P130004
ReSure® Sealant

James Bertram, Ph.D., R.A.C.
PMA Team Leader
Division of Ophthalmic and Ear, Nose and Throat Devices
FDA/CDRH/ODE
September 19, 2013
FDA Review Team

Sherri Berman, M.D.
James Bertram, Ph.D., R.A.C.
Jennifer Brown, M.S.
Shelley Buchen
John Gomes
Rajesh Nair, Ph.D.
Youlin Qi, M.D., M.P.H.
Bill Riemenschneider
Ming Shih, M.S.

Clinical Team Leader/Engineering
Microbiology
Biocompatibility
Manufacturing (GMP)
Statistics
Epidemiology
Bioresearch Monitoring
Chemistry
Proposed Indications for Use (IFU)

- ReSure Sealant is indicated for intraoperative management of clear corneal incisions with a wound leak demonstrated by a Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.

- There are currently no devices approved in the United States for such an indication.
Rationale for Meeting

To solicit Panel’s opinion on:

• Safety and effectiveness of ReSure Sealant, and

• Whether benefits outweigh risk for the proposed IFU
Device Description

- Hydrogel comprised mainly of water (89%) and PEG (9.4%)
- Formed by mixing PEG and trilysine components immediately before application
- Visualization aid (FD&C Blue #1)
- Polymerizes *in situ*
- Solidifies within approx. 20 seconds into a soft hydrogel that adheres to corneal surface
- Hydrogel softens, detaches, and is sloughed off in the tears ≤7 days
Device Description

Application Process

Dispense diluent solution from diluent bottle/dropper onto blue deposit

Mix hydrogel precursors rapidly w/ applicator

Gather material on foam tip of the applicator

Apply ReSure Sealant to corneal incision
Preclinical Studies

• Bench testing – physicochemical properties
• \textit{In vivo} (animal) - performance testing
• Biocompatibility
• Sterilization, packaging and shelf-Life
• Manufacturing
Regulatory History

- I-ZIP Ocular Bandage/Resure Adherent Ocular Bandage
  » G080019 study (approved Mar. 2009)
    ▪ Objective: Evaluate ocular surface protection and relief of pain/discomfort in subjects undergoing clear corneal cataract surgery
    ▪ Control: OASIS Soft-Shield Clear Corneal Shield
    ▪ Follow-up: 30 days (no long-term data collected)
    ▪ Outcomes: Almost 25% of subjects exited the study with bandage material remaining on their eye at 30 days post-operative (post-op).
Regulatory History

• ReSure Sealant
  » G110114 (approved Nov. 2011)
    ▪ Objective: Evaluate the safety and effectiveness of ReSure Sealant in “preventing incision leakage from clear corneal incisions within the first 7 days of surgery for patients undergoing uneventful clear corneal cataract surgery with phacoemulsification and IOL placement.”
    ▪ Control: sutures
  » Modular PMA (M120009) (received Aug. 2012)
    ▪ P130004 filed (Feb. 2013)
    ▪ Major deficiency letter (May 2013)
P130004
ReSure® Sealant

Sherri Berman, M.D.
Medical Officer
Division of Ophthalmic and Ear, Nose and Throat Devices
FDA/CDRH/ODE

September 19, 2013
Clinical Study Design

• Prospective, randomized, parallel arm, controlled, multicenter, subject-masked study

• 583 subjects consented/enrolled:
  » 95 screen failures
    ▪ 12 did not exhibit a pre-randomization wound leak
  » 488 randomized (305 ReSure Sealant, 183 suture control)

• Prophylactic use on non-leaking incisions not evaluated

• Objective: to establish non-inferiority of ReSure Sealant to suture control for prevention of incision leak within 7 days post-op

• Randomization:
  » Demonstrated incision leak by positive Seidel
  » Stratified by unprovoked or provoked by Calibrated Force Gauge (CFG)
  » Majority incisions leaked ≤ 0.25 ounce force (77% ReSure, 74% Suture)
  » Similar distribution of CFG-applied force between groups
Study Medications

