P170040
Refocus Group, Inc.
VisAbility™ Micro Insert System

LT Charles Chiang
PMA Team Leader
Division of Ophthalmic Devices
FDA/CDRH/OPEQ/OHT1

November 9, 2020

FDA Review Team

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Device Description

The VisAbility™ Micro Insert System:

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- VisAbility Micro Insert: a scleral implant

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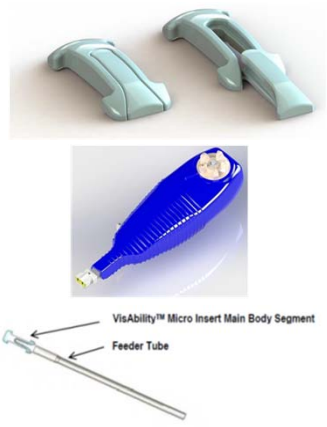
- VisAbility Micro Insert: a scleral implant
- VisAbility Scleratome: a surgical instrument to create scleral tunnel incisions

Device Description

The VisAbility™ Micro Insert System:

- VisAbility Micro Insert: a scleral implant
- VisAbility Scleratome: a surgical instrument to create scleral tunnel incisions
- VisAbility Feeder Tube: tubing used to place the insert in the scleral tunnel



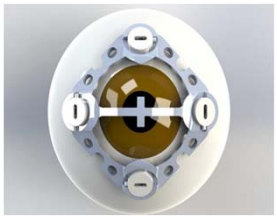
Device Description

The VisAbility™ Micro Insert System:

- VisAbility Micro Insert: a scleral implant
- VisAbility Scleratome: a surgical instrument to create scleral tunnel incisions
- VisAbility Feeder Tube: tubing used to place the insert in the scleral tunnel

In addition, a Docking Station is used in conjunction with the system.

Device Description



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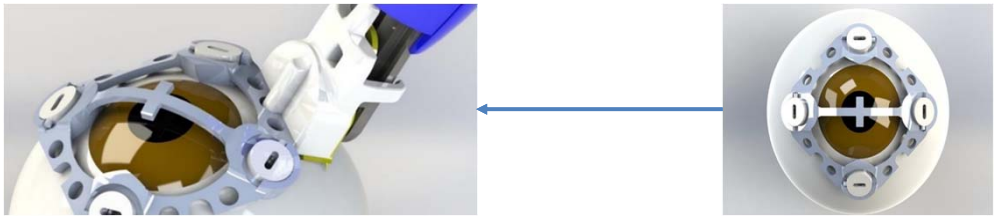

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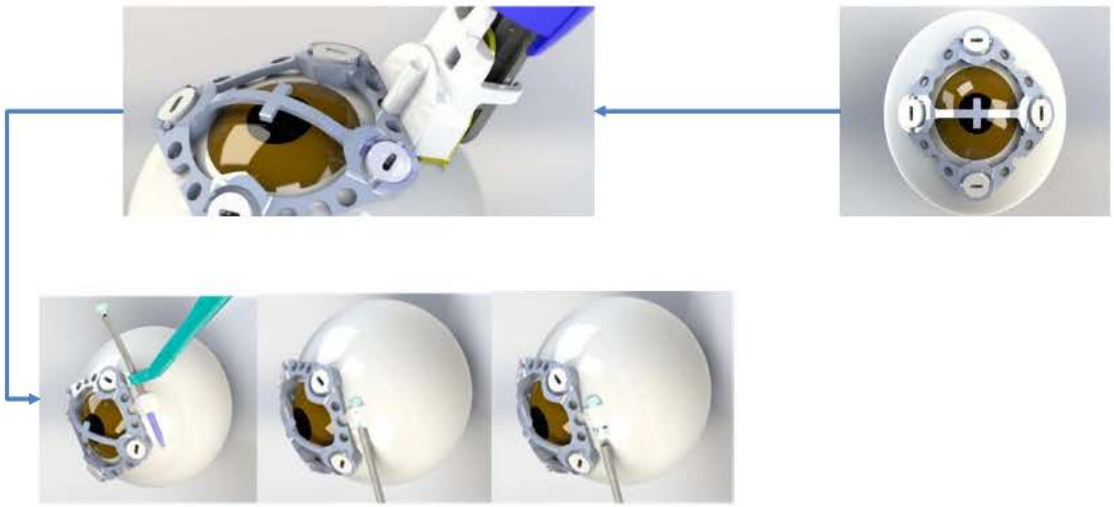

