow-Up
							PROPARACAINE	1 GTT	Lost to Follow-Up
							NEOSYNEPHRINE 0.75%	1 GTT	Lost to Follow-Up
							OCUFEN 0.03%	1 GTT	Lost to Follow-Up
							TROPICAMIDE 1%	1 GTT	Lost to Follow-Up
3903	2606	NGOIS	77	Male	17JAN2005	34	VIGAMOX 0.5%	1 GTT	Adverse Event
							TOPROL XL	50 MG	Adverse Event
							LISINOPRIL	20 MG	Adverse Event
							FUROSEMIDE	80 MG	Adverse Event
							ECOTRIN	325 MG	Adverse Event
							ALLOPURINOL	300 MG	Adverse Event
							ZOCOR	20 MG	Adverse Event
							GLUCOTROL XL	10 MG	Adverse Event
							MORPHINE SULPHATE	15 MG	Adverse Event
							IRON	25 MG	Adverse Event
							ALCAINE 0.5%	1 GTT	Adverse Event
							CYCLOGEL 1%	1 GTT	Adverse Event
							MYDRIACYL 1%	1 GTT	Adverse Event
							NEOSYNEPHRINE 2.5%	1 GTT	Adverse Event
							VIGAMOX 0.5%	1 GTT	Adverse Event
							ACULAR	1 GTT	Adverse Event
							VERSED	0.25 MG	Adverse Event
							FENTAMYL	25 MCG	Adverse Event

Disposition of Patients Enrolled in C-04-18

Three hundred forty-four patients were randomized to treatment at 31 study sites. All 344 patients enrolled into the study received test article and attended at least one postoperative study visit and were thus included in the safety and intent-to-treat data sets. Of the patients evaluable for the safety and intent-to-treat analyses, 333 were also evaluable for per protocol analyses.

Reviewers' Comments:

In the following table, Subject 2338 2206 developed Non-Hodgkin's Lymphoma with subsequent pleural effusions.

Subject 3239 2115 developed recurrent gastric cancer.

Subject 4792 2702 developed steroid dependant elevated intraocular pressure,

Subject 4839 3504 developed chronic renal failure.

Subject 3266 611, 4047 809, and 366 2901were lost to follow-up. No additional information is available on the subject's case report form. These subjects did not appear to discontinue for adverse events.

Patients Discontinued from Study C-04-18

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Reason	Study Eye	Eye	Concomitant Medication	Dose
3266	611	BSS PLUS	46	Male	07JUL2006	1	Lost to Follow-Up	OS		TYLENOL	650 MG
										VITAMIN C	1000 MG
										PHISOHEX	1 APPLICATION
										GENTAMICIN 0.3%	1 GTT.
										OCUFEN	1 GTT.
										NEO-SYNEPHRINE	1 GTT.
										MYDRIACYL	1 GTT.
										CYCLOGYL	1 GTT.
										VERSED	3 MG.
										PROPOFOL	180 MG.
										FENTANYL	1 MCG.
										FENTANYL	0.5 MCG
										LIDOCAINE 2%	5 ML.
										MARCAINE 0.5%	5 ML.
										ISOFLURANE	1.5 %

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Reason	Study Eye	Eye	Concomitant Medication	Dose
4047	809	BSS PLUS	76	Male	12SEP2006	1	Lost to Follow-Up	OS		NEURONTIN	300 MG
										TOPROL XL	100 MG
										COUMADIN	5 MG
										LANOXIN	.25 MG
										AVANDIA	4 MG
										VIGAMOX 0.5%	1 GTT
										MYDRIACYL 1%	1 GTT
										HYOSCINE .25%	1 GTT
										NEOSYNEPHRINE 2.5%	1 GTT
										PROPOFOL	50 MG
3239	2115	NGOIS	78	Male	29SEP2006	1	Adverse Event	OS		ZOLOFT	50 MG
									OD	ARTIFICIAL TEARS	1 GTT
										PROPARACAINE HCL	1 GTT
										PHENYLEPHRINE HCL 2.5%	1 GTT
										TROPICAMIDE 1%	1 GTT
										FLURBIPROFEN SODIUM 0.3%	1 GTT
										MOXIFLOXACIN HCL 0.5%	1 GTT
										CYCLOGYL 2%	1 GTT
										ECONOPRED PLUS 1%	1 GTT
										XYLOCAINE 4%	5 CC
										MARCAINE 0.75%	5 CC
										WYDASE	0.2 CC
										SODIUM PENTOTHAL	175 MG
2338	2206	NGOIS	75	Male	30OCT2006	1	Adverse Event	OS		HYDROCHLOROTHYAZIDE	25 MG
										TOPROL	50 MG
										LISINOPRIL	40 MG
										SIMVASTATIN	40 MG
										CQ10	1 TAB
									OS	ACULAR	1 DROP
										BUPIVACAINE 0.5%	5 ML
										LIDOCAINE 2%	5 ML
										POVIDONE IODINE	1 DROP
										EPINEPHRINE 1:1000	0.3 ML
										DIPRIVAN	80 MG IV
										CYCLOGYL 1%	1 DROP
										MYDFRIN 2.5%	1 DROP
										TROPICAMIDE 1%	1 DROP
4792	2702	NGOIS	77	Female	17OCT2006	1	Adverse Event	OD		TREAMTERENE HCTZ 5/25 MG	1 TAB
										ESTRADIOL	1 MG
										MULTIVITAMIN	1 TAB
									OU	ARTIFICIAL TEARS	1 GTT

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Reason	Study Eye	Eye	Concomitant Medication	Dose
										MARCAINE 0.75%	1 GTT
										MYDRIACYL 1%	1 GTT.
										PROPOFOL	100 MG
										HOMATROPINE 5%	1 GTT.
										LIDOCAINE	40 MG
										PHENYLEPHRINE 2.5%	1 GTT.
										FENTANYL	50 MCG
										VIGAMOX 0.5%	1 GTT.
										LIDOCAINE 2%	1 GTT
3663	2901	BSS PLUS	76	Male	14SEP2006	1	Lost to Follow-Up	OD		ASPIRIN	325 MG
										LIPITOR	80 MG
										NORVASC	5 MG
										ATACAND	32 MG
										ATENOLOL	50 MG
										FISH OIL	1000 MG
										TETRACAINE 0.5%	1 DROP OD
										VIGAMOX 0.5%	1 DROP OD
										CYCLOGYL 1%	1 DROP OD
										AK-DILATE 10%	1 DROP OD
										VOLTAREN 0.1%	1 DROP OD
										MYDRIACYL 1%	1 DROP OD

Inv.	Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Reason	Study Eye	Eye	Concomitant Medication	Dose
										NEOSYNEPHRINE 2.5%	1 DROP OD
										WYDASE	0.5 CC
4839	3504	NGOIS	73	Female	07NOV2006	1	Adverse Event	OS		LISINOPRIL	20 MG
										SPIRINOLACTONE	50 MG
										LASIX	20 MG
										FERROUS SULFATE	325 MG
										CLOPIDROGEL	75 MG
										PROTONIX	40 MG
										CALTRATE + D	600 MG
										DARVOCET N	100 MG
										FLU INJECTION	1 INJECTION
										TRAZODONE	50 MG
										VERSED	2 MG
										FENTANYL	150 MCG
										LIDOCAINE	60 MG
										PROPOFOL	110 MG
										DECADRON	6 MG
										EPHEDRINE	10 MG
										LACTATED RINGERS	1500 ML

Disposition of Patients Enrolled in C-04-64
Eighteen patients were randomized to treatment at 4 study sites. All of the 18 patients enrolled into the study received test article and were included in the safety analysis.

Patient Discontinued from Study C-04-64

Inv. Pat.	Treatment	Age (Years)	Sex	Last Visit	Duration Days	Reason	Study Eye	Eye	Concomitant Medication	Dose
3292 104	NGOIS	3	Female	23OCT2006	1	Lost to Follow-Up	OD	2	TOBRADEX	1 DROP
								2	PRED FORTE 1%	1 DROP
									CYCLOGYL 1%	1 GTT
									PHENYLEPHRINE 2 1/2%	1 GTT
									VERSED	6 MG
									ALCAINE	1 DROP
									PROPOFOL	30 MG
									DEXAMETHASONE	4 MG
									ZOFRAN	2 MG

One patient discontinued from the study because she was lost to follow-up.

Reviewers' Comments:

Per CRF, subject was called several times, and a certified letter was sent. This subject did not appear to discontinue for an adverse event.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 C-02-39

The primary efficacy variable in C-02-39 was phacoemulsification time.

The original analysis plan included analyses to be conducted in two parts: 1) Day 30 analysis of safety and primary efficacy and 2) final (Day 90) analysis primarily for safety follow-up. During the course of the conduct of this study, it was noted that subjects in the NGOIS 5 cps treatment group were presenting in the early post-operative period (6 hours) with a higher incidence of increased intraocular pressure (greater than or equal to 30 mmHg) compared to the BSS Plus treatment group. Based upon this observation, an unplanned interim database lock was performed to analyze IOP values by treatment group.

Subsequent to the interim analysis, the protocol and analysis plan were amended to 1) change the statistical objective from demonstration of superiority in terms of phacoemulsification energy to a descriptive comparison between treatment groups ---------- ; 2) add a third treatment group of NGOIS 5 cps followed by a BSS Plus rinse; 3) cancel the Day 30 analysis and 4) document the unplanned interim analysis.

Alcon Table 11.4.1.3.2.-1:
Descriptive Statistics for Phacoemulsification Time (sec) in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	43.9	24.4	34	0	122	0.2296
NGOIS 5 cps & BSS PLUS	43.3	18.5	35	15	107	0.2784
BSS PLUS	37.9	16.9	33	15	79	
Total	41.8	20.2	102	0	122	0.4174

Test=Anova, P-value in 'Total' row reflects the main effect of Treatment
P-value in Treatment group rows reflects LSMeans comparisons to BSS PLUS
Two patients had missing phacoemulsification time data.

Alcon Table 14.2.2.1.-1:
Descriptive Statistics for Phacoemulsification Time (sec) in C-02-39
(PP)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	43.9	24.4	34	0	122	0.1620
NGOIS 5 cps & BSS PLUS	43.3	18.5	35	15	107	0.1984
BSS PLUS	36.7	17.0	30	15	79	
Total	41.5	20.4	99	0	122	0.3062

Test=Anova, P-value in 'Total' row reflects the main effect of Treatment
P-value in Treatment group rows reflects LSMeans comparisons to BSS PLUS

Reviewer's Comments:

There does not appear to have been a correction for the interim analysis which was the subject of Amendment 3.