- Pain Medication
  - Topical/systemic NSAID, opiate/nonopiate, acetaminophen
  - Prophylactic use prohibited
  - Non-Prophylactic allowed for pain and cardiac maintenance

- Post-op Steroid regimen
  - Prednisolone acetate 1% ophthalmic steroid drops
  - Tapered regimen: QID 2 weeks, BID 1 week, QD 1 week
Surgical Procedure

• Cataract surgery parameters
  » Single plane clear corneal incision (CCI), no external groove
  » Maximum incision length ≤3.5 mm measured after implant
    ▪ Range 1.9 mm – 3.5 mm
    ▪ Mean 2.70 mm ReSure group, 2.73 mm Suture group
  » No additional surgical procedures (limbal relaxing incisions)
  » Eye brought to physiologic pressure 15-20 mmHg
Proposed IFU

“ReSure Sealant is indicated for intraoperative management of clear corneal incisions with a wound leak demonstrated by a Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.”

• Prophylactic use of ReSure on non-leaking incisions not evaluated in clinical study
• Maximum incision length not specified (≤3.5 mm measured after IOL implant)
• Incision architecture not specified (single plane incision)
The proposed Indication for Use (IFU) is as follows:

“ReSure Sealant is indicated for intraoperative management of clear corneal incisions with a wound leak demonstrated by a Seidel test, and for prevention of postoperative fluid egress following cataract or intraocular lens placement surgery.”

The proposed IFU does not specify the type of incision architecture or its maximum length. Do you believe:

a) Maximum incision length evaluated in the study (≤3.5mm) should be included in the IFU?

b) Incision architecture evaluated in the study (single plane Clear Corneal Incision (CCI) with no external groove) should be included in the IFU?

c) Prophylactic use is implied by the proposed IFU?
370 Protocol Deviations

- **Consent: 7**
- **Inclusion/Exclusion: 27**
  - 21 prohibited medications
  - 2 prior surgery
  - 2 pre-existing inflammation or pain
  - 1 pre-existing glaucoma
  - 1 subject bilateral treatments (fellow eye excluded from Per Protocol)
- **Required Assessment Not Performed: 97**
  - 36 missing topographic and keratometric assessments
  - 33 missing or incomplete Ocular Comfort Index (OCI) questionnaire
  - 17 missed visits
  - 11 missing protocol-required assessments
370 Protocol Deviations (cont.)

• **Required Assessment Not Done in Specified Time Frame: 149**
  » 12 for 1-hour post-op
  » 32 for Day 1
  » 17 for Day 7
  » 13 subjects missed a visit prior to or including Day 7 (excluded from PP)

• **Procedure/Device Related: 7**
  » 1 ReSure application prematurely discontinued
  » 1 not receive assigned ReSure application (excluded from PP)
  » 1 wound leak challenge less rigorous than required (excluded from PP)
  » 1 had the CFG applied to line 5
  » 1 prohibited medication
  » 2 randomization sequence deviations

• **Randomization Sequence: 6**

• **Other: 77**
<table>
<thead>
<tr>
<th>Category</th>
<th>ReSure Subjects (N=305)</th>
<th>Suture Subjects (N=183)</th>
<th>Total Subjects (N=488)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent</td>
<td>4 (1.3%)</td>
<td>3 (1.6%)</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Inclusion/Exclusion</td>
<td>15 (4.9%)</td>
<td>11 (6.0%)</td>
<td>26 (5.3%)</td>
</tr>
<tr>
<td>Required assessment not performed</td>
<td>51 (16.7%)</td>
<td>30 (16.4%)</td>
<td>81 (16.6%)</td>
</tr>
<tr>
<td>Required assessment not done in specified time frame</td>
<td>74 (23.9%)</td>
<td>45 (24.6%)</td>
<td>118 (24.2%)</td>
</tr>
<tr>
<td>Procedure/Device Related</td>
<td>4 (1.3%)</td>
<td>3 (1.6%)</td>
<td>7 (1.4%)</td>
</tr>
<tr>
<td>Other - Overall</td>
<td>47 (15.4%)</td>
<td>27 (14.8%)</td>
<td>74 (15.2%)</td>
</tr>
</tbody>
</table>
17 Major Protocol Deviations (17 subjects)