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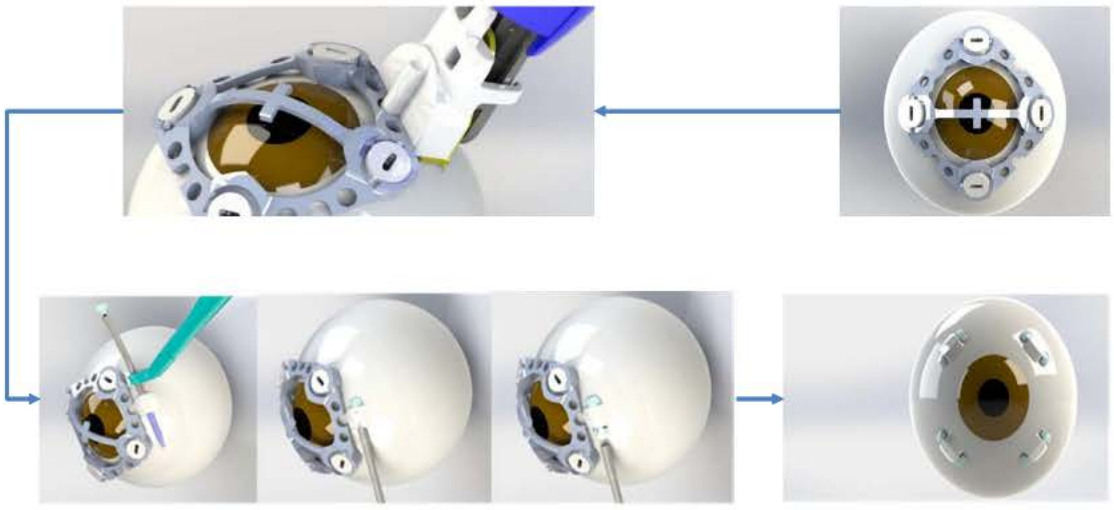


FDA believes scientific basis of mechanism of action not established

Target Condition and Available Treatment Options

- Presbyopia occurs naturally as you age (with the loss of accommodation) and results in the inability to focus up close.
- Approved available treatment options for presbyopia include the following:
  - Glasses
    - Trifocals, bifocals, progressive lenses, and monovision lenses (prescription glasses and over-the-counter readers)
  - Contact lenses
    - Multifocal contact lenses and CL monovision therapy (i.e., one eye corrected for far vision and the other corrected for near vision)
  - Corneal inlays[1]
  - Conductive keratoplasty[2]

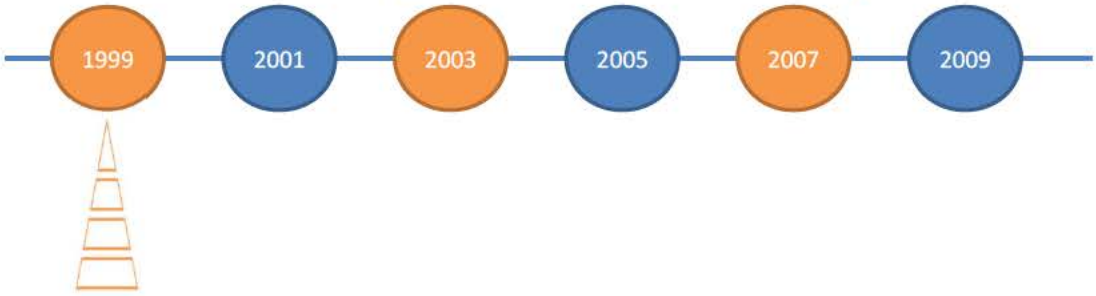
1 - https //www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma cfm?id=P150034, https://www accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P120023
2 - https //www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma cfm?id=P010018S005

VisAbility Micro Insert System: Experience Outside of U.S.