There are no statistically significant or clinically relevant treatment differences observed in the ITT data set. The results for the PP data set are similar to those in the ITT data set.

6.1.4.2 C-03-33

The primary efficacy variable in C-03-33 was the investigator's assessment of turbulence (lens fragment or fluid). See the scale in Section 6.1.1 of this review.

Alcon Table 11.4.1.2.1.-1:
Descriptive Statistics for Surgeon Rated Turbulence in C-03-33
(Intent-to-Treat)

	None		Minimal		Moderate		
	N	%	N	%	N	%	P-Value[a]
Stableyz 3.0	21	53.8	15	38.5	3	7.7	0.0005
Stableyz 4.0	21	61.8	12	35.3	1	2.9	<.0001
BSS PLUS	7	20.0	16	45.7	12	34.3	
Total	49	45.4	43	39.8	16	14.8	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

Surgeons rated turbulence in the anterior chamber during phacoemulsification on a scale ranging from 0 (none) to 3 (pronounced). Statistically significant differences were detected between NGOIS 3 cps and NGOIS 4 cps when compared to BSS Plus for mean turbulence ($p=0.0005$ and $p<0.0001$, respectively). The Per Protocol findings are similar.

6.1.4.3 C-04-14

The primary efficacy variable in C-04-14 was percent change in endothelial cell density. This study was designed to demonstrate statistical non-inferiority of NGOIS 3 cps relative to BSS Plus for percent decrease in endothelial cell density at the post-operative Day 90 visit relative to baseline.

Alcon Table 11.4.1.1.-1:
Descriptive Statistics for Mean Endothelial
Cell Density Percent Change from Baseline to Day 90 in C-04-14 (PP)

	Mean	Std	N	Min	Max	Lower 95% CL	Upper 95% CL	P-Value[a]
NGOIS	-7.7	15.1	165	-58	39	-1.5	5.2	0.2740
BSS PLUS	-9.6	15.6	166	-59	29			
Total[b]	-8.6	15.4	331	-59	39			

[a] Analysis of Variance
[b] 13 patients had missing endothelial cell density data

Alcon Table 14.2.1-1:
Descriptive Statistics for Mean Endothelial
Cell Density Percent Change from Baseline to Day 90 in C-04-14 (ITT)

	Mean	Std	N	Min	Max	Lower 95% CL	Upper 95% CL	P-Value[a]
NGOIS	-8.3	15.8	175	-58	39	-1.4	5.2	0.2678
BSS PLUS	-10.2	15.9	178	-59	29			
Total[b]	-9.3	15.8	353	-59	39			

[a] Analysis of Variance
[b] 16 patients had missing endothelial cell density data

Alcon Table 7:
Descriptive Statistics for Endothelial Cell Density by Treatment
Intent-to-Treat

		Mean	Std	N
Baseline	**NGOIS**	2531.1	399.8	182
	BSS PLUS	2504.7	430.5	183
Day 90	**NGOIS**	2335.0	514.5	177
	BSS PLUS	2269.9	511.5	179

Reviewer's Comments:

In the Per Protocol data set, those patients receiving NGOIS 3 cps demonstrated a -7.7% mean endothelial cell density change at the post-operative Day 90 visit relative to baseline compared to -9.6% in the BSS Plus treatment group. The observed mean percent change in the NGOIS 3 cps treatment group was within a cell loss threshold of -10%. The two-sided 95% confidence

interval on the treatment-group difference of 1.9% in mean percent change in endothelial cell density was (-1.5%, 5.2%). The lower confidence limit was within -7.5%, indicating that NGOIS 3 cps is non-inferior to BSS Plus for mean percent endothelial cell loss at the post-operative Day 90 visit.

6.1.4.4 C-04-18

The primary efficacy variable in C-04-18 was maintenance or improvement in best-corrected visual acuity measured on the logMAR scale.

The primary variable was the proportion of patients with maintenance or improvement in best-corrected visual acuity (BCVA) at the Day 90 visit. Maintenance or improvement was defined as a change from baseline in BCVA of < 0.1 logMAR units. (A line of change on the logMAR scale is defined as a change of 0.10 in logMAR value.) The results of the ITT population are similar.

A test of non-inferiority was performed for the proportion of patients with maintenance or improvement in BCVA at the Day 90 visit. A two-sided 95% confidence interval was constructed for the difference in proportions between the two test articles, and noninferiority was to be declared if the lower confidence limit (LCL) for the difference in proportions (NGOIS 3 cps – BSS Plus) was greater than -15%, the planned non-inferiority margin. Primary inference for non-inferiority was based on the per protocol (PP) data set.

Alcon Table 11.4.1.1.-1:
Maintenance or Improvement of BCLVA (< 1 Line Loss)
at Day 90 Relative to Baseline in C-4-18
(Per Protocol)

		Day 90					
	Total[b]	Maintenance					
Treatment	N	N	%	Delta	Lower	Upper	P-Value[a]
NGOIS	160	129	80.6	-6.7	-14.7	1.2	0.0974
BSS PLUS	166	145	87.3				

[a] Test = Chi-square (Fishers Exact test if N<5)
[b] 7 patients had missing maintenance or improvement of BCLVA data

Reviewer's Comments:

In the per protocol data set (Alcon Table 11.4.1.1.-1), the percentage of patients with maintenance or improvement in visual acuity (< 1 line loss) at the postoperative Day 90 was 80.6% for NGOIS 3 cps compared to 87.3% in the BSS Plus treatment group. The two-sided 95% confidence interval on the treatment-group difference of -6.7% was (-14.7%, 1.2%).

This efficacy variable maintenance or improvement of BCVA, defined as a change from baseline in BCVA of < 0.1 logMAR units, is not acceptable. The agency believes that a 3-line change in visual acuity (i.e. 15 ETDRS letters) is clinically significant. The agency would accept a statistically significant difference in the proportion of subjects who have 3 lines or more improvement from baseline based on the ETDRS evaluation. See Alcon Table 12.5.1.-1 which follows.

Alcon Table 12.5.1.-1:
LogMAR Visual Acuity
Decrease from Baseline for the Study Eye

	Total	Exit Visit ≥3 Line Decrease[b]		Any Visit ≥3 Line Decrease[c]	
	N	N	%	N	%
Total	**343**	**25**	**7.3**	**115**	**33.5**
NGOIS	**168**	**14**	**8.3**	**61**	**36.3**
18 to 64 years	31	4	12.9	11	35.5
≥ 65 years	137	10	7.3	50	36.5
BSS PLUS	**175** [a]	**11**	**6.3**	**54**	**30.9**
18 to 64 years	31	2	6.5	16	51.6
≥ 65 years	144	9	6.3	38	26.4

[a] 1 patient had missing baseline or follow-up visual acuity data.
[b] Test=Chi-square (Fishers Exact test if N<5), P-value=0.4658
[c] Test=Chi-square (Fishers Exact test if N<5), P-value=0.2849
Decrease in visual acuity is defined as ≥ 3 logMAR line decrease from baseline to exit visit or to any visit for the Study eye compared to the same eye at baseline.
To any visit is representative of the worst case scenario and is defined as the visit with the maximum change in visual acuity for the Study eye from baseline to any scheduled or unscheduled visit.
The last visit with a non-missing visual acuity was used as exit.

Reviewer's Comments:

Visual acuity is maintained by both NGIOS 3 cps and BSS Plus with no significant differences noted.

6.1.4.5 Efficacy Summary for Primary Variables

Results from three clinical studies in patients undergoing cataract surgery demonstrated that Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) is an effective irrigating solution for anterior segment surgical procedures. Results from an additional clinical study demonstrated that Navstel Intraocular Irrigating Solution is an effective irrigating solution for posterior segment surgical procedures.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 C-02-39

The secondary efficacy endpoints in C-02-39 were: surgeon's evaluation of lens fragment followability to the phacoemulsification tip; video panel evaluation of lens fragment followability to the phacoemulsification tip (observer-masked); surgeon's evaluation of lens fragment/fluid turbulence during phacoemulsification; video panel's evaluation of lens fragment/fluid turbulence during phacoemulsification (observer-masked); surgeon's evaluation of viscoelastic retention immediately following phacoemulsification; central corneal thickness; average phacoemulsification energy; and phacoemulsification duration (elapsed time).

Reviewer's Comments:

There has not been a correction for multiplicity for the numerous secondary endpoints. Only the results for the specified population are shown unless the other populations differ significantly.

Alcon Table 11.4.1.2.3.-1:
Descriptive Statistics for Surgeon Evaluation of Followability in C-02-39 (Intent-to-Treat)

	Poor		Fair		Good		Excellent		
	N	%	N	%	N	%	N	%	P-Value[a]
NGOIS 5 cps	0	0	0	0	20	57.1	15	42.9	0.0002
NGOIS 5 cps & BSS PLUS	0	0	4	11.4	15	42.9	16	45.7	0.0025
BSS PLUS	1	2.9	10	29.4	18	52.9	5	14.7	
Total	1	1.0	14	13.5	53	51.0	36	34.6	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

Surgeons rated lens fragment followability to the phacoemulsification tip on a scale ranging from 1 (poor) to 4 (excellent). Statistically significant differences are seen between NGOIS 5 cps and NGOIS 5 cps & BSS Plus when compared to BSS Plus alone for followability (p=0.0002 and p=0.0025, respectively).

Alcon Table 11.4.1.4.1.-1:
Descriptive Statistics for Video Panel Lens Fragment Followability to the Phacoemulsification Tip in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	3.0	0.2	30	2	3	0.1528
NGOIS 5 cps & BSS PLUS	2.8	0.4	32	2	3	
BSS PLUS	2.8	0.6	27	2	4	

Test=Cochran-Mantel-Haenszel rank scores test
Fifteen patients had missing video panel followability data.

Reviewer's Comments:

The independent observers rated lens fragment followability to the phacoemulsification tip on a scale ranging from 1 (poor) to 4 (excellent). No statistically significant or clinically relevant treatment differences are noted for videotape raters' evaluation of followability in the ITT data set.

Alcon Table 11.4.1.2.1.-1:
Descriptive Statistics for Surgeon Evaluation of Turbulence in C-02-39
(Intent-to-Treat)

	None		Minimal		Moderate		Pronounced		
	N	%	N	%	N	%	N	%	P-Value[a]
NGOIS 5 cps	12	34.3	21	60.0	2	5.7	0	0	<.0001
NGOIS 5 cps & BSS PLUS	13	37.1	22	62.9	0	0	0	0	<.0001
BSS PLUS	0	0	15	44.1	17	50.0	2	5.9	
Total	25	24.0	58	55.8	19	18.3	2	1.9	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

Statistically significant differences are seen between NGOIS 5 cps and NGOIS 5 cps & BSS Plus when compared to BSS Plus alone for mean turbulence ($p<0.0001$ and $p<0.0001$, respectively).