• 17 eyes excluded from Per Protocol (PP) population:
  » 14 missed a visit ≤ day 7 (7 ReSure and 7 Suture)
  » 1 with both eyes treated, fellow eye excluded (1 ReSure)
  » 1 with assigned treatment not applied (1 ReSure)
  » 1 with post-randomization wound leak challenge less rigorous than required (1 ReSure)
Question for Panel Discussion

Given the conduct of the study (370 protocol deviations), do you believe that the data generated allow you to adequately assess the benefits versus risks of ReSure Sealant?
Primary Effectiveness Outcomes

• Proportion of eyes with any CCI/suture leakage determined by a positive Seidel test indicating fluid egress within the first 7 days after surgery:
  » 4.1% (12/295) for ReSure Sealant group
  » 34.1% (60/176) for Suture control group
  » ReSure non-inferior to control
  » Test of superiority also met
Primary Effectiveness Outcomes: Stratification by Incision Leak Category

- ReSure Sealant significantly more effective than sutures for mitigating post-op incisional leaks, for both unprovoked and CFG-provoked corneal incisions

- Subgroup with unprovoked incisions had higher rate of post-op incision leakage, in both ReSure and Suture arms:
  - Unprovoked: 6.1% ReSure vs. 47.2% Suture
  - CFG-Provoked: 2.0% ReSure vs. 20.7% Suture
Wound Leak Assessment

• Operative (pre- and post-randomization):
  » Unless spontaneous leak, incision was provoked by Calibrated Force Gauge (CFG)
  » Applied 2-3 seconds at 0.5 mm from posterior of incision
  » Until leak observed or maximum force reached
  » Consistent with standard practice
    ▪ Weck-Cel sponge or suitable instrument
  » 1 ounce force using CFG results in mean IOP 43 mmHg
  » CFG not currently commercially available
Wound Leak

• Post-op assessment:
  » Seidel test performed at day 1, 3, 7 and 28 (no CFG)

• Onset of post-treatment incision leaks:
  » Intra-op leaks with CFG (Day 0): 69 eyes
  » Post-op leaks without CFG (Day 1 – Day 7): 3 eyes
    ▪ 1 ReSure eye: Day 3 and Day 5 (sutured on Day 5)
    ▪ 2 Suture eyes: Day 7
Calibrated Force Gauge (CFG)

- Pre-randomization: used in all subjects without unprovoked wound leak
- Post-randomization: used in all subjects to evaluate post-treatment leak
- Not currently commercially available

“Foot” which contacts the ocular surface

Maximum Force Line
Question for Panel Discussion

Wound leak assessment during the clinical study was conducted using the Calibrated Force Gauge (CFG), which is not commercially available. Do you believe current unavailability of the CFG raises safety or effectiveness concerns?
Secondary Effectiveness Outcomes

- Surgically induced corneal astigmatism (SIA) Day 28
  »ReSure: 0.600 ± 0.454 D
  »Suture: 0.597 ± 0.442 D

- BCVA worse than 20/40 at Day 1 and Day 28
  »15.8% for ReSure vs. 16.4% for Suture at Day 1
  »3.3% for ReSure vs. 3.9% for Suture at Day 28

- Test of superiority not met
Additional Effectiveness Assessments

- Presence of ReSure Sealant or suture(s)
- Presence of blue colorant visualization aid
- Device application ease of use
Additional Effectiveness Assessment: ReSure Sealant Persistence

• Duration:
  » 99% at 1 hour visit
  » 76.1% at Day 1
  » 31.3% at Day 3
  » 2.6% at Day 7
  » 0% at Day 14

• Adverse events (AEs) due to sloughing:
  » 1 foreign body with 95% ReSure sloughed from incision
  » 1 eye pain with ReSure lifted off corneal surface
Applicant’s Assessment of Adequacy of Duration of ReSure Persistence

