SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ophthalmic Sealant

Device Trade Name: ReSure® Sealant

Device Procode: PFZ

Applicant's Name and Address: Ocular Therapeutix, Inc.
36 Crosby Drive, Suite 101
Bedford, MA 01730 USA

Date(s) of Panel Recommendation: September 19, 2013

Premarket Approval Application (PMA) Number: P130004

Date of Notice of Approval: January 8, 2014

II. INDICATION FOR USE

ReSure Sealant is indicated for intraoperative management of clear corneal incisions (up to 3.5mm) with a demonstrated wound leak for which a temporary dry surface can be achieved, in order to prevent postoperative fluid egress from such incisions following cataract surgery with intraocular lens (IOL) placement in adults.

III. CONTRAINDICATIONS

None.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ReSure Sealant labeling.

V. DEVICE DESCRIPTION

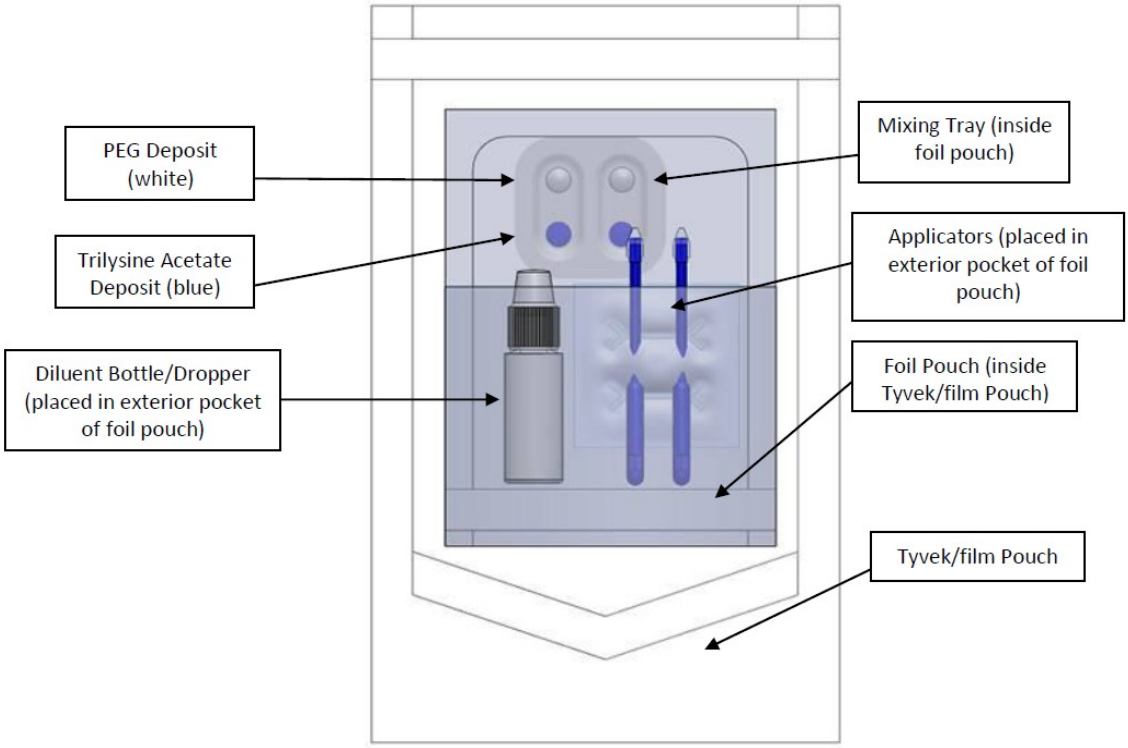
ReSure Sealant is an *in situ* formed polyethylene glycol (PEG) hydrogel that creates a temporary, soft and lubricious surface barrier to prevent leakage of clear corneal incisions following cataract surgery with intraocular lens (IOL) placement. It is comprised mainly of water (89% by weight) and PEG (9.44% by weight). The hydrogel is formed by mixing its components immediately prior to application to initiate a crosslinking reaction.

Two applications of ReSure Sealant are provided in each package. A package of ReSure Sealant (**Figure 1** below) is single use and consists of:

- One plastic bottle/dropper combination filled with diluent solution,
- One tray with two mixing wells (each well has two depressions containing lyophilized deposits of reactants, one blue deposit and one white deposit), and
- Two applicators.

The mixing tray subassembly is packaged within a foil pouch that has an exterior pocket where the diluent bottle/dropper and applicators are placed. The sealed foil pouch is then placed in a Tyvek/film pouch, which provides the sterile barrier. The product is manufactured under controlled conditions and is terminally sterilized using gamma irradiation.

Figure 1: ReSure Sealant Packaging and Components

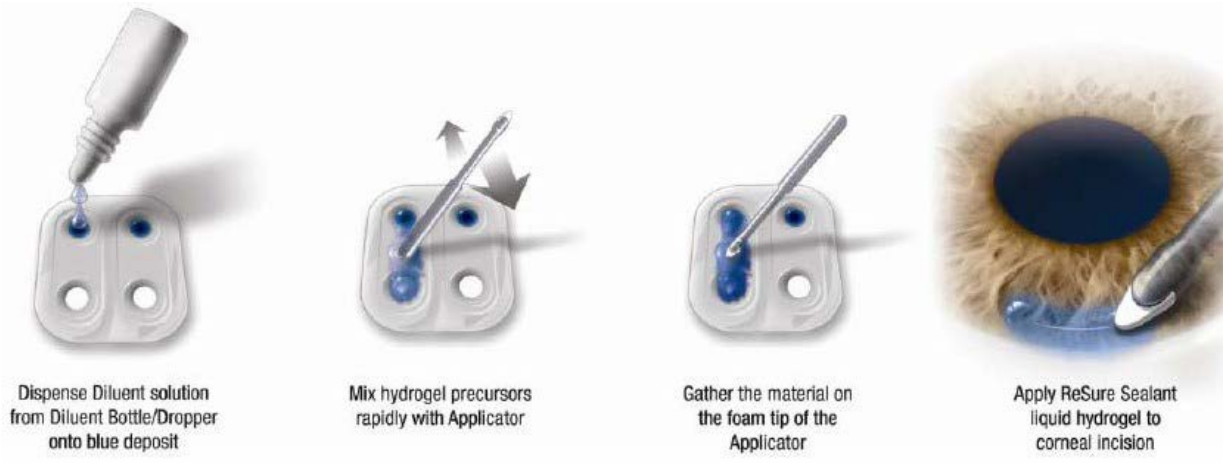


The diluent solution is comprised of phosphate and borate salt solution and is used to dissolve the lyophilized PEG (white deposit) and trilysine acetate (blue deposit) to facilitate the gelation reaction between the PEG and trilysine molecules. The trilysine acetate deposit contains a visualization aid/colorant (Food, Drug & Cosmetic (FD&C) Blue #1) to facilitate hydrogel application to the incision.

The applicator is a single use component that is designed exclusively for use with ReSure Sealant. The applicator consists of a polycarbonate handle and a polyethylene foam tip. The applicator handle is used to mix the reconstituted trilysine acetate deposit with the PEG

deposit within the tray mixing well. The foam tip is then used to apply ReSure hydrogel to the corneal incision. The applicator is used to apply a conformal coating of this liquid that adheres to the ocular tissue surfaces. The mixing and application processes are shown in **Figure 2**.

Figure 2: ReSure Sealant Application Process



The applied liquid solidifies within approximately 20 seconds into a hydrogel, typically remains on the corneal surface for approximately 1 to 3 days, and is no longer present after 7 days. During this period, the hydrogel softens, detaches, and is sloughed off in the tears. This process is aided by movement of the eyelid over the material as well as by hydrolysis/degradation of the PEG hydrogel. Ultimately, the breakdown products are cleared through the tear fluid.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures and practices for intraoperative management of clear corneal incisions (CCI) in order to prevent postoperative fluid egress from such incisions following cataract or IOL placement surgery include use of "self-sealing" CCI, stromal hydration, and use of sutures. Both CCIs and use of sutures have their own advantages and disadvantages as reported in the peer-reviewed scientific literature. While sutures are placed deep in the corneal tissue and may remain in place long-term, ReSure Sealant is applied only on the ocular surface surrounding the incision and remains on the eye typically less than 3 days (i.e., immediate post-op period). The surgeon should consider these factors in order to select the method that best meets the needs of the surgical procedure, individual incision parameters and other mitigating factors.

VII. MARKETING HISTORY

ReSure Sealant has not been marketed in the United States (US) or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential AEs associated with the subject device may include, but are not limited to, hypotony, induced corneal astigmatism, worsening in best corrected visual acuity (BCVA), inflammatory

reaction, corneal abrasion, corneal edema, allergic reaction and/or delayed healing, eye pain, eye irritation and foreign body sensation. For the specific AEs that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRE-CLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

ReSure Sealant was evaluated with regard to its toxicological properties in accordance with International Organization for Standardization (ISO) 10993-1: Biological Evaluation of Medical Devices - Part 1 Evaluation and Testing. *In vitro* biocompatibility testing was performed on the finished product, including tests conducted on the hydrogel itself, and packaging components with direct and/or indirect contact with the hydrogel or its components. All tests were performed in accordance with Good Laboratory Practices (GLP). **Table 1** shows the *in vitro* biocompatibility studies performed.