Alcon Table 11.4.1.4.3.-1:
Descriptive Statistics for Video Panel Evaluation of Turbulence in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	1.3	0.5	30	0	2	0.0062
NGOIS 5 cps & BSS PLUS	1.5	0.7	32	1	4	
BSS PLUS	1.9	0.8	27	1	5	

Test=Cochran-Mantel-Haenszel rank scores test
Fifteen patients had missing video panel turbulence data.

Reviewer's Comments:

A statistically significant treatment difference was observed (p=0.0062) for videotape raters' evaluation of turbulence favoring NGOIS 5 cps.

Alcon Table 11.4.1.2.2.-1:
Descriptive Statistics for Surgeon Evaluation of Viscoelastic Retention in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	18.9	26.1	35	0	100	0.0185
NGOIS 5 cps & BSS PLUS	3.3	5.7	35	0	20	0.1894
BSS PLUS	8.8	13.9	34	0	50	
Total	10.3	18.4	104	0	100	0.0012

Test=Anova, P-value in 'Total' row reflects the main effect of Treatment
P-value in Treatment group rows reflects LSMeans comparisons to BSS PLUS

Reviewer's Comments:

Surgeons estimated the percentage of viscoelastic retained immediately following phacoemulsification. Least squares means comparisons reveal greater viscoelastic retention reported in the NGOIS 5 cps group compared to the BSS Plus treatment group (p=0.0185), indicating that NGOIS 5 cps increases the amount of viscoelastic retained in the anterior chamber during phacoemulsification compared to BSS Plus.

Alcon Table 11.4.1.1.1.-1:
Descriptive Statistics for Central Corneal Thickness (μm) in C-02-39 (Intent-to-Treat)

		Mean	Std	N	Min	Max	P-Value
6Hr	NGOIS 5 cps	624.7	66.9	35	512.0	791.7	0.8305
	NGOIS 5 cps & BSS PLUS	613.4	58.1	35	513.3	850.0	0.2872
	BSS PLUS	627.5	76.9	34	549.3	923.0	
	Total	621.8	67.3	104	512.0	923.0	0.5588
24Hr	NGOIS 5 cps	611.6	56.1	35	518.0	802.0	0.6614
	NGOIS 5 cps & BSS PLUS	589.2	48.4	35	505.3	742.0	0.2092
	BSS PLUS	605.9	80.7	33	525.3	966.7	
	Total	602.2	63.0	103	505.3	966.7	0.4353
7 Day	NGOIS 5 cps	579.8	38.6	35	504.3	690.3	0.9145
	NGOIS 5 cps & BSS PLUS	568.3	32.1	34	503.7	649.0	0.4341
	BSS PLUS	570.1	43.5	33	488.3	668.3	
	Total	572.9	38.2	102	488.3	690.3	0.6743
30 Day	NGOIS 5 cps	575.3	43.5	34	498.3	674.7	0.8059
	NGOIS 5 cps & BSS PLUS	568.0	32.4	35	509.3	648.3	0.7282
	BSS PLUS	564.2	37.6	33	494.7	652.7	
	Total	569.2	38.0	102	494.7	674.7	0.7671
90 Day	NGOIS 5 cps	572.3	39.7	34	507.0	651.3	0.5495
	NGOIS 5 cps & BSS PLUS	564.0	30.6	35	502.0	644.7	0.9551
	BSS PLUS	556.7	35.0	32	488.3	629.7	
	Total	564.5	35.5	101	488.3	651.3	0.7523

Test=Anova, Main Effect of Treatment p-value=0.5359, Treatment by Visit interaction p-value=0.7436
Four patients had missing central corneal thickness data at one or more visits.

Reviewer's Comments:

In the intent-to-treat data set, no statistically significant or clinically relevant treatment differences are seen for central corneal thickness at any visit. Patients receiving NGOIS 5 cps and NGOIS 5 cps & BSS Plus had mean Day 90 (Exit) central corneal thickness of 572.3 μm and 564.0 μm, respectively, compared to 556.7 μm in the BSS Plus treatment group.

Alcon Table 11.4.1.3.1.-1:
Descriptive Statistics for Phacoemulsification Energy (%) in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	30.0	12.0	34	5.3	43.8	0.9138
NGOIS 5 cps & BSS PLUS	32.9	9.8	35	13.0	50.4	0.3324
BSS PLUS	30.3	11.2	33	7.7	43.8	
Total	31.1	11.0	102	5.3	50.4	0.4877

Test=Anova, P-value in 'Total' row reflects the main effect of Treatment
P-value in Treatment group rows reflects LSMeans comparisons to BSS PLUS
Two patients had missing phacoemulsification energy data.

Reviewer's Comments:

Phacoemulsification energy was measured in percent energy used. No statistically significant or clinically relevant treatment differences are seen in the ITT data set.

Alcon Table 11.4.1.3.3.-1:
Descriptive Statistics for Phacoemulsification Duration (sec) in C-02-39
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value
NGOIS 5 cps	144.8	49.3	35	48	278	0.0812
NGOIS 5 cps & BSS PLUS	141.2	52.6	35	58	303	0.1457
BSS PLUS	123.6	47.3	34	64	255	
Total	136.7	50.2	104	48	303	0.1752

Test=Anova, P-value in 'Total' row reflects the main effect of Treatment
P-value in Treatment group rows reflects LSMeans comparisons to BSS PLUS

Reviewer's Comments:

Phacoemulsification duration was measured in seconds. No statistically significant or clinically relevant treatment differences are seen in the ITT data set.

6.1.5.2 C-03-33

The secondary efficacy endpoints in C-03-33 were: surgeon's evaluation of lens fragment followability to the phacoemulsification tip; surgeon's evaluation of viscoelastic retention immediately following phacoemulsification; central corneal thickness (measured by Ultrasound pachymetry); average phacoemulsification energy; average phacoemulsification time; and average phacoemulsification duration (elapsed time).

Reviewer's Comments:

There has not been a correction for multiplicity for the numerous secondary endpoints. Only the results for the specified population are shown unless the other populations differ significantly.

Alcon Table 11.4.1.2.3.-1:
Descriptive Statistics for Surgeon Rated Lens Fragment Followability in C-03-33 (Intent-to-Treat)

	Poor		Fair		Good		Excellent		
	N	%	N	%	N	%	N	%	P-Value[a]
Stableyz 3.0	0	0	2	5.1	25	64.1	12	30.8	0.6966
Stableyz 4.0	1	2.9	3	8.8	21	61.8	9	26.5	0.7109
BSS PLUS	0	0	3	8.6	22	62.9	10	28.6	
Total	1	0.9	8	7.4	68	63.0	31	28.7	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

There are no statistically significant or clinically relevant treatment differences seen for surgeons' rating of lens fragment followability for either NGOIS 3 cps or NGOIS 4 cps when compared to BSS Plus (p=0.6966 and p=0.7109, respectively).

Alcon Table 11.4.1.2.2.-1:
Descriptive Statistics for Viscoelastic Retention (%) in C-03-33
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value	Hommel P-Value
NGOIS 3	24.7	21.1	39	5	90	0.0231	0.0231
NGOIS 4	28.1	24.9	34	5	90	0.0044	0.0087
BSS PLUS	13.9	13.0	35	0	60		
Total	22.3	21.0	108	0	90	0.0111	

Test=ANOVA, P-value in 'Total' row reflects the main effect of Treatment
P-values in Treatment group rows reflect LSMeans comparisons to BSS PLUS

Reviewer's Comments:

Surgeons estimated the percentage of viscoelastic retained immediately following phacoemulsification. Least squares comparisons reveals greater viscoelastic retention reported in both the NGOIS 3 cps and NGOIS 4 cps groups compared to the BSS Plus treatment group (p=0.0231 and p=0.0044, respectively).

Alcon Table 11.4.1.3.2.-1:
Descriptive Statistics for Phacoemulsification Time (sec) in C-03-33
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value	Hommel P-Value
NGOIS 3	73.0	44.3	36	6	162	0.5673	0.5673
NGOIS 4	80.0	43.0	31	30	153	0.2248	0.4496
BSS PLUS	67.2	38.6	33	18	148		
Total	73.3	41.9	100	6	162	0.4764	

Test=ANOVA, P-value in 'Total' row reflects the main effect of Treatment
P-values in Treatment group rows reflects LSMeans comparisons to BSS PLUS
No phaco time for patients:
4101,4102,4103,4104,4105,4201,4204,4205

Reviewer's Comments:

No statistically significant or clinically relevant treatment differences are noted in the ITT data set.

Alcon Table 11.4.1.3.3.-1:
Descriptive Statistics for Phacoemulsification Duration (sec) in C-03-33 (Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value	Hommel P-Value
NGOIS 3	137.5	52.3	39	56	311	0.9430	0.9430
NGOIS 4	163.4	65.1	34	62	335	0.0391	0.0783
BSS PLUS	136.6	40.3	35	78	232		
Total	145.3	54.3	108	56	335	0.0625	

Test=ANOVA, P-value in 'Total' row reflects the main effect of Treatment
P-values in Treatment group rows reflects LSMeans comparisons to BSS PLUS

Reviewer's Comments:

There is a statistically significantly longer mean phacoemulsification duration recorded for NGOIS 4 cps compared to BSS Plus (p=0.0391). No statistically significant or clinically relevant treatment difference is seen for mean phacoemulsification duration between NGOIS 3 cps and BSS Plus.

Alcon Table 11.4.1.1.1.-1:
Descriptive Statistics for Central Corneal Thickness (μm) in C-03-33
(Intent-to-Treat)

		Mean	Std	N	Min	Max	P-Value	Hommel P-Value
6HR	**NGOIS 3**	608.7	58.1	39	518.0	791.3	0.9814	0.9814
	NGOIS 4	600.3	54.6	34	504.7	695.3	0.4626	0.9814
	BSS PLUS	608.5	49.7	35	510.0	743.3		
24HR	**NGOIS 3**	590.6	65.0	39	512.0	841.3	0.3392	0.9814
	NGOIS 4	585.1	48.9	34	490.7	736.0	0.1569	0.9052
	BSS PLUS	600.9	41.0	35	493.0	678.7		
7 Day	**NGOIS 3**	572.5	45.5	39	510.3	705.7	0.2068	0.9429
	NGOIS 4	573.8	47.7	34	492.7	703.7	0.2661	0.9814
	BSS PLUS	586.2	35.7	35	533.0	666.3		
30 Day	**NGOIS 3**	563.1	38.7	37	508.0	708.0	0.6665	0.9814
	NGOIS 4	564.0	41.4	34	473.7	686.7	0.5591	0.9814
	BSS PLUS	570.5	29.1	35	515.7	637.0		
Exit Procedures	**NGOIS 3**	560.3	40.7	37	503.7	694.0	0.7543	0.9814
	NGOIS 4	560.1	41.5	34	487.7	684.7	0.5684	0.9814
	BSS PLUS	566.5	32.7	34	486.7	663.3		

Test=ANOVA, Main Effect of Treatment p-value=0.5613, Treatment by Visit interaction p-value=0.8841

Reviewer's Comments:

In the intent-to-treat data set, there are no statistically significant or clinically relevant treatment differences observed for pachymetry (central corneal thickness) at any visit. Patients receiving NGOIS 3 cps and NGOIS 4 cps had mean Day 90 (Exit) pachymetry measurements of 560.3 μm and 560.1 μm, respectively, compared to 566.5 μm in the BSS Plus treatment group.

