ANSI Standard for Implantable Glaucoma Devices: A Framework for Clinical Evaluation

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Utility of Standards in the Regulatory Process

- FDA has worked with American National Standards Institute (ANSI) since 1980’s
- FDA Recognized Standards
  - Consensus standards that satisfy a regulatory requirement
  - Published notice in the Federal Register
    (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm)
  - 36 recognized ophthalmic standards
- Help assure consistency & predictability
- Reduce data reporting requirements in PMA
- Result in decreased review time
Draft ANSI Z80.27 Standard for Implantable Glaucoma Devices

- **Scope**: Applies to devices which are implanted in the eye to treat glaucoma by facilitating aqueous outflow

- **Purpose**: To describe the physical, mechanical and biocompatibility properties, as well as the elements of clinical protocols that may be useful in assessing the clinical performance of these devices
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Clinical Trial Recommendations

• Enrollment criteria, sample size, length of follow-up, & clinical evaluations vary by intended target:
  – “Refractory” glaucoma
  – ”Non-refractory” glaucoma

• Analyses & adverse events similar for both
Refractory Glaucoma*

Eyes with glaucoma that are uncontrolled by medical therapy & that meet at least one of the following criteria:

- Failed one or more incisional intraocular glaucoma surgeries (e.g., glaucoma filtering surgery or tube shunt)
- Failed one or more cilioablative procedures (e.g., cryotherapy or cyclodiode therapy)
- Have neovascular glaucoma
- Have any other condition (e.g., conjunctival scarring, uveitis) in which a conventional incisional glaucoma surgery like trabeculectomy would be more likely to fail than for an eye with uncomplicated primary open-angle glaucoma (POAG)

*Draft ANSI Z80.27 American National Standard for Ophthalmics Implantable Glaucoma Devices
Non-refractory Glaucoma*

Eyes diagnosed with glaucoma which

• Do not meet any of the criteria for refractory glaucoma

• +/- treated with medications or laser trabeculoplasty

• May be candidates for medical therapy, laser treatment, and glaucoma filtering surgery (Sx)

• May have undergone uncomplicated cataract Sx, retinal laser, or extraocular muscle Sx

*Draft ANSI Z80.27 American National Standard for Ophthalmics Implantable Glaucoma Devices
Draft ANSI Recommendations: Refractory Glaucoma

Inclusion Criteria:

- Minimum (min) & maximum (max) IOP
- Max degree of visual field (VF) restriction in non-study eye
- Type of glaucoma
  - POAG
  - Narrow-angle glaucoma
  - Secondary glaucoma
    - Pseudoexfoliation
    - Pigmentary
    - Uveitic
    - Neovascular
Draft ANSI Recommendations: Refractory Glaucoma

Exclusion Criteria:

- No light perception (NLP)
- Need for combined procedure or anticipated need for ocular surgery or retinal laser within follow-up period
- Best corrected visual acuity (BCVA) worse than 20/200 in non-study eye
- Conditions and medications that could confound the outcome or ↓ patient safety (should be specified)
- Inadequate space in anterior chamber and/or angle for safe device placement, as applicable
Draft ANSI Recommendations: Refractory Glaucoma

Clinical Evaluations:

• BCVA
• Applanation tonometry; Central Corneal Thickness; Diurnal IOP assessment
• Motility
• Gonioscopy
• Slit lamp exam; Lens status (for phakic eyes)
• Vertical cup-to-disc ratio; Optic nerve imaging
• Dilated fundus exam
• Perimetry
• Validated patient questionnaire: pain/discomfort, foreign body sensation, droopy eyelid, dry eye, tearing, red eye, device’s impact on health-related quality of life, depression
Draft ANSI Recommendations: Refractory Glaucoma

• # Subjects (= eyes): minimum of 50 evaluable investigational device subjects at final time point

• Follow-up: minimum of 12 months

• Specify criteria for concomitant intraocular-pressure (IOP)-lowering interventions:
  – Stopping and starting medications
  – Laser treatment
  – Surgery
Draft ANSI Recommendations: Non-refractory Glaucoma

Inclusion Criteria:

- Min & max IOP
- Max degree of VF restriction of fellow eye
- Type of glaucoma
  - POAG
  - Narrow-angle glaucoma
  - Secondary glaucoma
- Criteria for confirming diagnosis of glaucoma – VF defects & nerve abnormalities
- Min endothelial cell density based on age at time of enrollment
Exclusion Criteria:

