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

Draft ANSI Z80.27 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

Draft ANSI Recommendations: Non-refractory Glaucoma

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