Table 1: *In Vitro* Biocompatibility Testing for ReSure Sealant

Test	Test article	Acceptance Criteria	Extraction conditions	Results
Cytotoxicity-Elution	Hydrogel	Is not cytotoxic	4g/20ml at 37°C for 24 hrs.	No cell lysis or toxicity to cells
Cytotoxicity-Elution	Applicator foam tip	Is not cytotoxic	4g/20ml at 37°C for 24 hrs.	No cell lysis or toxicity to cells
Cytotoxicity-Elution	Mixing tray, bottle/dropper assembly	Is not cytotoxic	4g/20ml at 50°C for 72 hrs.	No cell lysis or toxicity to cells
Cytotoxicity-Elution	Applicator handle	Is not cytotoxic	4g/20ml at 37°C for 24 hrs.	No cell lysis or toxicity to cells
Cytotoxicity-Elution	Dropper cap (screw cap)	Is not cytotoxic	4g/20ml at 37°C for 24 hrs.	No cell lysis or toxicity to cells
Cytotoxicity-Agar diffusion	Foil pouch	Is not cytotoxic	NA	No cell lysis or toxicity to cells

2. Physicochemical Properties

Physicochemical tests were conducted on ReSure Sealant (hydrogel and applicator). The hydrogel tests and results conducted for the final finished product are summarized in **Table 2** below.

Table 2: *In Vitro* Hydrogel Characterization

Test	Purpose	Acceptance Criteria	Results
Mixing time	Time required to mix the reconstituted PEG deposit and trilysine acetate deposit.	≤ 5 seconds	All samples were mixed in ≤ 5 seconds
Gel time	Time for the onset of gelation following mixing of the PEG and trilysine deposits with the diluent solution	Upon mixing of the precursor solutions, a gel should be formed in 18 seconds (-5/+10)	Gel times ranged from 14.39 to 17.82 seconds
Pot life	Time following removal of the mixing tray from foil pouch; the device must perform as specified (i.e., gel time).	30 minutes following removal of the mixing tray from the foil pouch, upon mixing the precursor solutions, a gel should be formed in 18 seconds (-5/+10)	Gel times following 30 minute pot life ranged from 15.99 to 18.53 seconds
Swelling	Percent weight increase in the hydrogel after being exposed to phosphate buffered saline (PBS) at 37ºC for 2.5 hours	≤ 51% after 2.5 hours at 37ºC	Maximum swell of hydrogel was 35.6%
Burst strength	Intraocular pressure required to rupture hydrogel after being applied to clinically representative incision in *ex vivo* porcine eye.	≥ 67 mmHg when tested in a clinically relevant *ex vivo* model	All devices met 67 mmHg burst pressure
Diluent volume	The amount of diluent solution dispensed from the diluent dropper in two drops	80 ± 16 µL of diluent solution in 2 drops.	Dropper delivered between 75.7 and 89.3 µL of solution in 2 drops.
Chemical diffusion from hydrogel	Rate at which chemical constituents (i.e., FD&C Blue #1 and N-Hydroxysuccinimide (NHS)) are released from hydrogel	NA	FD&C Blue #1 and NHS diffused readily. All FD&C Blue #1 was released from hydrogel within 8 hrs

			(half-life of 1 hour). All NHS was released within 1 hour (half-life of 9 minutes)
pH	pH of hydrogel	NA	Average pH was 6.524
Osmolality	Osmolality of hydrogel	NA	Average osmolality was 271.8 mOsm/Kg
Heat generation during polymerization	Polymerization reaction evaluated to determine whether process is endo/exo-thermic.	NA	No increase or decrease in temperature were observed
In vitro persistence	Evaluate the ability of the hydrogel to hydrolyze (degrade) in a simulated physiologic environment (i.e., in PBS solution).	NA	Samples fully degraded within approximately 81 hours (3.4 days)

The *in vitro* tests and results for the applicator are summarized below in **Table 3**.

Table 3: *In Vitro* Applicator Characterization

Test	Purpose	Acceptance Criteria	Results
Handle integrity	Force that applicator handle can withstand prior to breaking.	> 190 gf without mechanical failure	Handles withstood 1792.5 gf prior to failure
Foam tip integrity	Force required to pull foam tip from applicator	> 17 gf without mechanical failure	Foam tips withstood 146.8 gf prior to failure
Material transfer	Evaluate the amount of ReSure Sealant collected on the foam tip and to confirm its ability to transfer an adequate amount of material to an incision	Capable of transferring 0.34 to 2.71 mg of material	Applicators were capable of transferring 0.34 to 2.71 mg of material per application
Ocular tissue trauma	Cornea of *ex vivo* porcine eyes was coated with fluorescein stain pre- and post-application in order to detect trauma caused by	No trauma should be caused to the ocular surface due to the applicator	Applicator did not cause damage to ocular surface

	application		

B. Animal Studies

In vivo biocompatibility testing was performed on the hydrogel and packaging components with direct and/or indirect contact with the hydrogel or its components. All tests were performed in accordance with the GLP regulation. **Table 4** shows the *in vivo* biocompatibility studies performed.

Table 4: *In Vivo* Biocompatibility Testing for ReSure Sealant

Test	Test article	Acceptance Criteria	Extraction conditions	Results
Sensitization-Guinea pig maximization (GPM) Saline extract	Hydrogel	Does not demonstrate sensitization	4g/20ml at 37°C for 72 hrs.	No evidence of delayed dermal contact sensitization
Ocular irritation Saline extract (rabbit model)	Hydrogel	Does not demonstrate ocular irritation	4g/20ml at 37°C for 72 hrs.	No evidence of ocular irritation
Acute systemic toxicity Saline extract (mouse model)	Hydrogel	Does not demonstrate systemic toxicity	4g/20ml at 37°C for 72 hrs.	No evidence of systemic toxicity
Sensitization-GPM Saline extract	Applicator foam tip	Does not demonstrate sensitization	4g/20ml at 37°C for 72 hrs.	No evidence of delayed dermal contact sensitization
Ocular irritation Saline extract (rabbit model)	Applicator foam tip	Does not demonstrate ocular irritation	4g/20ml at 37°C for 72 hrs.	No evidence of ocular irritation
Ocular irritation Saline extract Sesame oil extract (rabbit model)	Mixing tray, bottle/dropper assembly	Does not demonstrate ocular irritation	4g/20ml at 50°C for 72 hrs.	No evidence of ocular irritation
Ocular irritation Saline extract Sesame oil extract (rabbit model)	Dropper cap (screw cap)	Does not demonstrate ocular irritation	4g/20ml at 37°C for 24 hrs.	No evidence of ocular irritation

In vivo performance and safety testing was performed on ReSure Sealant. **Table 5** summarizes the *in vivo* performance studies performed.

Table 5: *In Vivo* Safety and Performance Testing for ReSure Sealant

Test	Purpose	Acceptance Criteria	Results

Incision Sealing and Persistence (pig model)	Determine persistence and ability of hydrogel to seal full thickness corneal incision	Seal and cover incision	ReSure Sealant completely covered the incision for 24 hours and was no longer present by Day 2. Healing of the incision was comparable between ReSure Sealant and suture-treated. All eyes exhibited reepithelialization by Day 2 and received the maximum incision healing score graded by Day 3.
Removability (pig model)	Evaluate ability to remove hydrogel	Remove without trauma to the eye	ReSure Sealant was able to be removed completely from the target location immediately after application (worst case) without signs of ocular irritation or damage outside of clinical expectations when compared to sutured incision closure and removal. Microscopic evaluation revealed acceptable healing characteristics for ReSure Sealant treated eyes in comparison to suture-treated eyes.
Intraocular irritation-3 day study (rabbit model)	Evaluate intraocular toxicity associated with intraocular injection of hydrogel.	Does not demonstrate intraocular irritation	ReSure Sealant did not cause ocular irritation when administered as an intraocular injection into the anterior chamber.
Intraocular toxicity – 14 day study (rabbit model)	Evaluate intraocular toxicity associated with intraocular injection of hydrogel	Does not demonstrate intraocular toxicity	Well tolerated with no signs of intraocular toxicity. Under the conditions of the study, all animals remained in good general health and there were no significant macroscopic or microscopic ocular findings.
Maximum dose ocular irritation and persistence – 14 day study (rabbit model)	Evaluate ocular irritation associated with maximum clinical dose of hydrogel as well as its persistence on the	Does not demonstrate ocular irritation	No evidence of ocular irritation. Non-irritating. The disappearance was noted as early as 24 hours and the material was not seen in any eyes by Day 7.

	incision.		

C. Additional Studies

Sterilization validation studies were completed to demonstrate the ability of the radiation sterilization cycle using a sterilization dose range of 25 – 35 kGy achieves a sterility assurance level of 10^{-6} for the ReSure Sealant product. In addition, the shelf life and transport stability studies demonstrate that the ReSure Sealant product in its packaging is validated for a shelf life of 5 months when stored at room temperature. The tests conducted in support of the sterilization validation, package integrity, shelf life, and transport stability are summarized in **Table 6** below.