- CE Mark - 2005
- One commercial site - Ireland
- With exception of the one commercial site – No additional commercial sales

Regulatory History

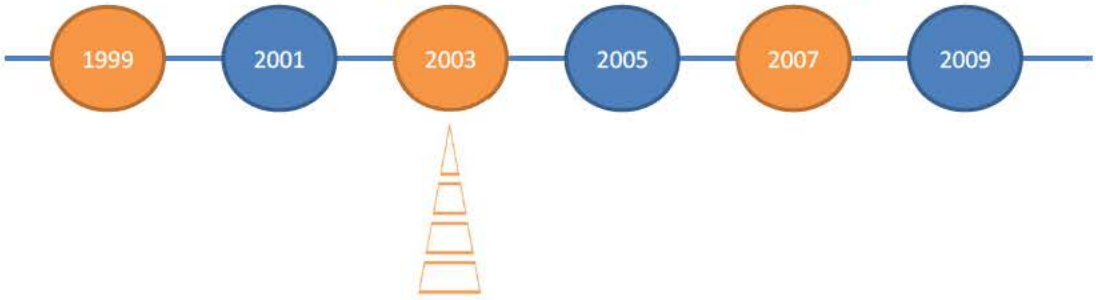
Regulatory History



March 1999 – (b) (4) Feasibility Study IDE Approved

- PresVIEW Scleral Implant (PSI) Model PSI-001

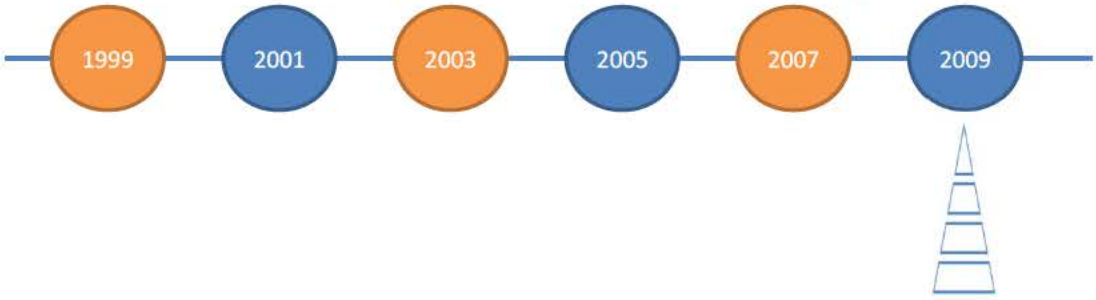
Regulatory History



December 2003 – (b) (4) Pivotal IDE Approved

- PSI Model PSI-001

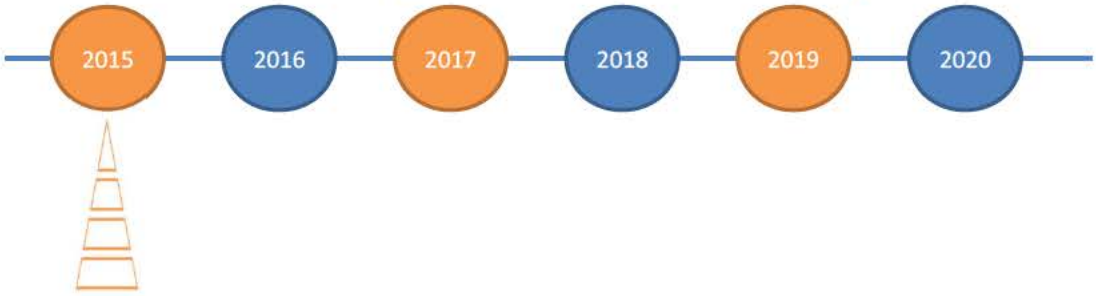
Regulatory History



June 2009 – (b) (4) Pivotal IDE Approved

- PSI Model SGP-046

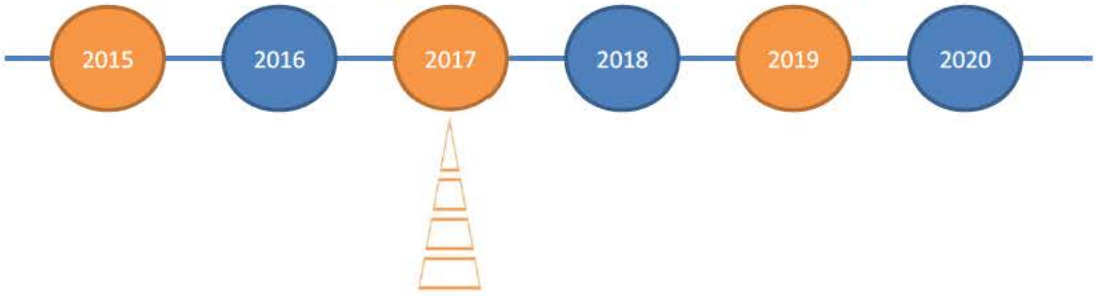
Regulatory History



January 30, 2015 – (b) (4) Protocol VIS-2014 IDE Approved

- 24 month study

Regulatory History



December 15, 2017 – P170040 Submitted

- Indications for Use (Original): The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to **1.00 D of refractive cylinder** in both eyes, and require a minimum near correction of at least +1.25 D reading add.
- **12 months of follow-up**
- Most subjects did not reach 24 months of follow-up

Regulatory History

March 15, 2018 – P170040 "Major Deficiencies" Letter

Regulatory History

March 15, 2018 – P170040 "Major Deficiencies" Letter

June 18, 2018 – P170040/A003 Response to FDA "Major Deficiencies" Letter

Regulatory History

March 15, 2018 – P170040 "Major Deficiencies" Letter

June 18, 2018 – P170040/A003 Response to FDA "Major Deficiencies" Letter

August 15, 2018 – (b) (4) VIS-2014-5YR IDE Approval