Alcon Table 11.4.1.3.1.-1:
Descriptive Statistics for Phacoemulsification Energy (%) in C-03-33
(Intent-to-Treat)

	Mean	Std	N	Min	Max	P-Value	Hommel P-Value
NGOIS 3	37.4	8.6	36	21	57	0.4228	0.5867
NGOIS 4	36.9	9.1	31	18	54	0.5867	0.5867
BSS PLUS	35.7	8.5	33	16	48		
Total	36.7	8.7	100	16	57	0.7146	

Test=ANOVA, P-value in 'Total' row reflects the main effect of Treatment
P-values in Treatment group rows reflects LSMeans comparisons to BSS PLUS
No phaco energy for patients:
4101,4102,4103,4104,4105,4201,4204,4205

Reviewer's Comments:

Phacoemulsification energy was measured in percent energy used. No statistically significant or clinically relevant treatment differences are seen in the ITT data set.

6.1.5.3 C-04-14

The secondary efficacy endpoints in C-04-14 were: Best corrected logMAR visual acuity, central corneal thickness, surgeon questionnaire regarding flow characteristics of the irrigating solution (turbulence and followability to the phacoemulsification tip) and retention of the viscoelastic.

Reviewer's Comments:

There has not been a correction for multiplicity for the numerous secondary endpoints. Only the results for the specified population are shown unless the other populations differ significantly.

Alcon Table 11.4.1.4.2.-2:
Best-Corrected logMAR Visual Acuity of ≤ 0.3 at Any Visit by Treatment (PP) in C-04-14

	≤ 0.3		> 0.3		
	N	%	N	%	P-Value[a]
NGOIS	129	75.0	43	25.0	0.1761
BSS PLUS	117	68.4	54	31.6	
Total	246	71.7	97	28.3	

[a] Chi-square test of independence (or Fishers Exact test if N<5)

Reviewer's Comments:

No statistically significant treatment differences are seen for percentage of patients with best-corrected logMAR visual acuity scores of ≤ 0.3 logMAR at any post-operative visit.

Alcon Table 11.4.1.4.1.-1:
Descriptive Statistics for Central Corneal Thickness (μm) in C-04-14
Mean Change from Baseline (PP)

		Mean	Std	N	Min	Max	Lower 95% CL	Upper 95% CL	P-Value
6HR	**NGOIS**	65.7	64.0	171	-55.3	377.0	-15.9	1.8	0.1166
	BSS Plus	72.9	59.4	167	-13.0	303.3			
Day 1	**NGOIS**	49.6	64.9	172	-38.7	430.7	-11.0	6.6	0.6230
	BSS Plus	52.1	57.9	169	-26.7	358.0			
Day 3	**NGOIS**	30.7	36.8	171	-77.0	225.0	-11.2	6.5	0.6055
	BSS Plus	32.7	32.5	166	-22.0	251.0			
Day 7	**NGOIS**	17.2	24.3	172	-86.7	112.7	-11.8	5.8	0.5073
	BSS Plus	20.4	23.0	170	-43.0	86.7			
Day 30	**NGOIS**	8.3	23.2	172	-93.3	135.0	-10.0	7.6	0.7882
	BSS Plus	9.8	23.6	170	-57.0	108.0			
Day 90	**NGOIS**	3.8	18.4	172	-88.3	65.0	-9.8	7.8	0.8266
	BSS Plus	5.4	23.1	169	-62.7	94.7			

Test=Anova, Main Effect of Treatment p-value=0.3643
Treatment by Visit interaction p-value=0.8611
16 patients had missing corneal thickness data for one or more visits

Reviewer's Comments:

No statistically significant differences are seen between NGOIS and BSS Plus for corneal thickness change from baseline at any post-operative visit.

Alcon Table 11.4.1.3.1.-1:
Descriptive Statistics for Turbulence by Treatment (PP) in C-04-14

	None		Minimal		Moderate		Pronounced		
	N	%	N	%	N	%	N	%	P-Value[a]
NGOIS	76	43.9	89	51.4	7	4.0	1	0.6	<.0001
BSS Plus	18	10.5	47	27.5	86	50.3	20	11.7	
Total	94	27.3	136	39.5	93	27.0	21	6.1	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

A statistically significant difference is seen between NGOIS and BSS Plus for surgeon rated turbulence ($p<0.0001$). More than 95% of the ratings for patients exposed to NGOIS are "none" or "minimal" compared to 38% for patients exposed to BSS Plus.

Alcon Table 11.4.1.3.2.-1:
Descriptive Statistics for Followability by Treatment (PP) in C-04-14

	Poor		Fair		Good		Excellent		
	N	%	N	%	N	%	N	%	P-Value[a]
NGOIS	1	0.6	16	9.2	107	61.8	49	28.3	0.8857
BSS Plus	2	1.2	30	17.5	80	46.8	59	34.5	
Total	3	0.9	46	13.4	187	54.4	108	31.4	

[a] Cochran-Mantel-Haenszel rank scores test

Reviewer's Comments:

Surgeons rated lens fragment followability to the phacoemulsification tip on a scale ranging from 1 (poor) to 4 (excellent). No statistically significant differences are seen for surgeon's rating of lens fragment followability ($p=0.8857$).

Alcon Table 11.4.1.3.3.-1:
Descriptive Statistics for Viscoelastic Retention by Treatment (PP) in C-04-14

	Mean	Std	N	Min	Max	P-Value[a]
NGOIS	41.9	25.9	172	0	90	<.0001
BSS Plus	27.9	24.6	171	0	80	
Total	34.9	26.2	343	0	90	

[a] Two-sample t-test

Reviewer's Comments:

Statistically significant differences favoring NGOIS over BSS Plus are seen for viscoelastic retention (p<0.0001); NGOIS appears to increase the amount of viscoelastic retained in the anterior chamber during phacoemulsification compared to BSS Plus.

6.1.5.4 C-04-18

There were no prespecified secondary efficacy endpoints in C-04-18.

6.1.6 Other Endpoints

None.

6.1.7 Subpopulations

Patients are predominately elderly and Caucasian. There is a slight predominance of female patients, which is typical of an elderly population. No clinically relevant differences are observed between the treatment groups comparing the demographic characteristics (i.e., age, race, sex, and iris color) of the population when integrated across studies, as well as within each individual clinical study.

Analyses by age category (adults and elderly), gender, race, and iris color did not identify any efficacy (or safety) concerns for any demographic subpopulation.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The primary efficacy variable in C-02-39 was phacoemulsification time. During the course of the conduct of this study, it was noted that subjects in the NGOIS 5 cps treatment group were presenting in the early post-operative period (6 hours) with a higher incidence of increased intraocular pressure (greater than or equal to 30 mmHg) compared to the BSS Plus treatment group. ---------- ---------- ---------- ----------

NGIOS 3 cps and NGIOS 4 cps were evaluated in C-03-33. Those results suggested that the risk for transient intraocular pressure elevations during the early postoperative period was lower in the NGOIS 3 cps treatment group compared to the NGOIS 4 cps treatment group.

NGIOS 3 cps alone was evaluated in C-04-14 and C-04-18 (and in C-04-64 for safety).

The addition of hypromellose to the irrigating solution results in a slight increase in viscosity from 1.0 cps for BSS Plus to approximately 3 cps for Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable. This drug product is an intraocular irrigating solution during surgical procedures involving perfusion of the eye.

6.1.10 Additional Efficacy Issues/Analyses

The original submitted labeling makes the following claims:

NAVSTEL™ Solution Labeling Claims

C-02-39			
C-03-33			
C-04-14			

Reviewer's Comments:

See the above table constructed by this Medical Officer. The labeling claims for ----------

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There is support for the claim of significantly reduced turbulent flow in the anterior chamber: the primary variable for C-03-33 is significant, and a secondary variable in C-04-14 is significant even after correction for multiplicity.

Reduced turbulent flow in the anterior chamber has clinical relevance. Bubbles generated by the phacoemulsification hand-piece may injure the corneal endothelium.[2]

2 Beesley RD, Olson RJ, Brady SE. The effects of prolonged phacoemulsification time on the corneal endothelium. Ann Ophthalmol 1986;18(6):216-9, 222.

Kim EK, Kim HY, Kim HB, Edelhauser HF. Scanning electron microscopy of endothelial lesion produced by air bubbles during phacoemulsification with various viscoelastics in human. Inv Ophthalmol Vis Sci 1996;37(3):S84.

Kim EK, Cristol SM, Geroski DH, McCarey BE, Edelhauser HF. Corneal endothelial damage by air bubbles during phacoemulsification. Arch Ophthalmol 1997;115:81-8.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Five clinical studies with 944 patients and 3 viscosities of NGOIS were submitted and reviewed. These studies encompass 3 anterior segment safety and efficacy studies in adults (C-02-39, C-03-33, and C-04-14), 1 posterior segment safety and efficacy study in adults (C-04-18), and 1 anterior segment safety study in pediatric patients (C-04-64).

7.1.2 Adequacy of Data

The safety information collected and contained in these five studies is adequate to evaluate the drug product for its intended use.

An adequate number of subjects were exposed to the drug product, including adequate demographic subsets. The doses and durations of exposure were adequate to assess safety for the intended use.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

See Section 7.4.1 of this review for pooled tables.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Alcon Table 2.7.4.1.1.-1:
Overview of Patient Exposure to Test article by Protocol: Anterior and Posterior Segment Studies (C-02-39, C-03-33, C-04-14, and C-04-18)

		NGOIS				Marketed Comparator
Protocol Number	**Safety N**	**NGOIS 3 cps**	**NGOIS 4 cps**	**NGOIS 5 cps**	**NGOIS 5 cps & BSS Plus**	**BSS Plus**
C-02-39	105			35	35	35
C-03-33	108	39	34			35
C-04-14	369	184				185
C-04-18	344	168				176
Total	926	391	34	35	35	431

Subjects in these trials are predominately elderly and Caucasian. There is a slight predominance of female patients, which is typical of an elderly population.