Table 6: Sterilization, Package Integrity, Shelf Life, and Transport Stability Tests for ReSure Sealant

Test	Purpose	Results/Acceptance Criteria
Radiation Validation	Evaluate sterility	Performed per ISO 11137-2: 2006, VD_{MAX} method. Acceptable Results justify a minimum radiation dose of 25 kGy.
Bioburden	Evaluate sterility	Pre-sterilization bioburden levels were below 1000 CFU as required for the VD_{MAX} 25 method. Average bioburden was calculated using a recovery efficiency of 91.2 %
Bacterial Endotoxin	Evaluate sterility	Testing for endotoxins was performed using the USP <85> kinetic turbidimetric method. Results indicated that samples were found to be within specification. All lots were found to be within acceptable limits ($\leq$ 0.5 EU/device).
Sterility Test	Evaluate sterility	Tested per ISO 11137-2: 2006. No microbial growth was detected
Bacteriostasis/ fungistasis test	Evaluate sterility	No bacteriostatic/fungistatic effect was observed
Package Evaluation – Peel Strength	Evaluate package seal integrity	All samples were within the specification of minimum seal strength 1.0 lbf.
Package Evaluation – Bubble Emission	Evaluate whole package integrity	Performed according to ASTM F2096: 2011. The packaging met the requirements. No evidence of bubbles was observed when packages were pressurized at 10 ± 2 in. H_2O.
Transport Stability	Evaluate package integrity and device stability	Manufacturing specifications met after exposing samples to simulated transport conditions. All kits passed specification for applicator handle and tip integrity, mixing time, pot life, swelling, applicator transfer, atraumatic tip, burst strength, diluent dropper drop size, label adherence and

		legibility, seal strength, and seal integrity.

X. SUMMARY OF CLINICAL STUDIES

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of ReSure Sealant for intraoperative management of clear corneal incisions (up to 3.5mm) with a demonstrated wound leak for which a temporary dry surface can be achieved, in order to prevent postoperative fluid egress from such incisions following cataract surgery with IOL placement in adults. The study was conducted in the US under IDE G110114. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

A prospective, randomized, parallel arm, active controlled, multicenter, subject-masked study was conducted to evaluate safety and effectiveness of ReSure Sealant compared with suture control. Patients with no ocular pathologic features other than cataracts undergoing uneventful clear corneal cataract surgery with phacoemulsification and IOL placement were recruited for this study. The study evaluated 488 eyes (487 subjects) and involved 24 investigational sites within the United States. Subjects were followed for 28 days. Subjects were treated between December 16, 2011 and August 16, 2012. The database for this PMA reflected data collected through January 30, 2013.

Subjects were randomized after CCI leakage was confirmed post IOL implantation, demonstrated by positive Seidel test, either as unprovoked spontaneous leakage, or provoked by a Calibrated Force Gauge (CFG). Prophylactic use of ReSure Sealant on non-leaking incisions was not evaluated in the clinical study. Subjects were randomized 5:3 to receive either ReSure Sealant or Sutures, and were stratified by incision leak category and investigational site, in order to minimize differences between treatment groups.

The study was designed to establish non-inferiority of ReSure Sealant to a suture control for prevention of incision leakage within the first 7 days of clear corneal cataract surgery with phacoemulsification and IOL implantation.

Briefly, all subjects were prescribed a standardized ophthalmic medication regimen following surgery and were instructed that use of prophylactic pain medications within one week prior to the Preoperative Baseline/Screening Assessment through post-operative Day 28 follow-up was prohibited. Cataract surgery was performed through a single plane CCI $\leq$3.5mm in length, measured with a calibrated tool such as internal calipers or an incision gauge, after IOL implantation. A single plane incision was defined as an incision that extended into the corneal stroma, then angled down toward the anterior capsule of the lens, with no external groove. At the conclusion of surgery, wound leak assessment was performed (pre-randomization). Subjects meeting all eligibility criteria and determined to have a leaking incision via positive Seidel test (either unprovoked or provoked following the standardized wound leak assessment, as described below) were randomized.

Following randomization, eyes either received ReSure Sealant (study group) or sutures

(control group). ReSure Sealant was applied over the length of the CCI using the applicator provided in the ReSure Sealant package. This was performed after removal of any standing moisture and ensuring that the incision site was dry and not actively leaking. While the number of sutures was not specified in the protocol, all control eye incisions were closed with one 10-0 nylon non-absorbable suture which was placed perpendicular to the incision. Unless premature suture removal was clinically indicated, the suture was to stay in place for the duration of study follow-up (i.e., Day 28). For both treatment groups, stromal hydration could be performed as necessary prior to wound leak assessment.

Following application of ReSure Sealant or suture, a second (post-randomization) wound leak assessment was performed to evaluate the integrity of the incision closure using the CFG. Any subject demonstrating a positive post-randomization wound leak assessment and/or required additional treatment for a leaking incision following post-randomization wound leak assessment was considered a primary endpoint failure.

1. <u>Inclusion and Exclusion Criteria</u>

Inclusion Criteria

Subjects were eligible for inclusion in the study if they met all of the following criteria:

- Subject must have been ≥22 years of age.
- Subject had a cataract and was expected to undergo clear corneal cataract surgery with phacoemulsification and implantation of a posterior chamber intraocular lens.
- Subject was informed of the nature of the study and was able to comply with study requirements and provided written informed consent, approved by the appropriate Institutional Review Board (IRB).

Exclusion Criteria

Pre-operative exclusion criteria

Subjects were to be excluded from the study if they met any of the following criteria:

- Any intraocular inflammation in the study eye present during the screening slit lamp examination or presence of ocular pain in the operative eye as rated on the Ocular Comfort Index (OCI) at the preoperative assessment.
- Previous corneal or retinal surgery (laser or incisional) or planned multiple procedures (e.g., limbal relaxing incisions) during cataract surgery.

- Previous ocular trauma if subject had visible scarring or any deformities due to the trauma.

- Potential best corrected visual acuity (BCVA) in fellow eye worse than 20/40 as assessed by the Investigator.

- Presence of congenital or other ocular anomaly (e.g., keratoconus with evidence of corneal ectatic disease pterygium, recurrent erosions), corneal dystrophy (e.g., anterior basement membrane dystrophy, stromal or endothelial dystrophies). Pterygium were allowed provided they were not near the incision, did not contribute to the irregularities in the cornea, were a maximum of 2 mm on the cornea, and did not affect vision/in the visual axis.

- Active or history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosisiritis).

- Evidence of acute external ocular infections, intraocular infection, dysthyroid ophthalmopathy, nasolacrimal duct obstruction, active chalazion, or uncontrolled blepharitis.

- Uncontrolled and clinically significant dry eye syndrome.

- Clinically significant guttae affecting corneal thickness (thickness <475 or >640 µm).

- Glaucoma or subjects on any glaucoma medications.

- Presence of ocular hypertension in the operative eye (IOP ≥ 25 mmHg).

- Use of topical ocular steroids within 14 days and/or systemic steroids (excluding inhalants) within 30 days prior to surgery.

- Use of prophylactic pain medications within one week prior to the Baseline/Screening Assessment through the 28 day follow-up period. This included prophylactic use of peri- and postoperative pain (analgesic) medications such as topical or systemic NSAIDS, opiates/non-opiates, and acetaminophen. Non-prophylactic pain medications (i.e., pain medication taken for pain that subject is experiencing) were allowed prior to and throughout the duration of the study. Medications taken for cardiac maintenance (e.g., 81 mg Aspirin) were allowed prior to and throughout the duration of the study.

- Subject had insulin-dependent diabetes, Proliferative Diabetic Retinopathy (PDR), compromised macular function or Clinically Significant Macular Edema (CSME).

- Subject currently had suspected or known malignancy or was currently receiving antineoplastic therapy.

- Subject had a compromised immune system or an autoimmune disease that in the opinion of the Investigator could affect the quality of the ocular surface.

- Pregnant or breast-feeding women or women who wished to become pregnant during the length of study participation.

- The Investigator determined that the subject should be not be included for reasons not already specified if the health of the subject or the validity of the study outcomes (e.g., ocular disease that would interfere with study evaluations, allergy to FD&C Blue #1) would be compromised by the subject's enrollment.

- Subject had been previously enrolled in this clinical study, or was participating in another clinical trial during the follow-up period that could confound the treatment or outcomes of this investigation.

Intra-operative exclusion criteria

All subjects who met any of the following intra-operative exclusion criteria were considered screen failures and were not eligible to be randomized in the study:

- Incidental finding of preoperative exclusion criteria.

- Subject determined not to be a suitable candidate for topical anesthesia.

- Subject required multiple procedures (e.g., limbal relaxing incisions) during cataract surgery.

- Subject had a floppy iris or required devices (iris hooks, etc.) or techniques not generally used in routine cataract surgery.

- Subject had another intraoperative condition that in the opinion of the Investigator precluded further participation in the study (e.g., subjects with intraoperative complications such as posterior capsule rupture, anterior vitrectomy, torn or ruptured zonules, phacoemulsification burns, incisions larger than 3.5 mm or torn incisions should have been excluded).

- Wound did not leak while applying force using the CFG.

2. <u>Follow-up Schedule</u>

Subjects were evaluated at approximately 1 hour and 1, 3, 7, 14, 21 and 28 days post-procedure.