• ReSure Sealant sloughed off (not present):
  » ~25% eyes before the Day 1 visit
  » ~70% eyes before the Day 3 visit

• ReSure adheres to de-epithelialized tissue, sloughs with re-epithelialization
  » Substantially reduces wound leak when incisions most vulnerable
  » Rarer to have wound leak after epithelium healed

• Literature search post-op wound leakage:
  » Corneal epithelial healing after radial keratotomy 12-48 hours
  » No reported incision leak after post-op Day 1 for uncomplicated clear corneal cataract surgery
Incision leaks were reported out to 7 days post-operative in the clinical study (one at Day 3 and two at Day 7). ReSure Sealant was present on 99% of eyes at 1 hour post-operative, 76.1% at Day 1, 31.3% at Day 3, 2.6% at Day 7, and 0% at Day 14 post-operative. Do you believe the duration of persistence observed in the clinical study is adequate for demonstration of effectiveness?
Safety Outcomes

- ReSure Sealant met ISO safety and performance endpoints (SPE*) rates for AEs

- Pre-specified Safety Endpoints:
  - Corneal Edema (moderate to severe stromal edema) at 1 Day:
    - 7.6% ReSure, 7.7% Suture, no significant difference
    - Superiority not demonstrated with regard to safety endpoints
  - Anterior Chamber (AC) Inflammation (≥grade 2+ AC cells) at 1 Day:
    - 9.5% ReSure eyes, 9.8% suture eyes
    - Since test of superiority for first endpoint did not achieve statistical significance, test of superiority not performed for second endpoint

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

- Ocular AEs per ISO SPE
- Ocular symptoms per Ocular Comfort Index (OCI)
- Hypotony due to wound leak
- Peripheral corneal edema affecting visual acuity
- Surgical re-intervention for management of wound leak
- BCVA and manifest refraction*
- SIA*
- IOP*
- Slit lamp findings
- Wound integrity/healing within normal limits (at 7 and 28 day visit)

*except at day 14 and day 21
### Additional Safety Assessment Outcomes

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>ReSure Sealant (N=304)</th>
<th>Suture (N=183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Major or Serious Adverse Ocular event</td>
<td>5 (1.6%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Surgical re-intervention for wound leak management</td>
<td>1 (0.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypotony due to wound leak</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Peripheral corneal edema affecting visual acuity</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Any Adverse Ocular event</td>
<td>69 (22.7%)</td>
<td>83 (45.4%)</td>
</tr>
</tbody>
</table>
Ocular Comfort Index (OCI) Questionnaire

- Assessment of ocular irritation/discomfort
  - dryness, grittiness, stinging, tiredness, pain, itching
- Screening visit, postop visit Days 1-7, 14, 21 and 28
- Masked administration
- Scores
  - Range 0-6 units individual symptom components
  - Range 0-100 units OCI overall score
    - Change ≥3 units regarded as an estimate of a minimally important treatment difference by OCI authors*

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

Overall Mean Scores

<table>
<thead>
<tr>
<th>Visit</th>
<th>ReSure Sealant (N=304)</th>
<th>Suture (N=183)</th>
<th>Difference in Means (Suture – ReSure) and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>20.42</td>
<td>20.62</td>
<td>0.20 (-2.31, 2.70)</td>
</tr>
<tr>
<td>Day 1</td>
<td>28.96</td>
<td>26.32</td>
<td>-2.63 (-4.82, -0.45)</td>
</tr>
<tr>
<td>Day 2</td>
<td>25.00</td>
<td>23.17</td>
<td>-1.83 (-4.13, 0.47)</td>
</tr>
<tr>
<td>Day 3</td>
<td>22.88</td>
<td>20.67</td>
<td>-2.21 (-4.64, 0.22)</td>
</tr>
<tr>
<td>Day 4</td>
<td>20.26</td>
<td>19.32</td>
<td>-0.94 (-3.36, 1.47)</td>
</tr>
<tr>
<td>Day 5</td>
<td>18.61</td>
<td>17.97</td>
<td>-0.64 (-3.12, 1.83)</td>
</tr>
</tbody>
</table>