In addition, C-04-64 enrolled 18 pediatric patients, including 10 patients with exposure to NGOIS 3 cps and 8 patients with exposure to BSS Plus.

7.2.2 Explorations for Dose Response

See Section 6.1.8 of this review.

7.2.3 Special Animal and/or In Vitro Testing

There was no special animal or in vitro testing indicated or performed for this drug product.

7.2.4 Routine Clinical Testing

This drug product is an intraocular irrigating solution for use during surgical procedures involving perfusion of the eye.

There was adequate monitoring of the anterior and posterior segments of the eye, intraocular pressure, corneal endothelium, and visual acuity.

There were no clinical laboratory evaluations conducted for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

There were no vital signs collected on the case report forms for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

There were no electrocardiograms conducted for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

7.2.5 Metabolic, Clearance, and Interaction Workup

All of the ingredients of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) Parts I and II are normally found in the aqueous humor with the exception of hypromellose. The specific hypromellose ------ formulation was chosen because ---- ----- ---------- ---------- ---------- --- --- - ---------- -- ---------- --- - ------- -- ---------- ---------- -- ----- ---------- ---------- ----- -- ----- ---------- ---------- - ------ -

No safety concerns were identified in patients receiving concomitant medications (anti-infective agents; cardiovascular drugs; antilipemic agents; central nervous system agents; analgesics and anti-pyretics; nonsteroidal anti-inflammatory agents; anxiolytics, sedatives and hynoptic drugs; replacement preparations; diuretics; EENT preparations; gastrointestional drugs; hormones and synthetic substitutes; local anesthetics; and vitamins).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The important safety issues for similar drugs in this class (see Section 2.4 of this review) have been adequately evaluated.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths (leukemia, congestive cardiac failure, and recurrent colon cancer) were reported in the five clinical trials.

All three subjects had been randomized to Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione), i.e. the NGOIS 3 cps group.

Alcon Table 2.7.4.2.1.2.-1:
Adverse Events Resulting in Death - Anterior and Posterior Segment Studies (C-02-39, C-03-33, C-04-14, and C-04-18)

Patient ID	Age	Treatment	Coded Adverse Event	Outcome of Event	Causality Assessment
C0333.847.1201	73	NGOIS 3 cps	Leukaemia	Patient Died	Not Related
C0414.3903.2606	77	NGOIS 3 cps	Congestive Cardiac Failure	Patient Died	Not Related
C0418.3239.2115	78	NGOIS 3 cps	Recurrent Colon Cancer	Patient Died	Not Related

Coded adverse event = MedDRA Preferred Term (version 10.0) presented by System Organ Class
Patient ID = Protocol number.Investigator number.Patient number
NGOIS = Next Generation Ophthalmic Irrigating Solution
cps = centipoise

Study C-03-33
Patient C0333.0847.1201, a 73-year-old Caucasian male who was randomized to receive NGOIS 3 cps, had an ocular history of cataracts (OU). The patient's nonocular ongoing medical history included diabetes mellitus and high blood pressure. Leukemia was diagnosed previously in June 1995 and was thought to be resolved by June 2003. On Study Day 27 ---------- -, the patient relapsed and died due to a worsening of leukemia (coded as leukemia).

Study C-04-14
Patient C0414.3903.2606, a 77-year-old Caucasian male who was randomized to receive NGOIS, had an ocular history of cataracts (OU), dermatochalasis (OU), and mild retinal pigment epithelium changes (OD). The patient's nonocular ongoing medical history included diabetes mellitus, osteoarthritis, hyperlipidemia, gout, hypertension, ophthalmic-related migraines, diabetic nephropathy, coronary artery disease, chronic obstructive pulmonary disease, chronic renal failure, and anemia. On Study Day 68 (----- - -- - ----------, the patient experienced congestive heart failure and died from the event.

Study C-04-18
Patient C0418.3239.2115, a 78-year-old Caucasian male who was randomized to receive NGOIS, had ongoing ocular conditions of dermatochalasis (OU), drusen (OU), dry eye (OU), ectropian (OU), guttata (OD) macular cyst (OS), pseudohole (OD) and ptosis (OU). The patient's nonocular ongoing medical conditions included arthritis and depression with a history of colon cancer. Concomitant baseline medications included artificial tears and Zoloft. On Study Day 10 (August 23, 2006), the patient experienced a recurrence of colon cancer. The patient was also diagnosed with metastatic stomach cancer on Study Day 33 (September 15, 2006) and the patient began chemotherapy. The colon cancer resulted in the patient's death on ----------

Reviewer's Comments:

The three terminal events seen is very likely due to the population studied in these trials and not due to the drug or route of administration of the drug.

7.3.2 Nonfatal Serious Adverse Events

See Section 7.3.4 of this review.

7.3.3 Dropouts and/or Discontinuations

Alcon Table 2.7.4.2.1.4.-2:
Patients Discontinued from the Study Due to Adverse Events – Anterior and Posterior Segment Studies (C-02-39, C-03-33, C04-14, and C-04-18)

Protocol	Inv	Patient	Treatment	Coded Adverse Event	Outcome of Event	Serious	Causal Assessment	Pt DC Due AE
C0418	2338	2206	NGOIS 3 cps	Pleural Effusion	Resolved W/Tx	Yes	NR	Yes
C0418	4792	2702	NGOIS 3 cps	Glaucoma	Continuing W/Tx	No	NR	Yes
C0418	4839	3504	NGOIS 3 cps	Renal Failure Chronic	Continuing W/Tx	Yes	NR	Yes
C0239	1346	402	BSS Plus	Detached Descemet's Membrane	Continuing W/Tx	No	NR	Yes
C0239	1346	410	BSS Plus	Procedural Complication[a]	Resolved wo/Tx	No	NR	Yes

[a] Surgical complications 3+ loose zonules and vitreous herniation
Coded adverse event = MedDRA Preferred Term (version 10.0)
Inv = Investigator
W/Tx = with treatment
wo/Tx = without treatment
Pt DC Due AE = Patient discontinued study participation due to the adverse event
NGOIS = Next Generation Ophthalmic Irrigating Solution
Table 2.7.4.2.1.4.-2 is sorted (in the following order) by (1) seriousness, (2) treatment, (3) causality, (4) protocol, (5) investigator, and (6) patient and includes only patients who discontinued study participation due to nonfatal adverse events.
Three additional patients with exposure to NGOIS 3 cps discontinued study participation due to a fatal adverse event not related to treatment and are presented in Table 2.7.4.2.1.2.-1.
cps = centipoise

Reviewer's Comments:

Five patients (0.5%) discontinued study participation due to nonfatal adverse events as summarized above. The CRFS for the patients were reviewed and were consistent with the information provided above.

7.3.4 Significant Adverse Events

Alcon Table 2.7.4.2.1.3.-1:
Other Serious Adverse Events – Anterior and Posterior Segment Studies
(C-02-39, C-03-33, C04-14, and C-04-18)

Prot	Inv	Pat	Treatment	Coded Adverse Event	Outcome of Event	Causality Assmnt	Pt DC Due to AE
C0418	2338	2206	NGOIS 3 cps	Pleural Effusion	Resolved W/Tx	NR	Yes
C0418	4839	3504	NGOIS 3 cps	Renal Failure Chronic	Continuing W/Tx	NR	Yes
C0414	3900	2311	NGOIS 3 cps	Bronchitis	Resolved W/Tx	NR	No
C0414	3903	1610	NGOIS 3 cps	Knee Operation	Resolved W/Tx	NR	No
C0418	2338	2206	NGOIS 3 cps	Non-Hodgkin's Lymphoma Recurrent	Continuing W/Tx	NR	No
C0418	2855	3006	NGOIS 3 cps	Chest Pain	Resolved wo/Tx	NR	No
C0418	3235	1213	NGOIS 3 cps	Cardiac Failure Congestive	Continuing W/Tx	NR	No
C0418	3256	1002	NGOIS 3 cps	Osteoarthritis	Resolved W/Tx	NR	No
C0418	3256	1004	NGOIS 3 cps	Cholecystitis Acute	Resolved W/Tx	NR	No
C0418	3523	1402	NGOIS 3 cps	Pneumonia	Resolved W/Tx	NR	No
C0418	4075	2009	NGOIS 3 cps	Colectomy	Resolved W/Tx	NR	No
C0418	4712	1704	NGOIS 3 cps	Vomiting	Resolved W/Tx	NR	No
C0418	4794	3210	NGOIS 3 cps	Injury[a]	Resolved W/Tx	NR	No
C0418	4839	3504	NGOIS 3 cps	Vomiting	Resolved W/Tx	NR	No
C0239	970	221	NGOIS 5 cps & BSS Plus	Endophthalmitis	Resolved W/Tx	NR	No
				Hiatus Hernia	Resolved W/Tx	NR	No
C0414	1007	4304	BSS Plus	Colonic Polyp	Resolved W/Tx	NR	No
C0414	1007	4307	BSS Plus	Chest Pain	Resolved W/Tx	NR	No
C0414	3828	1801	BSS Plus	Femur Fracture	Resolved W/Tx	NR	No
				Joint Dislocation	Resolved W/Tx	NR	No
				Hip Arthroplasty	Resolved W/Tx	NR	No
C0414	3900	1303	BSS Plus	Hypoaesthesia	Resolved W/Tx	NR	No
				Blood Pressure Increased	Resolved W/Tx	NR	No

Alcon Table 2.7.4.2.1.3.-1:
Other Serious Adverse Events – Anterior and Posterior Segment Studies
(C-02-39, C-03-33, C04-14, and C-04-18) – Continued

Prot	Inv	Pat	Treatment	Coded Adverse Event	Outcome of Event	Causality Assmnt	Pt DC Due to AE
C0414	3900	1308	BSS Plus	Thrombosis	Resolved W/Tx	NR	No
C0414	3903	2608	BSS Plus	Carotid Artery Occlusion	Resolved W/Tx	NR	No
C0418	2338	2201	BSS Plus	Chest Pain	Continuing W/Tx	NR	No
C0418	2855	3002	BSS Plus	Small Intestinal Obstruction	Resolved wo/Tx	NR	No
C0418	4063	303	BSS Plus	Pneumonia	Resolved W/Tx	NR	No
C0418	4070	1801	BSS Plus	Abdominal Strangulated Hernia	Resolved W/Tx	NR	No
C0418	4444	1603	BSS Plus	Cholecystitis	Resolved W/Tx	NR	No
				Knee Arthroplasty	Resolved W/Tx	NR	No
C0418	4712	1703	BSS Plus	Neuropathic Arthropathy	Resolved W/Tx	NR	No
C0418	4712	1718	BSS Plus	Hypokalaemia	Resolved W/Tx	NR	No

[a] Fractured left ankle
Coded adverse event = MedDRA Preferred Term (version 10.0)
Prot = Protocol Inv = Investigator Pat = Patient
W/Tx = with treatment wo/Tx = without treatment
Pt DC Due to AE = Patient discontinued study participation due to the adverse event.
Assmnt = assessment
NR = Not Related
NGOIS = Next Generation Ophthalmic Irrigating Solution
cps = centipoise
Table 2.7.4.2.1.3.-1 is sorted (in the following order) by (1) discontinuation due to event, (2) treatment, (3) protocol, (4) investigator, and (5) patient.