Scheduled Clinical Evaluations:

ReSure Sealant was assessed through spontaneously reported ocular AEs, as well as through thorough ophthalmic examinations including a slit lamp examination, BCVA, keratometry/topography, tonometry, assessment of ocular irritation via the OCI, wound leak and wound healing. AEs and complications were recorded at all visits, as was persistence of ReSure Sealant on the incision. A standard Seidel test was repeated at 1, 3, 7 and 28 Days post-procedure to test for wound leakage. Wound healing was determined via the slit lamp exam with fluorescein staining based on the presence or absence of a wound leak and/or epithelial defect as evidenced by moderate to severe incisional staining. Keratometry was used to evaluate surgically induced astigmatism.

Incision (Wound) Leak Assessment:

Incision leakage was assessed via a Seidel test intra-operatively, as well as during the 1, 3, 7 and 28 Day follow-up visits. The CFG was only used to provoke the incision during the intra-operative evaluations, not during post-operative visits (i.e., Day 1-28 visits).

During the intra-operative evaluation, pre- and post-randomization wound leak assessments were obtained by Seidel test in conjunction with application of force near the incision using the following standardized method. Briefly, after application of ReSure Sealant or suture, unless there was spontaneous fluid leakage (an unprovoked leak), a wound leak assessment was performed under a surgical microscope by applying up to 1 ounce of force near the incision using a CFG. The CFG has a 3 mm diameter foot which contacts the ocular surface and is used to apply a measured amount of force in order to standardize the method by which CCIs are tested for integrity and leakage. Using the CFG, force was gradually applied for approximately 2-3 seconds at a distance 0.5 mm away from the incision at the posterior aspects of the scleral side of the incision. During the Wound Leak Assessment, the eye was monitored for leakage via a Seidel test using fluorescein staining. The location and duration of the wound leak assessment was selected to be consistent with the standard practice whereby a Weck-Cel sponge is used to evaluate incision integrity.

Ocular Comfort Index (OCI) Evaluations:

The OCI questionnaire was used to assess patient reported outcomes (PROs) for symptoms of ocular discomfort and irritation, including dryness, grittiness, stinging, tiredness, pain and itching, at the screening visit and post-operative Days 1-7, 14, 21 and 28. Individual symptom component responses were scored on a scale from 0 to 6, with 6 representing severe symptoms. The overall OCI questionnaire score can range from 0 to 100, with higher scores reflecting a greater degree of discomfort. The OCI authors (see reference section XVI below) suggest that changes of 3 or more units are likely to be noticed by patients, and therefore this step can be regarded as an estimate of a minimally important treatment difference. Subjects were presented with the instructions for the OCI questionnaire by study staff masked to treatment assignment, in order to minimize the potential for bias. Furthermore, to the extent

possible, subjects were also masked to treatment assignment. Masking was only partially successful for this study, in which the treatment and control devices are rather different.

3. Clinical Endpoints

Safety:

The study was powered to detect AE rates of 1% in the ReSure group, as recommended in the ISO safety and performance endpoints (*SPE) for cataract surgery.

** SPE (safety and performance endpoints): basic historical safety and effectiveness data (FDA Grid) incorporated in ISO 11979-7.*

Safety Endpoints:

- Corneal Edema (moderate to severe stromal edema) at 1 Day
- Anterior Chamber (AC) Inflammation (≥grade 2+ AC cells) at 1 Day

Safety endpoints were pre-specified to be evaluated for superiority of ReSure Sealant to the Suture control, and to be tested for statistical significance using fixed sequence testing in the order listed above. Hierarchical testing was used to control the type I error rate for the multiple safety endpoints with the pre-specified hierarchy as listed above. The safety population of all treated subjects was the primary analysis population for the safety endpoints.

Additional Safety Assessments:

Additional Safety Assessments were also pre-specified and included evaluation of adverse event incidence, and ocular symptoms as reported on the OCI questionnaire. The safety assessments listed below were evaluated at each follow-up visit except where noted:

- Ocular AEs per ISO SPE
- Ocular symptoms per OCI
- Hypotony due to wound leak
- Peripheral corneal edema affecting visual acuity
- Surgical re-intervention for management of wound leak
- BCVA and manifest refraction*

- Surgically-Induced Astigmatism (SIA)*
- IOP*
- Slit lamp findings
- Wound integrity/healing within normal limits (at 7 and 28 Day visits)

* *Except at Day 14 and 21*

Effectiveness:

Primary Effectiveness Endpoint:

- Proportion of eyes with any clear corneal incision/suture leakage as determined by a positive Seidel test indicating fluid egress, within the first 7 days after surgery.

Any subject demonstrating a positive post-randomization wound leak assessment and/or requiring additional treatment for a leaking incision following the post-randomization wound leak assessment was considered a primary endpoint failure.

The primary effectiveness endpoint was analyzed using a one-sided test for non-inferiority based on the normal approximation at the 0.05 significance level. The protocol specified that if non-inferiority was demonstrated, a two-sided test for superiority based on Fisher's Exact Test was to be performed at the 0.05 significance level.

Secondary Effectiveness Endpoints:

- Surgically induced corneal astigmatism at day 28
- Best-Corrected Visual Acuity (BCVA) worse than 20/40 at day 1
- Best-Corrected Visual Acuity (BCVA) worse than 20/40 at day 28

The above secondary endpoints were specified to be evaluated for superiority of ReSure Sealant to suture control, and to be tested for statistical significance only if non-inferiority of the primary endpoint was demonstrated.

Additional Effectiveness Assessments:

The following additional assessments were specified in the protocol in order to characterize device performance:

- Presence of ReSure Sealant or sutures at each follow-up visit

- Presence of blue colorant visualization aid in ReSure Sealant at follow-up visits

- Device application ease of use

B. Accountability of PMA Cohort

Between December 16, 2011 and August 16, 2012, a total of 583 subjects were consented (enrolled) for potential participation and 488 eyes were randomized (305 eyes to ReSure group and 183 eyes to Suture group) at 24 investigational sites within the United States. 487 unique study subjects participated in the study as 1 study participant was consented twice, was assigned two different subject numbers, and had both eyes randomized and treated by ReSure Sealant. The data for both eyes was included in the safety analysis, but only the data from the first enrolled eye was included in the per protocol (PP) effectiveness analysis. Of the 488 eyes randomized, only 6 did not complete the study, representing a retention rate of 98.8%.

Of the 583 subjects consented and enrolled, 95 subjects were considered pre-operative or intra-operative screen failures, and were therefore not randomized to treatment. Among the 95 screen failures, 22 were intra-operative screen failures, which included 12 subjects whose incision failed to leak during the pre-randomization wound leak assessment. Thus only 12 incisions did not exhibit a pre-randomization wound leak. There were 488 eyes which met protocol eligibility criteria and had a positive pre-randomization wound leak assessment, who were randomized to treatment in the study, 305 eyes treated with ReSure Sealant, and 183 eyes treated with suture.

The Intent to Treat (ITT) population included all 488 randomized eyes from 487 unique subjects. The treatment group (ReSure Sealant) had 305 eyes and the control group (Suture) had 183 eyes. Of the 488 eyes randomized, 471 (96.5%) were considered part of the PP Population and 17 (3.5%) had major protocol deviations and were excluded from the PP population. Greater than 97% of eyes were available for analysis at each visit (see **Table 7** below).

Table 7: Cumulative Subject Accountability (ITT Population)

Parameter	ReSure Sealant (N=305)		Suture (N=183)		Total (N=488)	
Visit Compliance	*Eligible*[a] (N)	*Evaluated* n (%)	*Eligible*[a] (N)	*Evaluated* n (%)	*Eligible*[a] (N)	*Evaluated* n (%)
1Hour Assessment	305	305 (100.0)	183	183 (100.0)	488	488 (100.0)
Day 1 Visit	305	305 (100.0)	183	183 (100.0)	488	488 (100.0)
Day 3 Visit	304	300 (98.7)	183	178 (97.3)	487	478 (98.2)
Day 7 Visit	304	302 (99.3)	183	179 (97.8)	487	481 (98.8)
Day 14 Visit	304	302 (99.3)	183	181 (98.9)	487	483 (99.2)
Day 21 Visit	303	298 (98.3)	182	180 (98.9)	485	478 (98.6)
Day 28 Visit	302	300 (99.3)	182	182 (100.0)	484	482 (99.6)

Note: The denominator for the calculation of percentages is the number of eyes eligible at the given visit.

[a] Subjects who withdrew consent were not deemed eligible for the visit.

Of the 6 subjects that did not complete the study, 4 withdrew their consent, 1 ReSure Sealant subject discontinued from the study following the Day 3 visit due to development of acute postoperative inflammation requiring follow-up by a retinal specialist which was determined to be unrelated to the study treatment, and 1 ReSure Sealant subject was lost-to-follow-up after the Day 14 visit despite numerous attempts to contact the subject.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study performed in the US for patients undergoing cataract surgery. Subject demographics are presented in **Table 8**, and surgical parameters are presented in **Tables 9** and **10**, below.

Treatment groups were similar among demographic and baseline characteristics evaluated. Randomized subjects ranged from 31.9 to 91.4 years of age, with similar percentages of males and females enrolled. In addition, subjects enrolled had similar racial composition (primarily Caucasian subjects), with similar distribution of tobacco users and diabetic subjects, characteristics with potential to impact incisional healing and ocular AE rate.