- **Extending f/up of PMA Cohort subjects to 60 months**
- **36 months beyond original 24 months f/up**
- **Trial is still on-going**

Regulatory History

March 15, 2018 – P170040 "Major Deficiencies" Letter

June 18, 2018 – P170040/A003 Response to FDA "Major Deficiencies" Letter

August 15, 2018 – (b) (4) VIS-2014-5YR IDE Approval

September 12, 2018 – P170040 and P170040/A003 "Not Approvable Letter"

Regulatory History

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June 18, 2018 – P170040/A003 Response to FDA "Major Deficiencies" Letter

August 15, 2018 – (b) (4) VIS-2014-5YR IDE Approval

September 12, 2018 – P170040 and P170040/A003 "Not Approvable Letter"

- **Safety Concerns**
  - **Scleral perforations**
  - **Anterior segment ischemia (ASI)**
  - **Secondary surgical interventions (SSI)**

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- Safety Concerns
  - Scleral perforations
  - Anterior segment ischemia (ASI)
  - Secondary surgical interventions (SSI)
- **Effectiveness Concerns**
  - **Study success criteria not met**
  - **Wavefront aberrometry - no clinically significant changes per applicant**
  - **Defocus curve - no clinically significant changes per FDA**

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  - Defocus curve - no clinically significant changes per FDA
- **FDA did not believe benefits outweighed the risks**

Regulatory History

April 26, 2019 – P170040/A005 Response to September 15, 2018 "Not Approvable" Letter