Reviewer's Comments:

A serious adverse event was defined as any adverse experience that results in death, a life-threatening event, requires in-patient hospitalization or prolongs an existing hospitalization, causes a persistent or significant disability/incapacity, or results in a congenital anomaly or birth defect. Thirty-three other serious adverse events were reported in 26 patients, including 12 patients (3.1%) with exposure to NGOIS 3 cps, 1 patient (2.9%) with exposure to NGOIS 5 cps & BSS Plus, and 13 patients (3.0%) with exposure to BSS Plus. The types of nonocular serious adverse events that were observed are not unexpected for an aging population.

7.3.5 Submission Specific Primary Safety Concerns

7.3.5.1 Endothelial Cell Counts

Alcon Table 12.5.5.1.-1:
Mean Endothelial Cell Density (cells/mm2) Change from Baseline for the Study Eye in C-02-39

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
Total	Mean	2552.7	-171.9	-6.6		
	Std	342.7	324.1	12.7		
	N	104	97	97 [a]		
	Min	1577	-1630	-57.2		
	Max	3742	384.7	18.9		
NGOIS 5 cps	Mean	2470.4	-178.1	-7.0	0.5880 [f]	0.5222 [f]
	Std	302.8	349.2	14.1		
	N	35	32	32 [b]		
	Min	1697	-1036	-41.8		
	Max	2989	384.7	18.9		
18 to 64 years	Mean	2524.9	-22.9	-0.9		
	Std	406.6	210.3	8.4		
	N	9	9	9		
	Min	1697	-400	-13.4		
	Max	2989	322.3	14.5		
≥ 65 years	Mean	2451.5	-238.9	-9.4		
	Std	265.3	376.9	15.3		
	N	26	23	23 [b]		
	Min	2020	-1036	-41.8		
	Max	2913	384.7	18.9		

Alcon Table 12.5.5.1.-1:
Mean Endothelial Cell Density (cells/mm2) Change from Baseline for the Study Eye in C-02-39 – Continued

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
NGOIS 5 cps & BSS PLUS	Mean	2605.8	-134.8	-5.0	0.3648 [g]	0.3692 [g]
	Std	303.1	332.6	12.2		
	N	35	35	35		
	Min	1577	-1630	-57.2		
	Max	3428	198.7	7.6		
18 to 64 years	Mean	2663.2	-2.5	0.0		
	Std	316.5	72.9	2.8		
	N	7	7	7		
	Min	2144	-92	-3.1		
	Max	3013	115.0	4.6		
≥ 65 years	Mean	2591.4	-167.9	-6.3		
	Std	303.9	363.9	13.3		
	N	28	28	28		
	Min	1577	-1630	-57.2		
	Max	3428	198.7	7.6		

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
BSS PLUS	Mean	2582.9	-208.7	-7.9	0.7134 [h]	0.7914 [h]
	Std	407.7	290.9	11.8		
	N	34	30	30 [c]		
	Min	1842	-945	-44.5		
	Max	3742	373.7	15.9		
18 to 64 years	Mean	2678.4	-63.4	-1.7		
	Std	359.0	219.2	8.5		
	N	9	9	9 [d]		
	Min	2066	-352	-11.9		
	Max	3076	373.7	15.9		
≥ 65 years	Mean	2548.6	-270.9	-10.5		
	Std	425.4	299.8	12.2		
	N	25	21	21 [e]		
	Min	1842	-945	-44.5		
	Max	3742	214.0	9.7		

[a] 8 patients had missing baseline or follow-up Endothelial Cell Density data.
[b] 3 patients had missing baseline or follow-up Endothelial Cell Density data.
[c] 5 patients had missing baseline or follow-up Endothelial Cell Density data.
[d] 1 patient had missing baseline or follow-up Endothelial Cell Density data.
[e] 4 patients had missing baseline or follow-up Endothelial Cell Density data.
Change from Baseline P-value=0.6561
Percent Change from Baseline P-value=0.6468
P-values are from Analysis of Variance.
[f] Comparison of NGOIS 5 cps to NGOIS 5 cps & BSS PLUS.
[g] Comparison of NGOIS 5 cps & BSS PLUS to BSS PLUS.
[h] Comparison of NGOIS 5 cps to BSS PLUS.
mm^2 =square millimeters

Reviewer's Comments:

The mean endothelial cell density change from baseline to exit for the study eye for the NGOIS 5 cps, NGOIS 5 cps & BSS Plus, or BSS Plus treatment groups were similar (7.0%, 5.0%, and 7.9%, respectively). These differences are not clinically relevant.

Alcon Table 12.5.5.1.-1:
Mean Endothelial Cell Density (cells/mm2) Change from Baseline for the Study Eye in C-03-33

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
Total	Mean	2519.2	-50.5	-1.9		
	Std	351.9	309.0	12.6		
	N	105	100	100 [a]		
	Min	1055	-1247	-50.5		
	Max	3215	900.0	38.9		
NGOIS 3 cps	Mean	2514.5	-72.1	-2.9	0.6476 [f]	0.5782 [f]
	Std	336.3	331.8	13.6		
	N	38	35	35 [b]		
	Min	1468	-1247	-50.5		
	Max	3040	731.0	31.3		
18 to 64 years	Mean	2673.9	32.9	1.7		
	Std	306.5	232.3	9.3		
	N	11	9	9 [c]		
	Min	1965	-201	-7.8		
	Max	3040	382.0	14.8		
≥ 65 years	Mean	2449.6	-108.4	-4.6		
	Std	331.1	356.6	14.7		
	N	27	26	26 [c]		
	Min	1468	-1247	-50.5		
	Max	3003	731.0	31.3		

Alcon Table 12.5.5.1.-1:
Mean Endothelial Cell Density (cells/mm2) Change from Baseline for the Study Eye in C-03-33 – Continued

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
NGOIS 4 cps	Mean	2499.6	-36.8	-1.2	0.9578 [g]	0.9047 [g]
	Std	442.0	314.0	12.7		
	N	32	31	31 [d]		
	Min	1055	-904	-34.2		
	Max	3215	900.0	38.9		
18 to 64 years	Mean	2422.6	-4.6	-0.1		
	Std	390.8	101.6	4.3		
	N	5	5	5		
	Min	2146	-152	-6.1		
	Max	3077	127.0	5.8		
≥ 65 years	Mean	2513.9	-43.0	-1.4		
	Std	456.2	341.1	13.8		
	N	27	26	26 [d]		
	Min	1055	-904	-34.2		
	Max	3215	900.0	38.9		

Treatment		Baseline	Change at Exit	%Change at Exit	Change LSMeans p-value	%Change LSMeans p-value
BSS PLUS	Mean	2542.1	-40.9	-1.6	0.6791[h]	0.6554[h]
	Std	276.8	287.3	11.8		
	N	35	34	34[e]		
	Min	1754	-1043	-43.4		
	Max	3021	464.0	19.3		
18 to 64 years	Mean	2560.2	9.7	0.7		
	Std	349.2	164.1	6.6		
	N	6	6	6		
	Min	2155	-135	-4.7		
	Max	3021	240.0	9.3		
≥ 65 years	Mean	2538.4	-51.8	-2.0		
	Std	266.8	308.6	12.7		
	N	29	28	28[e]		
	Min	1754	-1043	-43.4		
	Max	2933	464.0	19.3		

[a] 8 patients had missing baseline or follow-up Endothelial Cell Density data.
[b] 4 patients had missing baseline or follow-up Endothelial Cell Density data.
[c] 2 patients had missing baseline or follow-up Endothelial Cell Density data.
[d] 3 patients had missing baseline or follow-up Endothelial Cell Density data.
[e] 1 patient had missing baseline or follow-up Endothelial Cell Density data.
Change from Baseline P-value=0.8785
Percent Change from Baseline P-value=0.8384
P-values are from Analysis of Variance.
[f] Comparison of NGOIS 3 cps to NGOIS 4 cps
[g] Comparison of NGOIS 4 cps to BSS PLUS
[h] Comparison of NGOIS 3 cps to BSS PLUS.
mm^2=square millimeters

Reviewer's Comments:

In C-03-33, a statistically significant differences were noted for either the mean endothelial cell density change from baseline to exit for the study eye (p=0.6476) or the mean endothelial cell density percent change from baseline to exit for the study eye (p=0.5782) between the NGOIS 3 cps and NGOIS 4 cps treatment groups.

7.3.5.2 Pediatric Study C-04-64

See also Section 5.3. 5 and 6.1.3 in this review. This was a multi-center, randomized, observer- and patient-masked, active-controlled, parallel-group clinical safety trial of irrigating solution used during cataract surgery in pediatric patients with a 90-day post-surgery follow-up period.

This study was designed to demonstrate the safety of NGOIS compared to BSS Plus for use during cataract surgery in a pediatric population. No efficacy measurements were planned or collected in this trial. The safety measurements were standard for this type of trial. They included endothelial cell density, visual acuity, intraocular pressure, ocular signs of the anterior segment and fundus examination (retina/macula/choroid), and adverse events. Randomization was stratified across the study by age (infants, toddlers, children, and adolescents).

The safety population included a total of 18 pediatric patients (2 months to 17 years). Although patients between the ages of 1 week and 17 years of age were eligible for participation in this study, no one younger than 2 months enrolled in the study. Since no infants were enrolled in the study, the overall pediatric population consists of toddler, children, and adolescent age categories.

Of the 18 patients in the safety analysis, 12 (66.7%) were male and 6 (33.3%) were female. Races reported in this study included White (14, 77.8%), Black (3, 16.7%) and Asian (1, 5.6%). Ethnicity categories reported in this study included Hispanic, Latino or Spanish (2, 11.1%) and Not Hispanic, Latino or Spanish (16, 88.9%). Iris colors were brown (9, 50.0%), hazel (2, 11.1%), green (1, 5.6%) and blue (6, 33.3%).