Surgical procedural characteristics were similar with respect to operative eye, incision length, incision location, and tunnel length (as per protocol, all subjects received single plane incisions in the clear cornea, and operative eyes were brought to physiologic pressure, 15 to 20 mmHg, prior to randomization). Mean surgery duration for subjects treated with ReSure Sealant was somewhat longer than for the Suture group (17.6 ± 6.4 vs. 16.1 ± 5.2 minutes), primarily attributed to the instruction to wait at least 60 seconds after

ReSure Sealant application prior to post-randomization wound leak assessment (to allow time for the hydrogel to solidify). The range of incision width reported in this study was 1.9 – 3.5 mm; the mean was 2.70 mm for the ReSure group, vs. 2.73 mm for the Suture group.

Randomization was stratified by type of pre-randomization incisional leak, "unprovoked" or "provoked," and the distribution was similar within each treatment group (i.e., 49.5% of the wounds leaks were unprovoked in the ReSure Sealant group, vs. 50.8% unprovoked in the Suture group).

The protocol permitted stromal hydration when administering treatment. 74.4% of ReSure Sealant eyes received stromal hydration before, after, or before and after ReSure Sealant application (but prior to the post-randomization wound leak assessment). Stromal hydration after sealant application was performed in 18.4% of ReSure Sealant treated eyes. In comparison, 77.0% of suture eyes received stromal hydration before, after, or before and after suture placement (but prior to the post-randomization wound leak assessment). Stromal hydration was performed after suture placement for 31.7% of eyes in the Suture group.

Table 8: Demographic and Baseline Characteristics (ITT Population)

Variable	ReSure Sealant (N= 305)	Suture (N=183)	Total (N=488)
Age (years)[a]			
Mean	68.80	68.84	68.81
Median	69.08	69.08	69.08
SD	8.93	8.55	8.78
Min. – Max.	31.9-91.0	43.8-91.4	31.9-91.4
Gender, n (%)			
Female	167 (54.8)	107 (58.5)	274 (56.1)
Male	138 (45.2)	76 (41.5)	214 (43.9)
Ethnicity, n (%)			
Hispanic or Latino	14 (4.6)	4 (2.2)	18 (3.7)
Not Hispanic or Latino	291 (95.4)	179 (97.8)	470 (96.3)
Race, n (%)			
White (Caucasian)	279 (91.5)	169 (92.3)	448 (91.8)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Asian	5 (1.6)	1 (0.5)	6 (1.2)
Black or African American	12 (3.9)	9 (4.9)	21 (4.3)

Other	9 (3.0)	4 (2.2)	13 (2.7)
Tobacco Smoker, n (%)			
Current	41 (13.4)	18 (9.8)	59 (12.1)
Past	114 (37.4)	73 (39.9)	187 (38.3)
Never	150 (49.2)	92 (50.3)	242 (49.6)
Diabetic, n (%)			
No	243 (79.7)	149 (81.4)	392 (80.3)
Yes	62 (20.3)	34 (18.6)	96 (19.7)
Insulin Dependent, n (%)			
Yes	0 (0.0)	0 (0.0)	0 (0.0)
No	62 (100.0)	34 (100.0)	96 (100.0)
Uses Oral Hyperglycemic Agents, n (%)			
Yes	48 (77.4)	28 (82.4)	76 (79.2)
No	14 (22.6)	6 (17.6)	20 (20.8)

[a] Age = (Date of informed consent - date of birth)/365.25

Table 9: Summary of Procedural Characteristics (ITT Population)

Variable	ReSure Sealant (N=305)	Suture (N=183)
Operative Eye, n (%)		
Right Eye (OD)	152 (49.8)	100 (54.6)
Left Eye (OS)	153 (50.2)	83 (45.4)
Incision in the Clear Cornea, n (%)		
Yes	305 (100.0)	183 (100.0)
No	0 (0.0)	0 (0.0)
Incision Type, n (%)		
Single Plane	305 (100.0)	183 (100.0)
Other	0 (0.0)	0 (0.0)
Incision Location, n (%)		
Temporal	281 (92.1)	169 (92.3)
Supra Temporal	14 (4.6)	10 (5.5)
Nasally	1 (0.3)	1 (0.5)
Supra Nasally	1 (0.3)	0 (0.0)
Superior	8 (2.6)	3 (1.6)
Estimated Tunnel Length (mm)		

Mean	2.25	2.28
Median	2.50	2.50
SD	0.48	0.49
Minimum - Maximum	0.8-3.2	1.0-4.0
Study Eye Brought to Physiological Pressure (15-20 mmHg), n (%)		
Yes	305 (100.0)	183 (100.0)
No	0 (0.0)	0 (0.0)
Incision Width (mm)		
Mean	2.70	2.73
Median	2.70	2.70
SD	0.23	0.21
Minimum - Maximum	1.9-3.5	2.0-3.5
Length of Surgery (min)		
Mean	17.6	16.1
Median	16.0	15.0
SD	6.4	5.2
Minimum - Maximum	7-60	5-35

Table 10: Pre-Randomization Wound Leak Assessments (ITT Population)

Parameter	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)
Wound Challenge		
No Leak[a]	0 (0.0)	0 (0.0)
Leak	305 (100.0)	183 (100.0)
Unprovoked - Seidel Test without CFG	151 (49.5)	93 (50.8)
Provoked - Seidel Test with CFG	154 (50.5)	90 (49.2)
Number of Lines of Force Applied with CFG		
1 line (0.25 oz)	85 (55.2)	42 (46.7)
2 lines (0.5 oz)	42 (27.3)	21 (23.3)
3 lines (0.75 oz)	21 (13.6)	22 (24.4)

4 lines (1.0 oz)	6 (3.9)	5 (5.6)
> 4 Lines	0 (0.0)	0 0.0)

[a] Subject could not be enrolled unless there was either an unprovoked or provoked leak.

D. Safety and Effectiveness Results

In the PMA clinical study, the analysis of safety was based on the safety population of 487 subjects available for the 28 Day visit.

The study was powered to detect AE rates of 1% in the ReSure group, as recommended in the ISO SPE for cataract surgery. ReSure sealant met SPE rates for AEs.

1. Safety Results

Safety endpoints were pre-specified for the study as the proportion of eyes with corneal edema at Day 1, and proportion with anterior chamber inflammation at Day 1, to be evaluated for superiority of ReSure Sealant to the Suture control, and to be tested for statistical significance using fixed sequence testing in the order listed above. Hierarchical testing was used to control the type I error rate for the multiple safety endpoints. The study failed to demonstrate superiority of ReSure Sealant to the suture control for the pre-specified safety endpoints as follows:

- Moderate to severe corneal stromal edema at 1 day was reported in 7.6% of ReSure subjects and 7.7% of control subjects.

- Anterior chamber inflammation at 1 day of grade 2+ cells or greater was reported in 9.5% of ReSure subjects and 9.8% of suture subjects.

No significant difference in the rates of corneal edema at Day 1 between the ReSure and Suture groups was detected as indicated by the p-value of 1.000 for this comparison. Therefore, superiority of ReSure sealant was not demonstrated. According to the pre-specified hierarchical testing plan the safety endpoint of anterior chamber inflammation at day 1 was not tested for statistical significance since the previous endpoint in the hierarchical sequence was not met.

Additional safety assessment outcomes:

- The incidence of major or serious ocular AEs was 1.6% in the ReSure group and 0.5% in the suture group.

- Surgical re-intervention for wound leak management occurred in 1 eye in the ReSure group (0.3%) vs. 0% in the suture group.

- Hypotony due to wound leak was 0% incidence in both groups.

- Peripheral corneal edema affecting acuity was 0% incidence in both groups.

- Incidence of any Ocular AE was 22.7% for ReSure vs. 45.4% for suture group.

- SIA, defined as the difference in anterior corneal astigmatism before and after surgery calculated as a vector quantity, showed no statistically or clinically significant difference between the ReSure and Suture groups at any of the post-operative time period. The SIA dropped slightly from Day 1 to Day 28 in both groups, noted as a reflection of the healing process. This change in SIA over time is not statistically significantly different between the groups. Day 1 data in both groups shows a slightly higher level of corneal astigmatism, presumably due to short term effects of the corneal incision and edema in the immediate post-operative period. The corneal astigmatism measured from Day 3 onward is similar to that measured preoperatively.

- BCVA distribution was not reported to be statistically significantly different between groups at any visit, nor is the change in BCVA from baseline to any visit different between groups. There was no statistical difference in the incidence of BCVA worse than 20/40 at day 28 between ReSure and Suture groups, 3.3% (95% CI: 1.6, 6.0) and 3.9% (95% CI: 1.6, 7.8), a difference of 0.6% [95% CI of difference: -2.9, 4.0]. There does not appear to be a safety concern in terms of visual acuity when using ReSure Sealant.

- OCI mean overall scores were similar between the ReSure group and the suture control group at all post-operative time points. Minor increases in discomfort were observed in both groups early post-operative (higher score). However, overall mean OCI scores returned to baseline by Day 4. Overall mean scores were marginally higher for the ReSure group than the suture group on post-operative Days 1 – 5, consistent with marginally greater discomfort.