- Indications for Use (IU Cohort): The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years who meet the following criteria in both eyes: manifest spherical equivalent between -0.75D and +0.50D, **refractive astigmatism less than or equal to 0.75 D**, minimum near add at least +1.25D **and scleral thickness between 530 and 680 microns**.
- 12 and **24 months of follow-up (Original and IU Cohorts)**

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October 22, 2019 – P170040/A005 IU Cohort "Not Approvable" Letter

Regulatory History

October 22, 2019 – P170040/A005 IU Cohort "Not Approvable" Letter

- IU Cohort
  - Reduction of 0.25D refractive astigmatism
  - Limiting scleral thickness to 530-680 µm
- **<u>Safety Concerns</u> – No reduction in risk (scleral perforations, ASI, SSI)**

Regulatory History

October 22, 2019 – P170040/A005 IU Cohort "Not Approvable" Letter

- IU Cohort
  - Reduction of 0.25D refractive astigmatism
  - Limiting scleral thickness to 530-680 µm
- Safety Concerns – No reduction in risk (scleral perforations, ASI, SSI)
- **Effectiveness Concerns**
  - **First co-primary endpoint met - Post-hoc analysis**
    - **Measurement based on distance corrected near visual acuity (DCNVA) - not clear why reduction of 0.25 D of astigmatism should impact endpoint**
  - **Wavefront Aberrometry – No clinically significant changes per applicant**
  - **Defocus Curve - No clinically significant changes per FDA**

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- 12 and **24 months of follow-up (Original and IU Cohorts)**

October 22, 2019 – P170040/A005 IU Cohort "Not Approvable" Letter

November 21, 2019 – Appeal of P170040/A005 October 22, 2019 "Not Approvable" Letter

Regulatory History

January 17, 2020 – Appeal Decision

- **October 22, 2019 "Not Approvable" decision set aside, file re-opened for review, and referred to the Ophthalmic Devices Advisory Panel**

Regulatory History

January 17, 2020 – Appeal Decision

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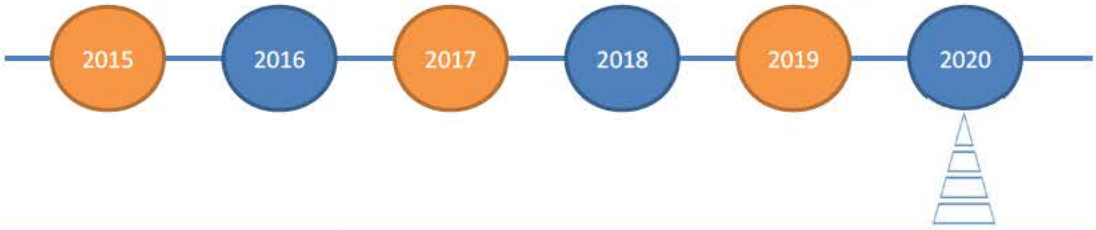
February 4, 2020 – Applicant's Request to Revise IFU for Panel Consideration

- Indications for Use: The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to **1.00 D of refractive cylinder** in both eyes, and require a minimum near correction of at least +1.25 D reading add.
- **12 and 24 months** of follow-up

Regulatory History



August 31, 2020 – (b) (4) VIS-2014-5YR Report

Eyes/Subjects Examined at Each Visit in VIS-2014-5YR			
	36 Months	48 Months	60 Months
Eyes Available	**368**	**519**	**132**
Enrolled In Visit Period	368	188	0
Attended Prior Visit	n/a	331	132
Subjects Available	**186**	**263**	**67**
Enrolled In Visit Period	186	96	0
Attended Prior Visit	n/a	167	67

Regulatory History

November 9, 2020 – P170040 Ophthalmic Devices Advisory Committee Meeting

Non-Clinical

- Biocompatibility
- Sterilization, packaging, and shelf-life
- Physico-chemical and mechanical bench testing
- Human factors
- Manufacturing
  - ongoing

Rationale for Meeting

To solicit Panel's opinion on:

- Safety and effectiveness, and
- Do Benefits outweigh Risk for the proposed IFU:

> The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.