Alcon Table 11.2.1.-5:
Age Demographic Statistics by Treatment (Safety)

Age Demographic Statistics by Treatment (Safety)

	1-23 Months		2-11 Years		12-17 Years		
	N	%	N	%	N	%	P-Value[a]
NGOIS	2	20.0	6	60.0	2	20.0	1.00
BSS PLUS	2	25.0	5	62.5	1	12.5	
Total	4	22.2	11	61.1	3	16.7	

[a] Test = Chi-square (Fishers Exact test if N<5)

Alcon Table 12.2.3.2.-1:
Common Adverse Events – Overall Safety Population in C-04-64

Coded Adverse Event	NGOIS N = 10		BSS Plus N = 8	
	N	%	N	%
Infections and Investigations				
Bronchitis	1	10.0		
Nasopharnygitis			1	12.5
Eye Disorders				
Eye Discharge	1	10.0		
Eye Irritation[a]	1	10.0		
Uveitis	1	10.0		
Vision Blurred	1	10.0		
Corneal Disorder[b]			1	12.5
Corneal Oedema			1	12.5
Keratopathy			1	12.5
Visual Acuity Reduced			1	12.5
Investigations				
Intraocular Pressure Increased	2	20.0		
Surgical and Medical Procedures				
Cataract Operation[c]			1	12.5

[a] Ocular irritation associated with loosened suture
[b] Clinically relevant endothelial cell loss OD
[c] Planned cataract extraction OS
NGOIS = Next Generation Ophthalmic Irrigating Solution
Common Adverse Events = related and not related combined occurring at an incidence of greater than 1.0% in either treatment group.
Coded adverse event = MedDRA Preferred Term (version 9.0) presented by System Organ Class in the International Agreed Order

Reviewer's Comments:

The most frequently reported adverse event (related and not related combined) was increased intraocular pressure which occurred at an incidence of 20.0% (2 reports) in the NGOIS group. All other adverse events were reported as a single report in both treatment groups.

Alcon Table 12.5.1.-1:
Mean Endothelial Cell Density (cells/mm2) Change from Baseline to Exit for the Study Eye – Overall Safety Population in C-04-64

		Baseline	Change at Exit	% Change at Exit
Total	Mean	3000.0	-352.8	-11.1
	Std	360.1	809.3	24.9
	N	8	6	6
	Min	2232	-1967	-61
	Max	3356	206	6
NGOIS[a]	Mean	2964.3	-59.7	-2.4
	Std	199.9	230.1	7.6
	N	3	3	3[a]
	Min	2841	-195	-7
	Max	3195	206	6
1-23 Months	Mean	0.0	0.0	0.0
	Std	0.0	0.0	0.0
	N	0	0	0
	Min	0	0	0
	Max	0	0	0
2-11 Years	Mean	3195.0	206.0	6.4
	Std	0.0	0.0	0.0
	N	1	1	1
	Min	3195	206	6
	Max	3195	206	6
12-17 Years	Mean	2849.0	-192.5	-6.8
	Std	11.3	3.5	0.2
	N	2	2	2
	Min	2841	-195	-7
	Max	2857	-190	-7

		Baseline	Change at Exit	% Change at Exit
BSS PLUS[b]	Mean	3021.4	-646.0	-19.8
	Std	453.3	1151.8	35.6
	N	5	3	3[b]
	Min	2232	-1967	-61
	Max	3356	148	5
1-23 Months	Mean	0.0	0.0	0.0
	Std	0.0	0.0	0.0
	N	0	0	0
	Min	0	0	0
	Max	0	0	0
2-11 Years	Mean	2965.0	14.5	0.6
	Std	502.7	188.8	6.0
	N	4	2	2
	Min	2232	-119	-4
	Max	3356	148	5
12-17 Years	Mean	3247.0	-1967	-60.6
	Std	0.0	0.0	0.0
	N	1	1	1
	Min	3247	-1967	-61
	Max	3247	-1967	-61

[a] 7 patients had missing baseline and/or follow-up endothelial cell density data as presented in Table 14.3.5.1.-1.
[b] 5 patients had missing baseline and/or follow-up endothelial cell density data as presented in Table 14.3.5.1.-1.
mm^2 =square millimeters
NGOIS = Next Generation Ophthalmic Irrigating Solution

Reviewer's Comments:

No patient exposed to NGOIS exhibited any clinically relevant changes from baseline in corneal endothelial cell density for the study eye or the fellow eye as assessed by the study investigator. One patient exposed to BSS Plus exhibited a clinically relevant decrease in corneal endothelial cell density for the study eye at Day 90 (exit) as assessed by the study investigator and an adverse event was reported.

Alcon Table 12.5.2.-2:
logMAR Visual Acuity Decrease from Baseline Greater Than or Equal to 3 Lines for the Study Eye - Overall Safety Population in C-04-64

	Total	Exit Visit ≥3 Line Decrease		Any Visit ≥3 Line Decrease	
	N	N	%	N	%
Total	**5**	**0**	**0.0**	**0**	**0.0**
NGOIS	**3[a]**	**0**	**0.0**	**0**	**0.0**
1-23 Months	0	0	0.0	0	0.0
2-11 Years	2	0	0.0	0	0.0
12-17 Years	1	0	0.0	0	0.0
BSS PLUS	**2[b]**	**0**	**0.0**	**0**	**0.0**
1-23 Months	0	0	0.0	0	0.0
2-11 Years	1	0	0.0	0	0.0
12-17 Years	1	0	0.0	0	0.0

[a] 7 patients had missing baseline and/or follow-up logMAR visual acuity data.
[b] 6 patients had missing baseline and/or follow-up logMAR visual acuity data.
Decrease in visual acuity is defined as ≥ 3 logMAR line decrease from baseline to exit visit or to any visit for the study eye compared to the same eye at baseline.
To any visit is representative of the worst case scenario and is defined as the visit with the maximum change in visual acuity for the study eye from baseline to any scheduled or unscheduled visit.
NGOIS = Next Generation Ophthalmic Irrigating Solution

Reviewer's Comments:

13 patients who were assessed by measurement procedures other than logMAR. For the 6 patients (NGOIS: 4 patients; BSS Plus: 2 patients) who were assessed by a fixation and follow test (objective-preverbal visual acuity assessment) at baseline (Screening) and at Day 90/Exit, all 6 patients showed normal visual acuity results (score = yes) after surgery for both the study eye and the fellow eye (Table 12.5.2.-8). For the 7 other patients (NGOIS: 3 patients; BSS Plus: 4 patients) whose visual acuity was assessed by methods other than logMAR or the fixation and

follow test, none experienced a clinically relevant decrease in visual acuity from baseline as assessed by the study investigator.

No overall safety issues were identified in a population of 18 pediatric patients exposed to Next Generation Ophthalmic Irrigating Solution (NGOIS) while undergoing cataract surgery based upon a review of adverse events and an assessment of ocular safety parameters.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Alcon Table 2.7.4.2.1.1.1.-1 summarizes the most common adverse events (those occurring at an incidence of 1.0% or greater in the NGOIS 3 cps or the BSS Plus treatment group) reported among patients in the anterior and posterior segment studies (C-02-39, C-03-33, C-04-14, and C-04-18) regardless of Alcon's assigned causality assessment.

Alcon Table 2.7.4.2.1.1.1.-1: Most Common Adverse Events - Anterior and Posterior Segment Studies (C-02-39, C-03-33, C-04-14, and C-04-18)

Treatment	NGOIS 3 cps N=391		NGOIS 4 cps N=34		NGOIS 5 cps N = 35		NGOIS 5 cps & BSS Plus N = 35		BSS Plus n=431	
Coded Adverse Events	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Infections and infestations										
Sinusitis	5	1.3							4	0.9
Nasopharyngitis	2	0.5					1	2.9	5	1.2
Immune system disorders										
Seasonal Allergy	4	1.0					1	2.9	5	1.2
Nervous system disorders										
Headache	10	2.6	1	2.9			3	8.6	11	2.6
Eye disorders										
Cataract	18	4.6							12	2.8
Ocular Discomfort	18	4.6	1	2.9	2	5.7	1	2.9	11	2.6
Macular Oedema	15	3.8	1	2.9			1	2.9	15	3.5
Conjunctival Hyperaemia	14	3.6					1	2.9	12	2.8
Dry Eye	13	3.3	3	8.8	1	2.9	4	11.4	20	4.6
Iritis	10	2.6	1	2.9	1	2.9			5	1.2
Retinal Haemorrhage	10	2.6							3	0.7
Vision Blurred	9	2.3							6	1.4
Posterior Capsule Opacification	8	2.0	7	20.6	5	14.3	7	20.0	11	2.6
Eye Pain	6	1.5							10	2.3
Blepharitis	6	1.5	3	8.8					5	1.2
Vitreous Detachment	6	1.5			1	2.9			4	0.9
Corneal Oedema	6	1.5							4	0.9
Conjunctival Haemorrhage	5	1.3							9	2.1
Ocular Hyperaemia	5	1.3							4	0.9
Photophobia	5	1.3							3	0.7
Diplopia	5	1.3							1	0.2
Foreign Body Sensation in Eyes	4	1.0							9	2.1
Retinal Detachment	4	1.0							4	0.9
Visual Acuity Reduced	4	1.0			2	5.7			4	0.9
Photopsia	4	1.0							3	0.7
Eye Irritation	4	1.0	1	2.9			1	2.9		
Retinal Exudates	4	1.0							2	0.5
Punctate Keratitis	3	0.8			1	2.9	1	2.9	7	1.6
Hypotony Of Eye	3	0.8							7	1.6
Retinal Disorder	2	0.5							10	2.3
Eye Pruritus	2	0.5	1	2.9					6	1.4
Visual Disturbance	2	0.5							5	1.2

Alcon Table 2.7.4.2.1.1.1.-1: Most Common Adverse Events - Anterior and Posterior Segment Studies (C-02-39, C-03-33, C-04-14, and C-04-18) - Continued

Treatment	NGOIS 3 cps N=391		NGOIS 4 cps N=34		NGOIS 5 cps N = 35		NGOIS 5 cps & BSS Plus N = 35		BSS Plus n=431	
Coded Adverse Events	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Vascular disorders										
Hypertension	9	2.3							7	1.6
Gastrointestinal disorders										
Vomiting	5	1.3							2	0.5
Investigations										
Intraocular Pressure Increased	47	12.0	6	17.6	6	17.1	3	8.6	46	10.7
Blood Pressure Increased	12	3.1							8	1.9
Injury, poisoning and procedural complications										
Injury	4	1.0							5	1.2

Coded adverse event = MedDRA Preferred Term (version 10.0) presented by System Organ Class
Most common adverse events represent all adverse events (related and not related combined) occurring at an incidence equal to or greater than 1.0% in either the NGOIS 3 cps or the BSS Plus treatment group.
NGOIS = Next Generation Ophthalmic Irrigating Solution
cps = centipoise

Reviewer's Comments:

Patients in the anterior and posterior segment studies with exposure to NGOIS 3 cps reported a similar incidence of the most commonly reported adverse events versus patients with exposure to BSS Plus. This included reports of increased intraocular pressure (12% versus 11%), cataract (5% versus 3%), ocular discomfort (5% versus 3%), macular edema (4% versus 4%), conjunctival hyperemia (4% versus 3%), and dry eye (3% versus 5%).