- OCI individual subcomponent mean scores revealed some differences between ReSure and Suture groups. Three subcomponents were reported with mean scores statistically significantly higher in the ReSure group than in the Suture group. However, it should be noted that these analyses were not adjusted for multiplicity, and the differences were <0.5 units, for grittiness frequency on Day 1, itching frequency and itching intensity on Day 1, itching frequency on Day 2 and itching intensity on Day 2. No significant differences in mean scores were reported at any other OCI individual subcomponents at any visit.

- **Table 11** below summarizes all AEs occurring in 2 or more subjects.

Table 11: Most Commonly Reported Ocular Adverse Events ≥ 2 Subjects – Subject Level (Safety Population)

Adverse Ocular Event	ReSure Sealant (N = 304)		Suture (N = 183)	
	n (%)	95% CI for %[b]	n (%)	95% CI for %[b]
Anterior chamber cells greater than level 1+ persisting beyond Day 7 visit	4 (1.3)	(0.0036, 0.0333)	2 (1.1)	(0.0013, 0.0389)
Corneal abrasion	1 (0.3)	(0.0001, 0.0182)	1 (0.5)	(0.0001, 0.0301)
Corneal edema greater than level 1 persisting beyond Day 7 visit	1 (0.3)	(0.0001, 0.0182)	2 (1.1)	(0.0013, 0.0389)
IOP > or = 30 mmHg or 10 mmHg over baseline	16 (5.3)	(0.0304, 0.0841)	15 (8.2)	(0.0466, 0.1316)
Induced corneal astigmatism with a threshold of 3 diopters	9[c] (3.0)	(0.0136, 0.0555)	3 (1.6)	(0.0034, 0.0472)
Posterior vitreous detachment	5 (1.6)	(0.0054, 0.0380)	1 (0.5)	(0.0001, 0.0301)
Subconjunctival hemorrhage	1 (0.3)	(0.0001, 0.0182)	40 (21.9)	(0.1610, 0.2855)
Worsening in BCVA > 2 lines (>10 letters)	21 (6.9)	(0.0433, 0.1037)	9 (4.9)	(0.0227, 0.0913)
Cystoid macular edema	0 (0.0)	(0.0000, 0.0121)	2 (1.1)	(0.0013, 0.0389)
Eye irritation	0 (0.0)	(0.0000, 0.0121)	8 (4.4)	(0.0191, 0.0843)
Eye pain	8 (2.6)	(0.0114, 0.0512)	7 (3.8)	(0.0155, 0.0772)
Foreign body sensation	2 (0.7)	(0.0008, 0.0236)	7 (3.8)	(0.0155, 0.0772)
Suture related complication	0 (0.0)	(0.0000, 0.0121)	2 (1.1)	(0.0013, 0.0389)

Note: The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of subjects with at least one adverse ocular event of the given type.

[b] Clopper-Pearson exact confidence interval for a binomial proportion.

[c] These ReSure Sealant subjects include: 1) one subject who received a suture intra- operatively subsequent to partial application of ReSure Sealant due to lack of a dry ocular surface, and 2) two subjects who had localized elevation changes consistent with having residual ReSure Sealant on the eye.

2. Effectiveness Results

Primary Effectiveness Endpoint:

The proportion of eyes with any clear corneal incision/suture leakage as determined by a positive Seidel test indicating fluid egress within the first 7 days after surgery was considered a primary endpoint failure.

Based on the 471 subjects in the PP population, the proportion of subjects with incision leakage within the first 7 days of surgery was 4.1% in the ReSure group and 34.1% in the Suture group. The ReSure incision leak rate was determined to be non-

inferior to the suture control rate. Since ReSure was determined non-inferior to suture control for the primary effectiveness endpoint, as specified in the protocol a test of superiority was conducted, and ReSure was determined to be superior to the suture control rate for this endpoint. Thus for the PP population, the primary endpoint incision leak rate for the ReSure group was significantly less than for the suture control group. Refer to **Table 12** below:

Table 12: Primary Effectiveness Endpoint (PP Population and ITT Population)

Variable	ReSure Sealant (N=295)	Suture (N=176)	Difference in % (Suture – ReSure Sealant) and 95% CI[a]
Per Protocol Population			
Any clear corneal incision leakage at any time within the first 7 days after surgery, n/N (%)	12/295 (4.1)	60/176 (34.1)	30.0 (22.7, 37.4)
95% CI for %[b]	(2.1 , 7.0)	(27.1 , 41.6)	
p-value[c]			<0.0001
p-value[d]			<0.0001
p-value[e]			0.2985
Day Leakage First Occurred, n			
Day 0	11 (91.7)	58 (96.7)	
Day 1	0 (0.0)	0 (0.0)	
Day 2	0 (0.0)	0 (0.0)	
Day 3	1 (8.3)	0 (0.0)	
Day 4	0 (0.0)	0 (0.0)	
Day 5	0 (0.0)	0 (0.0)	
Day 6	0 (0.0)	0 (0.0)	
Day 7	0 (0.0)	2 (3.3)	
Intent-to-Treat Population[f]			
Any clear corneal incision leakage at any time within the first 7 days after surgery, n/N (%)	12/297 (4.0)	60/176 (34.1)	30.1 (22.7, 37.4)
95% CI for %[b]	(2.1 , 7.0)	(27.1 , 41.6)	
p-value[c]			<0.0001
p-value[d]			<0.0001
Day Leakage First Occurred, n (%)			
Day 0	11 (91.7)	58 (96.7)	
Day 1	0 (0.0)	0 (0.0)	
Day 2	0 (0.0)	0 (0.0)	
Day 3	1 (8.3)	0 (0.0)	

Day 4	0 (0.0)	0 (0.0)	
Day 5	0 (0.0)	0 (0.0)	
Day 6	0 (0.0)	0 (0.0)	
Day 7	0 (0.0)	2 (3.3)	

[a] Confidence interval based on the normal approximation.

[b] Clopper-Pearson exact confidence interval for a binomial proportion.

[c] p-value from a one-sided normal approximation test of non-inferiority of ReSure Sealant to suture with respect to a binomial proportion, with a non-inferiority margin of 0.05.

[d] p-value from a two-sided test for superiority based on Fisher's Exact Test, testing for a difference in proportions between treatments.

[e] p-value for the treatment by site interaction term from a logistic regression analysis with terms for treatment, site and the treatment by site interaction.

[f] The ITT Population excludes 16 subjects who had at least one missing value for leak evaluation from intra-operatively (post treatment) through Day 7. Because there is no imputation of missing values, such subjects are excluded from the analysis of the primary endpoint as missing.

An analysis was performed to stratify the primary effectiveness endpoint outcome by the pre-randomization incision leak category, either unprovoked spontaneous leak or CFG-provoked leak:

- For eyes with unprovoked, spontaneous pre-randomization wound leaks, the incidence of post-op incision leakage was 6.1% for ReSure vs. 47.2% for the Suture group.

- For eyes with CFG-provoked pre-randomization wound leaks, the incidence of post-op incision leakage was 2.0% for ReSure vs. 20.7% for the Suture group.

The incidence of incision leakage in the first 7 days post-operative was greater in the subgroup with spontaneous, unprovoked pre-randomization incision leakage, for both ReSure and Suture treatment groups. However, , it was still concluded that ReSure Sealant was significantly more effective than suture for mitigating post-operative Day 1-7 incisional leaks, irrespective of whether the pre-randomization wound leak was unprovoked or provoked.

Most post-treatment wound leaks in the study occurred during the Day 0 post-treatment wound leak assessment, accounting for 91.7% of all leaks in the ReSure group and 96.7% in the suture group. Of the 72 eyes reported with incision leak at any time within 7 days of surgery, 69 eyes had incision leak onset reported during the intraoperative post-treatment wound leak assessment performed after application of ReSure Sealant or Suture.

There were only 3 subjects with onset of incision leakage observed in the post-

operative follow-up period from Day 1 to Day 7, as follows:

- 1 ReSure eye had an incision leak with a positive Seidel noted on post-op day 3, with sealant absent and IOP 16 mmHg. Two days later, on post-op day 5, the eye remained Seidel positive and the incision was sutured. No leak was detected at the day 7 visit.

- 2 Suture eyes had incision leak with positive Seidel at day 7, with IOP normal in both, 12 and 17 mmHg. No further action was taken. Both were Seidel negative at day 28.

The packaging for ReSure Sealant contains sufficient material for up to 2 applications of the device, if deemed necessary by the surgeon in order to achieve adequate coverage of the incision. However, in the clinical study, multiple applications of ReSure Sealant were required for the majority of subjects treated with ReSure, as seen in the **Table 13** below:

Table 13: Distribution of ReSure Sealant Applications

# Applications	n (%) N=305
0	1 (0.3)
1	54 (17.7)
2	128 (42.0)
3	76 (24.9)
4	32 (10.5)
5	11 (3.6)
6	0 (0.0)
7	2 (0.7)
8	1 (0.3)

Multiple applications of ReSure Sealant were required for the majority of subjects treated with ReSure. Overall, a total of 459 packages of ReSure Sealant were used for 305 eyes treated:

- 59.7% of eyes required 1 package

- 35.4% of eyes required 2 packages

- 3.6% of eyes required 3 packages

- 1% of eyes required 4 packages

In eyes treated with ReSure Sealant, 40% of eyes required >1 package for incision coverage. **Tables 14** below shows the primary effectiveness endpoint (incision leak

rate) stratified by number of ReSure Sealant applications. Wound leak rates were found to increase with the number of applications.