- Ocular hypertension; Known corticosteroid responder
- Complicated cataract surgery
- NLP; BCVA worse than 20/80 in the non-study eye
- Degenerative visual disorders (e.g., macular degeneration or other retinal disorders)
- Non-laser retinal surgery/ scleral buckling; History of silicone oil
- Corneal surgery (except LASIK), opacity, or disease; CCT > 620 μ
- Iris neovascularization; Proliferative retinopathy
- Chronic or recurrent uveitis
- Iridocorneal endothelial syndrome; Epithelial or fibrous downgrowth
- Need for combined procedure or anticipated need for ocular surgery or retinal laser
Draft ANSI Recommendations: Non-refractory Glaucoma

Clinical Evaluations:

• Same as for Refractory
• Specular microscopy
  – All subjects enrolled in initial phase
  – Additional subjects based on data from initial phase & risk analysis
Draft ANSI Recommendations: Non-refractory Glaucoma

• # Subjects (= eyes): minimum 300 evaluable investigational device subjects for safety at final time point
• Follow-up: 24 months recommended*
• Concomitant IOP-lowering interventions:
  – Specify criteria for stopping and starting medications, laser treatment, surgery
  – “Washout” all topical IOP-lowering meds before the baseline visit and before or at 1° endpoint visit window should be considered

*length dependent upon risk analysis (min 12 mo.; > 24 mo. may be needed)
Draft ANSI Recommendations: Refractory & Non-refractory Analyses:

- Subject accountability
- Safety analyses
- Efficacy analyses
- Additional analyses of interest
Draft ANSI Recommendations: Refractory & Non-refractory

Safety Analyses:

• % eyes ≥ 2 lines* BCVA loss at the final visit compared to baseline
• If + cataract surgery, % eyes ≥ 2 lines* BCVA loss at the final visit compared to the best Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA recorded at any visit during the study
• Incidence of lens opacities or worsening of pre-existing lens opacities (phakic eyes only)
• Endothelial cell density changes
• Rates of adverse events (intraoperative complications and postoperative adverse outcomes)

*10 or more ETDRS letters
Draft ANSI Recommendations: Refractory & Non-refractory

Adverse Events:

- Corneal edema
- Progression of cataract requiring cataract extraction
- Wound leak
- Suture abscess or other local infection
- Endophthalmitis
- Chronic iritis
- Hyphema
- Strabismus
- Macular edema
- Vitreous hemorrhage
- Suprachoroidal hemorrhage
Draft ANSI Recommendations: Refractory & Non-refractory Adverse Events (cont.):

- Retinal detachment
- Device malfunction; Tube blockage requiring surgical revision
- Implant migration requiring surgical revision; Implant migration (of any kind); Implant exposure or extrusion
- Flat anterior chamber requiring anterior chamber reformation
- **Hypotony (IOP < 6 mmHg)**
- Hypotony maculopathy
- Choroidal effusion requiring surgical drainage
- **Substantial increase in IOP vs. baseline**
- **Substantial visual field loss vs. baseline (e.g., 10 db loss)**
- Event requiring unplanned ocular surgical re-intervention*

*definition based on population characteristics and study duration
Draft ANSI Recommendations: Refractory & Non-refractory

Efficacy Analyses:

- Change # ocular hypotensive medications (meds) from preoperative (preop)
- Distribution % reduction in mean diurnal IOP from baseline*
- Changes in mean diurnal IOP*
- Box-plots of mean diurnal IOP measurements at baseline, each annual postoperative (postop) visit, and at the primary effectiveness time point
- Scatter plots of postop IOP as a function of preop IOP (If washout is not possible, distinguishing postop IOP with meds vs. IOP without meds)

* If postop “washout” not possible, stratify by postoperative med status (e.g., equal or lower # of meds vs. those on a greater number of meds)
Draft ANSI Recommendations: Refractory & Non-refractory

Efficacy Analyses (cont.):

• Survival analyses (e.g., time to first IOP-lowering interventions, such as 2° surgery, laser procedure, or additional medication, except for those meds discontinued at or by a predetermined postop period)
  – Perform one analysis with a single outcome which includes all intervention categories
  – Repeat the analysis excluding the medication intervention category

• Stratification of the above analyses by certain baseline patient characteristics (e.g., IOP and number of medications) as well as by postop medication status
Draft ANSI Recommendations: Refractory & Non-refractory

Additional Analyses:

• Change in patient-reported outcomes (patient questionnaire) from baseline
Draft ANSI Standard: Limitations for MIGS Devices

- Definition of minimally invasive glaucoma surgery (MIGS) implantable devices
- Appropriate patient population
- Safety:
  - 1° & 2° endpoints
  - some adverse events ambiguous
- Effectiveness:
  - 1° & 2° endpoints
  - composite endpoints?
  - study success