- Similar scores ReSure and Suture at all visits
  » Marginally higher for ReSure post-op Days 1-5 (marginally more discomfort)
- Minor increase in discomfort in both groups early post-op
- Overall OCI scores return to baseline by Day 4
OCI Individual Component Mean Scores

• Higher mean score for ReSure group:
  » “Grittiness” on Day 1
  » “Itching” on Day 1 and Day 2

• No difference in mean score reported for other OCI components at any visit
Mean OCI Scores: Stratification by Pain Medication Use Prior to Visit

- 81 mg aspirin:
  - ≥3 points higher in ReSure subjects than Suture subjects on post-op Days 1-5 (more discomfort)

- No pain medication:
  - No clinically relevant difference

- >81 mg aspirin or any prohibited pain medication:
  - No clinically relevant difference through Day 21
  - 3.7 points lower for ReSure group on Day 28
Question for Panel Discussion

Overall mean Ocular Comfort Index (OCI) scores were higher for the ReSure group at post-operative Day 1 through Day 5, consistent with more discomfort in the first several days following the procedure. In addition, sub-group analyses to isolate the effect of pain medications revealed that ReSure subjects who took 81 mg aspirin experienced more discomfort than Suture subjects who took the same dose. How do these outcomes impact the assessment of reasonable assurance of safety?
### Number of ReSure Applications

<table>
<thead>
<tr>
<th>Number of applications</th>
<th>% of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.7</td>
</tr>
<tr>
<td>2</td>
<td>42.0</td>
</tr>
<tr>
<td>3</td>
<td>24.9</td>
</tr>
<tr>
<td>4</td>
<td>10.5</td>
</tr>
<tr>
<td>5</td>
<td>3.6</td>
</tr>
<tr>
<td>6</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>0.7</td>
</tr>
<tr>
<td>8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

- Multiple applications required for the majority of subjects
- Package contains sufficient material for 2 applications
Impact of Number of Applications on Incision Leakage

![Bar chart showing the impact of ReSure Sealant Applications on incision leakage. The chart indicates that the percentage of incision leak increases with the number of applications, with the highest percentage observed at 5 applications (n=11).](image)

number of reSure sealant applications
Number of ReSure Packages Used

- ReSure Sealant package contains 2 applications

- 459 packages used for 305 subjects:
  - 59.7% - 1 package
  - 35.4% - 2 packages
  - 3.6% - 3 packages
  - 1% - 4 packages

40% required >1 package
Impact of Number of Packages Used on Incision Leak Rate

- Use of >1 package (>2 applications) of ReSure may not be as effective
  - 6.7% incision leak rate for >1 package (>2 applications)
  - 2.3% incision leak rate for 1 package (1-2 applications)
Question for Panel Discussion

The ReSure Sealant package configuration allows for two applications. However, multiple sealant applications (i.e., requiring more than one package) were required in 40% of ReSure subjects. In addition, wound leak rates were higher in subjects receiving >2 applications of ReSure Sealant compared to those receiving 2 or fewer applications (6.7% vs. 2.3%). How do these data impact the assessment of reasonable assurance of effectiveness for ReSure Sealant?
Statistical Considerations in PMA P130004
ReSure® Sealant

Rajesh Nair, Ph.D.
Statistician
Division of Biostatistics
Office of Surveillance and Biometrics
FDA/CDRH
September 19, 2013
Outline

• Study design and statistical analysis plan
• Main results
• Consistency of treatment effect across subgroups
Study Design

• Treatment groups and randomization scheme
  » 488 subjects randomized after confirmation of leaking incision post IOL implantation
  » 5:3 randomization to ReSure Sealant (treatment) or Sutures (control)
  » Randomization stratified by incision leak category (with/out provocation) and investigational site
## Analysis Populations

- Protocol specified analysis populations
  - Intent-to-Treat (ITT): All randomized subjects
  - Per-Protocol (PP): All randomized subjects with no major protocol deviations
  - Safety population (SP): All treated subjects