Table 14: Wound Leak Rate by Number of Applications ITT Population – ReSure Subjects

Number of Applications	n/N (%)
0	0/0 (---)
1	1/52 (1.9)
2	3/125 (2.4)
3	5/76 (6.6)
4	2/30 (6.7)
5	1/11 (9.1)
6	0/0 (---)
7	0/2 (0.0)
8	0/1 (0.0)

A post-hoc analysis was performed to evaluate the impact of the number of ReSure Sealant applications on the primary effectiveness endpoint, incision leakage within the first 7 days post-operative, stratified by 1 package (1-2 sealant applications) versus more than 1 package (> 2 applications). Incision leak rates within the first 7 days after surgery were higher in subjects who required more than 1 package of Resure Sealant (rate of incision leak 6.7%) compared to subjects who required only 1 package (rate of incision leak 2.3%). However, for both ReSure groups, the outcomes were still better than the control with regard to the primary effectiveness outcome.

Secondary Effectiveness Endpoints:

Surgically induced corneal astigmatism at Day 28, and BCVA worse than 20/40 at Day 1 and 28 were specified to be evaluated for superiority of ReSure Sealant to Suture control, and to be tested for statistical significance only if non-inferiority of the primary endpoint was demonstrated. The following outcomes were reported:

- Surgically-induced corneal astigmatism at Day 28 was reported as 0.600 ± 0.454D in the ReSure group, vs. 0.597 ± 0.442D in the Suture group.

- BCVA worse than 20/40 was reported as 15.8% for ReSure, vs. 16.4% for Suture at Day 1.

- BCVA worse than 20/40 was reported as 3.3% for ReSure vs. 3.9% for Suture at

Day 28.

The ReSure outcome was determined not to be superior to the Suture group outcome for these secondary endpoints. No significant difference in the mean surgically induced astigmatism at Day 28 between the ReSure and Suture groups was detected. Therefore, this endpoint was not met. According to the pre-specified hierarchical testing plan, the other secondary effectiveness endpoints were not tested for statistical significance since the first endpoint in the hierarchical sequence was not met.

Additional Effectiveness Assessments:

The following additional assessments were specified in the protocol in order to characterize device performance:

- Presence of ReSure Sealant or sutures at each follow-up visit
- Presence of blue colorant visualization aid in ReSure Sealant at follow-up visits
- Device application ease of use.

ReSure Sealant was reported as present on the corneal incision as follows:

- 99% of eyes at the 1 hour post-op visit
- 76.1% of eyes at day 1
- 31.3% of eyes at day 3
- 2.6% of eyes at day 7
- 0% of eyes at the day 14 post-op visit

Of the 1% of cases when ReSure Sealant was absent by 1 hour post-operative, 1 subject did not receive ReSure treatment, 1 subject had incomplete application, and 1 subject had ReSure removed after a failed leak test and the incision was sutured.

The device blue visualization aid was visible in 54% of eyes at 1 hour, 6.5% at day 1, 0% at day 3.

There were 2 device-related AEs related to ReSure Sealant sloughing off from the incision:

- 1 case of foreign body in the eye, where 95% of ReSure sloughed from the incision and needed to be removed with forceps.
- 1 case of eye pain, with ReSure lifted off of the corneal surface on one side; this event resolved after 4 days.

Overall, ReSure Sealant was observed to have sloughed off (not present) from approximately 25% of treated eyes at a time prior to the post-operative Day 1 exam, and sloughed off from approximately 70% of eyes prior to the post-operative Day 3 exam. To justify whether the observed persistence of ReSure Sealant is of clinically sufficient duration as compared to the window of time in which incision leakage typically occurs after uncomplicated clear corneal cataract surgery, the applicant noted that ReSure Sealant adheres to de-epithelialized tissue and sloughs as re-epithelialization occurs. The applicant concluded that ReSure covers the incision until epithelial healing has completed, which substantially reduces the likelihood of post-operative incision leak during the period that incisions are most vulnerable to leakage, and that although wound leak may occur after the epithelium is healed since the stroma is not yet healed, it is rarer to have a wound leak after the epithelium has healed. To further address this concern, the applicant conducted a literature search on post-operative wound leakage. They note that corneal epithelial healing after radial keratotomy is reported to last from 12 – 48 hours, and that there were no reports of post-operative incision leak beyond the first post-operative day after uncomplicated clear corneal cataract surgery.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

OCI sub-group analyses: These were performed to isolate the effect that pain medication use prior to a given visit may have had on OCI responses. The analysis revealed outcome differences between ReSure and Suture groups for subjects taking 81mg aspirin prior to a given visit. Mean OCI score was 3 or more points higher in the ReSure group than the Suture group at post-op Day 1 through Day 5, indicating greater discomfort in the ReSure group during this time period. However, because no similar differences were noted for subjects taking no aspirin, or subjects taking >81 mg aspirin or other prohibited pain medications, it is difficult to draw a meaningful conclusion regarding the observed difference between ReSure and Suture groups for the 81mg aspirin subgroup. In the study, aspirin usage increased slightly from baseline to day 1, with about 36 more subjects on aspirin at day 1, but appears to be evenly distributed across both groups. Thus it does not appear that a large number of subjects in one of the groups started taking aspirin to manage pain. Panel members concluded that this outcome did not impact the assessment of reasonable assurance of safety.

Gender: In the Suture group 33.7% of Females and 34.7% of males had an incision leak within the first 7 days after surgery. In the ReSure sealant group the percent with incision leak was 3.7% of females and 4.5% of males. Based on logistic regression analysis no treatment by gender interaction was detected.

Age: The incision leak rate is smaller in the ReSure Sealant group than the Suture group in all age groups.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 77 investigators of which none were full-time or part-time employees of the sponsor and 8 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Significant equity interest held by investigator in sponsor of covered study: 8 investigators

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Protocol Deviations:

Of the 370 protocol deviations reported for 244 subjects in the clinical study, the applicant considered 17 as major protocol deviations that were excluded from the PP population. The definition of major deviations was pre-specified in the protocol as follows: "Major protocol violations will include: Not receiving any study treatment, Not receiving the correct study treatment, Failing to meet eligibility criteria, Not completing the study through 7 days, Other major protocol violations, as determined by a review of the data prior to database lock." The 17 major deviations included 10 eyes from the ReSure Sealant group and 7 eyes from the Suture group, as follows:

- 14 subjects had incomplete follow-up, having missed Day 3 or Day 7 visits due to withdrawal or non-compliance. They were excluded from the PP population because the protocol made no provisions for imputing missing data, and this time period was critical to the assessment of primary effectiveness.

- 1 subject was enrolled in the study and both eyes were treated; the fellow eye was excluded from the PP population in order not to confound data analysis.

- 1 subject did not receive the assigned treatment with ReSure Sealant because the surgeon was unable to achieve a dry ocular surface for application.

- 1 subject received an inadequate post-randomization wound leak assessment, in that the CFG was only applied to line 3 by the surgeon (rather than to line 4, representing the maximum 1 ounce of force as per the study protocol). This was attributed to the observation of a Seidel-negative conjunctival leak by the surgeon.

- 1 subject did not receive complete treatment with ReSure Sealant application, which was prematurely discontinued due to the lack of a dry surface. This subject was included in the PP population.

Refer to **Table 15** below for a summary of protocol deviations in the study.

Table15: Protocol Deviations (ITT Population)

Deviation	ReSure Sealant (N=305)	Suture (N=183)	Total (N=488)
Total Subjects with Deviations		**n (%)**	
Consent	4 (1.3)	3 (1.6)	7 (1.4)
Inclusion/Exclusion	15 (4.9)	11 (6.0)	26 (5.3)
Required Assessment Not Done[a]	51 (16.7)	30 (16.4)	81 (16.6)
Required Assessment Not Done within Specified Timeframe[b]	74 (23.9)	45 (24.6)	118 (24.2)
Procedure/ Device Related	4 (1.3)	3 (1.6)	7 (1.4)
Overall-Other[c]	47 (15.4)	27 (14.8)	74 (15.2)
Steroid Taper Regimen Deviation	33 (10.8)	22 (11.5)	55 (10.9)
Use of Prohibited Medications	7 (2.3)	4 (2.2)	11 (2.3)
Post-Operative Antibiotic Use (Not a 4th generation fluoroquinolone)	2 (0.7)	4 (2.2)	6 (1.2)
Out of Sequence Randomization[d]	4 (1.3)	2 (1.1)	6 (1.2)
Other Deviations[e]	6 (2.0)	1 (0.6)	7 (1.4)

[a] Excludes 1 ReSure Sealant subject incorrectly categorized.

[b] Includes 2 ReSure Sealant subjects incorrectly categorized as "Required Assessment Not Done" and "Other".

[c] A subject can have more than one deviation in the "other" category.

[d] Includes 2 reports of randomization sequence break deviations reported in the category of "Procedure/Device Related."

[e] Includes 1 subject for whom the masking was broken.

Notes:
(1) The percentages are based on the number of subjects in each treatment group or overall, as appropriate.
(2) A subject can have more than one type of protocol deviation, so the percentages may sum to more than 100%
(3) Multiple deviations per subject within the same category are counted only once, including deviations from the randomization schema.