This is the adverse event table utilized by this reviewer for Section 6.1 of the Package Insert and not Alcon Table 2.7.4.2.1.-1 summarizing all treatment-related adverse events.

An Adverse Event Form was completed for any intraocular pressure of 40 mmHg or more in either eye at any visit following administration of the test article. An Adverse Event Form was also completed for any elevated IOP (<40 mmHg) that was treated and did not adequately respond (in the opinion of the investigator) within 24 hours after initiation of IOP reducing therapy. These are the percentages shown in the table above.

Since operating surgeons frequently treat IOPs of ≥ 25 mmHg, the following four tables were generated by Alcon to describe the percentage of subjects with IOP ≥ 30 mmHg and the percentage of subjects with IOP ≥ 25 mmHg.

Intraocular Pressure ≥ 30 mmHg by Visit Day for the Study Eye
Anterior and Posterior Segment Studies
(C-03-33, C-04-14, C-04-18)

	Total	6 Hour	Day 1	Day 3	Day 7	Day 14	Day 30	Day 60	Day 90
NGOIS 3 cps									
# Patients	391	223	389	220	389	166	385	163	384
# with IOP ≥ 30		46	16	3	8	6	5	2	1
% with IOP ≥ 30		21	4	1	2	4	1	1	0.3
BSS Plus									
# Patients	396	219	395	215	393	171	394	171	391
# with IOP ≥ 30		42	13	2	5	1	3	1	1
% with IOP ≥ 30		19	3	1	1	1	1	1	0.3

47 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Intraocular Pressure ≥ 25 mmHg by Visit Day for the Study Eye
Anterior and Posterior Segment Studies
(C-03-33, C-04-14, C-04-18)

	Total	6 Hour	Day 1	Day 3	Day 7	Day 14	Day 30	Day 60	Day 90
NGOIS 3 cps									
# Patients	391	223	389	220	389	166	385	163	384
# with IOP ≥ 25		85	50	13	15	17	7	4	4
% with IOP ≥ 25		38	13	6	4	10	2	2	1
BSS Plus									
# Patients	396	219	395	215	393	171	394	171	391
# with IOP ≥ 25		76	40	9	14	6	7	5	4
% with IOP ≥ 25		35	10	4	4	4	2	3	1

47 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Reviewer's Comments:

C-02-39 is not included in the pooled data since it did not include NGOIS 3 cps. The percentage of subjects with IOP ≥ 30 mmHg and the percentage of subjects with IOP ≥ 25 mmHg are very similar between the NGOIS 3 cps and the BSS Plus subjects.

Per the protocol, IOP lowering medication was not administered until after the first IOP assessment at hour 6 (anterior segment studies) or Day 1 (posterior segment study).

Intraocular Pressure ≥ 30 mmHg by Visit Day for the Study Eye
Anterior Segment Studies
(C-03-33, C-04-14)

	Total	6 Hour	Day 1	Day 3	Day 7	Day 30	Day 90
NGOIS 3 cps							
# Patients	223	223	223	220	222	220	220
# with IOP ≥ 30		46	11	3	0	0	0
% with IOP ≥ 30		21	5	1	0	0	0
BSS Plus							
# Patients	220	219	220	215	220	220	218
# with IOP ≥ 30		42	11	2	0	0	0
% with IOP ≥ 30		19	5	1	0	0	0

23 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Intraocular Pressure ≥ 25 mmHg by Visit Day for the Study Eye
Anterior Segment Studies
(C-03-33, C-04-14)

	Total	6 Hour	Day 1	Day 3	Day 7	Day 30	Day 90
NGOIS 3 cps							
# Patients	223	223	223	220	222	220	220
# with IOP ≥ 25		85	38	13	1	0	1
% with IOP ≥ 25		38	17	6	0.5	0	0.5
BSS Plus							
# Patients	220	219	220	215	220	220	218
# with IOP ≥ 25		76	32	9	0	0	0
% with IOP ≥ 25		35	15	4	0	0	0

23 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Reviewer's Comments:

C-02-39 is not included in the pooled data since it did not include NGOIS 3 cps. The majority of subjects with IOP ≥ 30 mmHg or with IOP ≥ 25 mmHg were in the anterior segment studies.

The percentage of subjects with IOP ≥ 30 mmHg and the percentage of subjects with IOP ≥ 25 mmHg are very similar between the NGOIS 3 cps and the BSS Plus subjects.

Intraocular Pressure ≥ 30 mmHg by Visit Day for the Study Eye
Posterior Segment Study
(C-04-18)

	Total	Day 1	Day 7	Day 14	Day 30	Day 60	Day 90
NGOIS 3 cps							
# Patients	168	166	167	166	165	163	164
# with IOP ≥ 30		5	8	6	5	2	1
% with IOP ≥ 30		3	5	4	3	1	1
BSS Plus							
# Patients	176	175	173	171	174	171	173
# with IOP ≥ 30		2	5	1	3	1	1
% with IOP ≥ 30		1	3	1	2	1	1

26 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Intraocular Pressure ≥ 25 mmHg by Visit Day for the Study Eye
Posterior Segment Study
(C-04-18)

	Total	Day 1	Day 7	Day 14	Day 30	Day 60	Day 90
NGOIS 3 cps							
# Patients	168	166	167	166	165	163	164
# with IOP ≥ 25		12	14	17	7	4	3
% with IOP ≥ 25		7	8	10	4	2	2
BSS Plus							
# Patients	176	175	173	171	174	171	173
# with IOP ≥ 25		8	14	6	7	5	4
% with IOP ≥ 25		5	8	4	4	3	2

26 patients had missing IOP data.
mmHg = millimeters of mercury.
cps = centipoise.

Reviewer's Comments:

C-02-39 is not included in the pooled data since it did not include NGOIS 3 cps. The majority of subjects with IOP ≥ 30 mmHg or with IOP ≥ 25 mmHg were in the anterior segment studies.

The percentage of subjects with IOP ≥ 30 mmHg and the percentage of subjects with IOP ≥ 25 mmHg are very similar between the NGOIS 3 cps and the BSS Plus subjects.

7.4.2 Laboratory Findings

There were no clinical laboratory evaluations conducted for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

7.4.3 Vital Signs

There were no vital signs collected on the case report forms for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

7.4.4 Electrocardiograms (ECGs)

There were no electrocardiograms conducted for any of the Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) studies.

7.4.5 Special Safety Studies

See also Section 7.3.5 of this review regarding endothelial cell counts and the Pediatric Study C-04-64.

7.4.6 Immunogenicity

Not applicable. Drug product is not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The adverse events reported during the use of ophthalmic irrigating solutions include postoperative inflammatory reactions, corneal edema, corneal clouding, corneal decompensation, and bullous keratopathy. Due to the nature of intraocular surgery, the dose of the drug product utilized is generally directly proportional to the length of the intraocular procedure.

7.5.2 Time Dependency for Adverse Events

A review of time to onset of adverse events did not identify any safety concerns.

7.5.3 Drug-Demographic Interactions

An analysis of adverse events by age category (adults and elderly), gender, race, and iris color did not identify any safety concerns for any demographic subpopulation.

7.5.4 Drug-Disease Interactions

No safety concerns were identified in patients with specific concomitant diseases (arthritis, diabetes, gastrointestinal disorders, hyperlipidemia, hypertension, musculoskeletal disorders, and nervous system disorders).

7.5.5 Drug-Drug Interactions

No safety concerns were identified in patients receiving concomitant medications (anti-infective agents; cardiovascular drugs; antilipemic agents; central nervous system agents; analgesics and anti-pyretics; nonsteroidal anti-inflammatory agents; anxiolytics, sedatives and hynoptic drugs; replacement preparations; diuretics; EENT preparations; gastrointestional drugs; hormones and synthetic substitutes; local anesthetics; and vitamins).

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

The carcinogenic potential of Navstel Intraocular Irrigating Solution has not been investigated.

7.6.2 Human Reproduction and Pregnancy Data

The hypromellose in Navstel Intraocular Irrigating Solution has been demonstrated to be non-mutagenic in the *in vitro* Ames assay and the bacterial reverse mutation assay. A similar modified cellulose polymer (methyl cellulose) was also non-mutagenic at concentrations up to 5,000 mg/kg in the rat bone marrow cytogenic assay. Fertility studies have not been conducted with hypromellose; however, rats fed a diet of up to 5% methylcellulose had no significant adverse effects relative to reproductive function.

There are no adequate and well-controlled studies of Navstel Intraocular Irrigating Solution in pregnant women. Although Navstel Intraocular Irrigating Solution does not have any pharmacological activity, it should be used during pregnancy only if clearly needed. Caution should be exercised when Navstel Intraocular Irrigating Solution is administered to a nursing woman.

7.6.3 Pediatrics and Effect on Growth

Safety and efficacy of Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) have been demonstrated in pediatric patients.

Assessment of effect on growth was not studied by the applicant. With the exception of hypromellose, all the ingredients of Parts I and II are physiologic.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

All the ingredients of Part I and Part II are normally found in the eye with the exception of hypromellose; hypromellose has no known receptor affinity, pharmacological action, or side effect potential. Distribution of hypromellose into ocular tissues is unlikely because of its molecular weight ------- ----------

There is no overdose, drug abuse potential, withdrawal or rebound associated with this drug product.

7.7 Additional Submissions

The 120-day safety update was submitted on January 14, 2008. There is no new safety information regarding Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione).

8 Postmarketing Experience

Navstel Intraocular Irrigating Solution (balanced salt ophthalmic solution with hypromellose, dextrose and glutathione) is not currently approved or marketed in any foreign country.

9 Appendices

9.1 Literature Review/References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by Alcon in this application for this indication.

9.2 Advisory Committee Meeting

No Advisory Committee was necessary or convened for this drug product.

9.3 Labeling Recommendations

It is recommended that NDA 22-193 be approved with the revised package insert labeling which follows.

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