<table>
<thead>
<tr>
<th></th>
<th>Suture</th>
<th>ReSure Sealant</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>183</td>
<td>305</td>
</tr>
<tr>
<td>PP</td>
<td>176</td>
<td>295</td>
</tr>
<tr>
<td>SP</td>
<td>183</td>
<td>304</td>
</tr>
</tbody>
</table>
Analysis Populations

• Analysis of the primary effectiveness endpoint:
  » PP population

• Missing data handling
  » No imputation of missing data pre-specified
  » No sensitivity analyses pre-specified
Primary Effectiveness Endpoint

• Proportion of subjects with clear corneal incision leakage within the first 7 days after surgery

• Objective - Demonstrate non-inferiority of ReSure to Suture

• Hypothesis (Non-inferiority)

\[ H_0 : \pi_T \geq \pi_C + \delta \]
\[ H_1 : \pi_T < \pi_C + \delta \]

\[ \delta = 5\% \text{ is non-inferiority Margin} \]

» One-sided type I error rate of 0.05
Primary Effectiveness Endpoint

- Superiority claim
  - If non-inferiority objective met, testing for superiority was pre-specified
    \[
    H_0 : \pi_T = \pi_C \\
    H_1 : \pi_T \neq \pi_C
    \]
  - Two-sided type I error rate of 0.05
## Primary Effectiveness Endpoint Results

<table>
<thead>
<tr>
<th></th>
<th>Suture (n=176)</th>
<th>ReSure Sealant (n=295)</th>
<th>P-value (non-inferiority)</th>
<th>P-value (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision Leak</td>
<td>60</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% with Incision Leak</td>
<td>34.1%</td>
<td>4.1%</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Primary effectiveness endpoint was met
Primary Effectiveness Endpoint: Stratification by Leak Category

- No treatment by leak category interaction detected

<table>
<thead>
<tr>
<th>Unprovoked</th>
<th>Provoked</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=147</td>
<td>n=148</td>
</tr>
<tr>
<td>n=89</td>
<td>n=87</td>
</tr>
</tbody>
</table>
FDA Analysis of Missing Data and Worst Case Scenario

- Missing Data (ITT population)
  - 8 ReSure subjects
  - 7 Suture subjects

<table>
<thead>
<tr>
<th></th>
<th>Suture (n=183)</th>
<th>ReSure Sealant (n=305)</th>
<th>P-value (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with Incision Leak</td>
<td>32.8%</td>
<td>6.6%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

- Results robust to missing data
Subgroup Analyses

- Subgroup analyses not proposed in protocol
- Post-submission subgroup analyses:
  - Gender
  - Age
- Consistency of results across gender and age groups
Primary Effectiveness Endpoint by Gender

- **Female**
  - ReSure: n=163
  - Suture: n=101

- **Male**
  - ReSure: n=132
  - Suture: n=75

% Incision Leak

- Female: 35%
- Male: 35%
Primary Effectiveness Endpoint Across Age Groups

- Treatment appears to be less effective in subjects older than 80 years.
Question for Panel Discussion

In subjects ≥80 years, the observed incisional leak rate was 13% (3/23) for ReSure Sealant and 17.6% (3/17) for Suture. For subjects <80 years it was 3.3% (9/272) for ReSure Sealant and 35.9% (57/159) for Suture. Do you believe the current data warrant one of the following:

a) Limitation of IFU to patients <80 years of age?
b) Precaution about potential for reduced effectiveness in subjects ≥80 years?
c) Further investigation in the post-market setting?
Secondary Effectiveness Endpoints

• Objective
  » Demonstrate superiority of ReSure to Suture

• Hierarchical testing of secondary effectiveness endpoints:
  1) Mean SIA at Day 28 visit
  2) Proportion of eyes with BCVA worse than 20/40 at Day 1
  3) Proportion of eyes with BCVA worse than 20/40 at Day 28

• Analysis of secondary effectiveness endpoints:
  » ITT population
Secondary Effectiveness Endpoints Results

• SIA at Day 28 visit
  » Suture (n=177): 0.597 ± 0.442 D
  » ReSure (n=288): 0.600 ± 0.454 D