Device Malfunctions:

During the course of the study there were 10 ReSure Sealant device malfunctions among the 459 devices opened and used (2.2% of devices used). Nine of the ten device malfunctions

were reports of "fast gel time" and 1 report that the applicator bent 45 degree angle where the foam tip meets the handle. These malfunctions were investigated by Ocular Therapeutix. During investigation of the "fast gel time" reports, the failure could not be repeated under controlled conditions at Ocular Therapeutix, and it was concluded that manufacturing confirmation of the diluent bottle/dropper cap tightness was needed. The manufacturing operators were retrained to ensure the caps were secured tightly onto the diluent dropper/bottle during assembly. Since the retraining, there were no additional reports of fast gel times.

Masking Effectiveness in the clinical study:

Refer to **Table 16** below for a summary of masking effectiveness in the study.

Table 16: Masking Effectiveness Assessment

Variable	ReSure Sealant (N=305) n (%)	Suture (N=183) n (%)
Masking Effectiveness Assessment Response		
ReSure Sealant	194 (65.3)	72 (39.6)
Suture	32 (10.8)	46 (25.3)
Unsure	71 (23.9)	64 (35.2)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on September 19, 2013, the Ophthalmic Devices Advisory Panel voted (9/1/1) (Yes/No/Abstain) that there is reasonable assurance the device is safe, (5/3/3) that there is reasonable assurance that the device is effective, and (5/1/5) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. During panel deliberations the panel expressed concern regarding the proposed Indications for Use. The panel recommended that the Indications for Use be revised in an effort to eliminate implied prophylactic use, identify a lower age limit for use, and define the maximum incision size. If the Indications for Use were modified based on these deliberations, many panel members stated they would have voted more favorably. The panel meeting summary can be located at the following link:

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OphthalmicDevicesPanel/ucm346386.htm

B. FDA's Post-Panel Action

During discussions and deliberations, there were a number of concerns which the panel recommended be addressed in the Indications for Use (see above), labeling and a post approval study (PAS) for ReSure Sealant. With regard to labeling, the panel recommended that appropriate information be presented which identified device limitations (e.g., 1 to 3

day persistence and the number of applications/packages required for complete incision coverage) as well as situations when the subject device should not be utilized. This includes incisions with copious/brisk leaks for which a temporary dry ocular surface cannot be obtained, and incisions at higher risk of wound leak which may require mechanical support of sutures. Regarding the PAS, the panel recommended that a study be undertaken by the applicant and that rates of endophthalmitis for patients who receive ReSure Sealant be documented. In addition, the panel identified parameters (e.g., symptoms, AEs, and necessity for secondary procedures) for evaluation in the PAS. The Indications for Use and labeling were modified accordingly, and a PAS was developed based on these recommendations.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For the single-plane CCI architecture evaluated in the PMA clinical study, incision leakage occurred significantly less frequently in subjects treated with ReSure Sealant than in subjects treated with placement of a single suture. The primary effectiveness endpoint was met with superiority demonstrated. ReSure Sealant was demonstrated to be effective in reducing the incidence of CCI leakage in the early post-operative period as compared to placement of a single suture.

B. Safety Conclusions

The overall incidence of AEs reported for eyes treated with ReSure Sealant was significantly lower than for eyes treated with suture (22.7% vs. 45.4%). However, the incidence of any major or serious AEs did not differ between the two groups 1.6% vs. 0.5% respectively. AE rates were consistent with ISO safety and performance endpoints. Superiority of ReSure Sealant was not demonstrated for the pre-specified safety endpoints. However, the panel did not raise concern about the safety endpoint outcomes which are similar for both ReSure and Suture control groups. Safety of ReSure Sealant when applied to CCIs was established in this clinical study powered to detect any safety events occurring at 1% or greater. The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in a clinical study conducted to support PMA approval, as described in Section X above.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. ReSure Sealant provides improved benefit over use of one suture (control group) for intraoperative management of single-plane CCIs with demonstrated leakage, as evaluated in the PMA clinical study, and has low risks. The probability of benefit is high as ReSure Sealant was demonstrated to be superior to suture under the conditions evaluated in the clinical study (e.g., 3.5mm clear corneal single-plane incision, use of single suture as control). The potential frequency of harmful events associated with the device is low as the device was demonstrated to be associated with fewer device-related AEs than suture and the nature of these events is not serious. Therefore, it is reasonable to conclude that the benefits of use of the device

outweigh the risk of injury when used as indicated in accordance with the Instructions for Use.

Additional factors that were considerations in determining probable risks and benefits for ReSure Sealant included the following:

- Clinical relevance of provoked pre-randomization incision leaks: The majority of incision leaked prior to randomization with either no force or 0.25 ounce of force (1st line on CFG), 77% of eyes randomized to ReSure and 74% of eyes randomized to suture. Also the CFG has a relatively small diameter tip used to provoke incisions. Panel members raised concern regarding the clinical meaningfulness of the provoked leakage that was treated with ReSure Sealant or suture control in the study.

- Generalizability of study results to other types of CCI architectures and size parameters: The clinical study evaluated only 3.5mm width single-plane incisions.

- Availability of alternative treatments: ReSure was compared to suture control, however, in the study only 1 suture was placed in all eyes. In clinical practice, perhaps additional sutures would have been optimal in certain cases.

- Novelty of technology: This ReSure Sealant material sloughs off in a relatively short time period after surgery, typically within 1-3 days, whereas sutures are placed deep in the corneal tissue and may remain in place for a long period, until removed by the surgeon. However, a sealant device may have the clinical disadvantages present with use of sutures, as described in the peer-reviewed literature.

In conclusion, given the available information above and the FDA and panel deliberations, the data support that for intraoperative management of CCIs (up to 3.5mm) with a demonstrated wound leak for which a temporary dry surface can be achieved, in order to prevent postoperative fluid egress from such incisions following cataract surgery with intraocular lens (IOL) placement in adults, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this ReSure Sealant device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on January 8, 2014. The applicant's manufacturing facility has been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820). The final conditions of approval cited in the approval order are described below:

A. Device Exposure Registry Study

The purpose of this study is to evaluate the incidence of endophthalmitis for cataract surgery patients treated with ReSure Sealant when used by a broad group of physicians. A prospective multicenter observational single-arm registry study will be conducted that will include up to 100 centers in the United States with enrollment of at least 4,857 patients treated with ReSure Sealant. The primary endpoint will be endophthalmitis. Patients will be identified as having undergone cataract surgery using the surgeon's standard techniques and if ReSure Sealant is applied the patient will be considered enrolled and their data will be linked to Medicare to ascertain if they are diagnosed or treated for enophthalmitis within 30 days of the procedure. Follow-up will consist of query of the Medicare database on at least an annual basis starting from the date Medicare data is available, for at least one year after enrollment of the last patient. A sample size of 4,857 achieves an alpha of 0.05 and approximately 82% power to detect a difference (P1-P0) of -0.0020 using a one-sided binomial test, where P0 is the proportion of endophthalmitis within 30 days under the null hypothesis (0.0040) and P1 is the proportion of endophthalmitis within 30 days under the alternative hypothesis (0.0020).

B. Clinical PAS

The purpose of this study is to evaluate the incidences of the major ocular AEs in the postmarket setting for cataract surgery patients treated with ReSure Sealant. A prospective multicenter observational single-arm study will be conducted in at least 598 patients enrolled at up to 40 centers. Patients enrolled in this study will be evaluated in the immediate post-operative period (Visit 1: Day 1 to Day 3) and again at approximately 4 weeks post-procedure (Visit 2: Day 20 to Day 40).

Perioperative observations to be recorded will include:

- Number of ReSure Sealant devices used
- ReSure Sealant lot number(s)
- Concomitant suture use (before and/or after use of ReSure Sealant)
- Ocular AEs (device related events recorded after the first application of ReSure Sealant).

The primary endpoint will be the following adverse events occurring in the post-operative follow-up period:

- AC cells greater than level 1+ persisting at Visit 2
- Hypotony (</= 5 mmHg)
- Ocular discomfort (an OCI score greater than 51.7 or a within-person change from baseline of greater than 37.8)
- Surgical reintervention.

The following ocular examinations will be performed:

- IOP
- Slit lamp examination with fluorescein staining including an assessment of ReSure Sealant presence.

Patients will complete an OCI questionnaire at the screening and follow-up visits. Positive responses to the OCI will not be reported as endpoint events unless: (1) the OCI score is outside of normal limits for the post-cataract surgical period observed (i.e., an OCI score greater than 51.7 or a within-person change of 37.8 or more) and (2) ReSure Sealant is still present in the eye at the time that the event is reported. All endpoint ocular AEs, device-related ocular AEs, and ocular SAEs (including the nature, severity, seriousness, and relationship to ReSure Sealant) occurring during the course of the study will be documented.

A sample size of 598 achieves an alpha of 0.05 and 80% power to detect a difference (P1-P0) of -0.025 using a one-sided binomial test, where P0 is the proportion of individual primary endpoint ocular AEs in the post-operative follow-up period under the null hypothesis (0.075) and P1 is the proportion of individual primary endpoint ocular AEs under the alternative hypothesis (0.050).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Johnson ME, Murphy PJ. Measurement of ocular surface irritation on a linear interval scale with the Ocular Comfort Index. IOVS 2007:48: 4451-4458.