• BCVA worse than 20/40
  » Day 1
    ▪ Suture (n=183): 16.4%
    ▪ ReSure (n=304): 15.8%
  » Day 28
    ▪ Suture (n=180): 3.9%
    ▪ ReSure (n=300): 3.3%
Secondary Effectiveness Endpoints Results

• Secondary effectiveness endpoints not met
  » P-value = 0.80 for SIA
  » Statistical significance not tested for BCVA at Days 1 and 28
Safety Assessments

• Study powered to detect AE rates of 1% as recommended in ISO SPE* (“FDA grid”)
  » ReSure Sealant met SPE rates for AEs

• Pre-specified safety endpoints:
  1) Proportion of eyes with corneal edema at Day 1
  2) Proportion of eyes with AC inflammation at Day 1
    » Objective - Demonstrate superiority of ReSure to Suture
    » Hierarchical testing of safety endpoints

• Analysis of safety endpoints: SP population

---

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

<table>
<thead>
<tr>
<th>Safety Endpoints (Day 1)</th>
<th>Suture (n=183)</th>
<th>ReSure Sealant (n=304)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal Edema</td>
<td>7.7%</td>
<td>7.6%</td>
<td>1.000</td>
</tr>
<tr>
<td>AC Inflammation</td>
<td>9.8%</td>
<td>9.5%</td>
<td></td>
</tr>
</tbody>
</table>

- Superiority not demonstrated
The study met the ISO Safety and Performance Endpoints (SPE) rate. However, it did not meet pre-specified safety endpoints meant to establish superiority of ReSure compared to Suture. The percent of subjects with corneal edema were 7.6% and 7.7% at Day 1 for ReSure and Suture respectively, and those with anterior chamber inflammation were 9.5% and 9.8%, respectively. Do these outcomes raise a safety concern?
Summary

• Effectiveness
  » Pre-specified non-inferiority primary effectiveness endpoint met:
    ▪ Pre-specified superiority criterion met
    ▪ Results robust to missing data
  » ReSure Sealant may be less effective in subjects older than 80 years

• Safety
  » Superiority not demonstrated for pre-specified safety endpoints
  » AE rates consistent with ISO SPE
Post-Approval Study (PAS) Considerations in PMA P130004

Youlin Qi, M.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Biometrics
September 19, 2013
Reminder

• The inclusion of PAS questions should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

• The presence of a PAS plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits.

• The premarket data must reach the threshold for providing reasonable assurance of safety and benefit before the device can be found approvable and any PAS could be considered.
General Principles for PAS

• Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.

• PAS should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.
Need for PAS

• Gather postmarket information
  » Long-term performance including effects of re-treatments & device changes
  » Real-world device performance (patients and clinicians)
  » Effectiveness of training programs
  » Sub-group performance
  » Outcomes of concern (safety and effectiveness)

• Account for Panel recommendations
PAS Components

• Fundamental study question or hypothesis
• Safety endpoints and methods of assessment
• Acute and chronic effectiveness endpoints and methods of assessment
• Duration of follow-up
Important Postmarket Issues

• Evaluation of the safety profile in the real world device experience,
• Estimating AE rates in the postmarket setting.
# Applicant Proposed PAS Outline

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Prospective multicenter registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>At least 760 sequentially-enrolled patients from up to 40 centers in the United States</td>
</tr>
</tbody>
</table>
| Primary AE Endpoints | • AC cells greater than level 1+ persisting at Visit 2  
• Raised IOP (IOP ≥ 30 mmHg or 10 mmHg over baseline)  
• Posterior vitreous detachment  
• Eye pain  
• Foreign body sensation  
• Endophthalmitis |
### Outline for Proposed PAS (cont’d)

<table>
<thead>
<tr>
<th>Follow-up Schedule</th>
<th>Visit 1: Day 1 to Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 2: Day 20 to Day 40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Statistical Analysis &amp; Precision</th>
<th>• 1-sided upper 95% confidence intervals (CI) will be calculated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Distance from estimated AE rate to the upper 95% CI will be ≤1.5% for AEs of 5% or less</td>
</tr>
</tbody>
</table>
FDA Assessment - PAS Outline

• Should a PAS be needed, the proposal is viable for:
  » Sample size
    ▪ Sufficient to capture AEs with rates of 5% or more
  » Follow-up duration
    ▪ Sufficient for the currently proposed endpoints
Questions for Panel Discussion

A. Please discuss the need for a Post-Approval Study (PAS) to evaluate device performance; and if needed,

B. Please discuss whether the proposed safety endpoints for the PAS (listed below) are adequate. If not, how should they be modified?

- Anterior chamber cells greater than level 1+ persisting at Visit 2
- Raised IOP (IOP ≥ 30 mmHg or 10 mmHg over baseline)
- Posterior vitreous detachment
- Eye pain
- Foreign body sensation
- Endophthalmitis

C. Please discuss if there are any additional considerations that need to be taken into account for the PAS.
Back Up Slides
# Primary Effectiveness Endpoint across Age Groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ReSure</th>
<th>Suture</th>
<th>Difference in % (Suture - ReSure) and 95% CI</th>
<th>Difference in % and 95% CI adjusted for multiplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60 Years</td>
<td>2/46</td>
<td>6/32</td>
<td>14.4 (-0.3, 29.2)</td>
<td>14.4 (-4.4, 33.2)</td>
</tr>
<tr>
<td>60-69 Years</td>
<td>6/114</td>
<td>29/66</td>
<td>38.7 (26.0, 51.3)</td>
<td>38.7 (22.5, 54.8)</td>
</tr>
<tr>
<td>70-79 Years</td>
<td>1/112</td>
<td>22/61</td>
<td>35.2 (23.0, 47.3)</td>
<td>35.2 (19.7, 50.7)</td>
</tr>
<tr>
<td>80+ Years</td>
<td>3/23</td>
<td>3/17</td>
<td>4.6 (-18.2, 27.4)</td>
<td>4.6 (-24.4, 33.6)</td>
</tr>
</tbody>
</table>
Incision leak rate by force required to provoke leak pre-randomization

Unprovoked Leak

<table>
<thead>
<tr>
<th>Force required to provoke leak (post-randomization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Line</td>
</tr>
<tr>
<td>% incision leak</td>
</tr>
</tbody>
</table>

ReSure (n=151)

Suture (n=93)

Provoked (1 Line) Leak

<table>
<thead>
<tr>
<th>Force required to provoke leak (post-randomization)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Line</td>
</tr>
<tr>
<td>% incision leak</td>
</tr>
</tbody>
</table>

ReSure (n=85)

Suture (n=42)

Provoked (2 Line) Leak

<table>
<thead>
<tr>
<th>% incision leak</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Line</td>
</tr>
</tbody>
</table>

ReSure (n=42)

Suture (n=21)

Provoked (3 Line) Leak

<table>
<thead>
<tr>
<th>% incision leak</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Line</td>
</tr>
</tbody>
</table>

ReSure (n=21)

Suture (n=22)
# Incision Length (mm)

<table>
<thead>
<tr>
<th></th>
<th>ReSure Sealant</th>
<th>Suture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leak</td>
<td>No Leak</td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>12</td>
<td>285</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>2.68</td>
<td>2.70</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>0.27</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Minimum - Maximum</strong></td>
<td>2.4 – 3.2</td>
<td>1.9 – 3.5</td>
</tr>
</tbody>
</table>
Impact of number of packages and patient age on the primary endpoint

<table>
<thead>
<tr>
<th>Subject Age</th>
<th>1 package</th>
<th>&gt;1 package</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80 years</td>
<td>5.88% (1/17)</td>
<td>28.6% (2/7)</td>
</tr>
<tr>
<td>70-79 years</td>
<td>1.45% (1/69)</td>
<td>0% (0/43)</td>
</tr>
<tr>
<td>60-69 years</td>
<td>1.52% (1/66)</td>
<td>10.2% (5/49)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>4% (1/25)</td>
<td>4.76% (1/21)</td>
</tr>
</tbody>
</table>