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VisAbility™ Micro Insert System

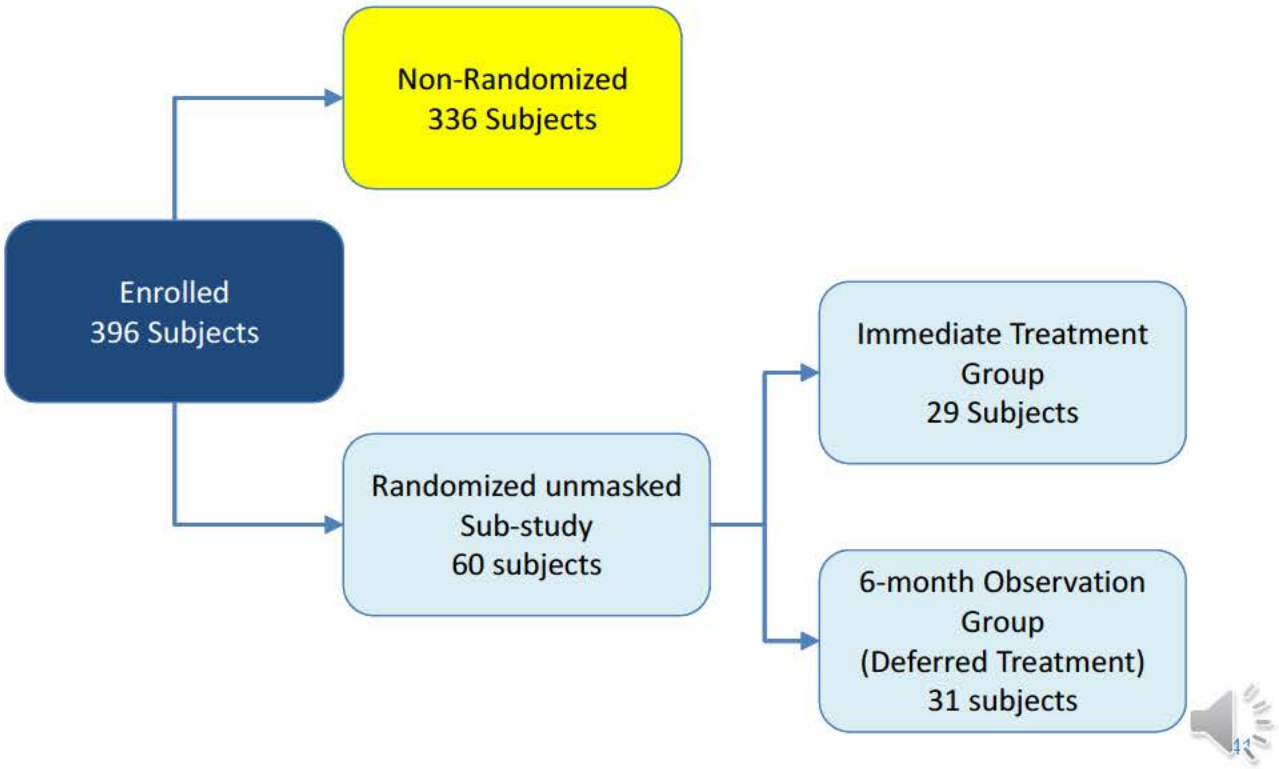
Eva Rorer, M.D.
Medical Officer
Division of Ophthalmic Devices
FDA/CDRH/OPEQ/OHT1

November 9, 2020

Clinical Trial Design

- Pivotal trial - VIS-2014 - IDE (b) (4) [redacted]
- Prospective, multicenter, non-masked, bilateral intervention trial conducted at 13 U.S. sites
- Objective – to evaluate the safety and effectiveness of the VisAbility Implant System with the VisAbility Implant, model SGP-046, for improvement of distance corrected near visual acuity (DCNVA) in presbyopic subjects

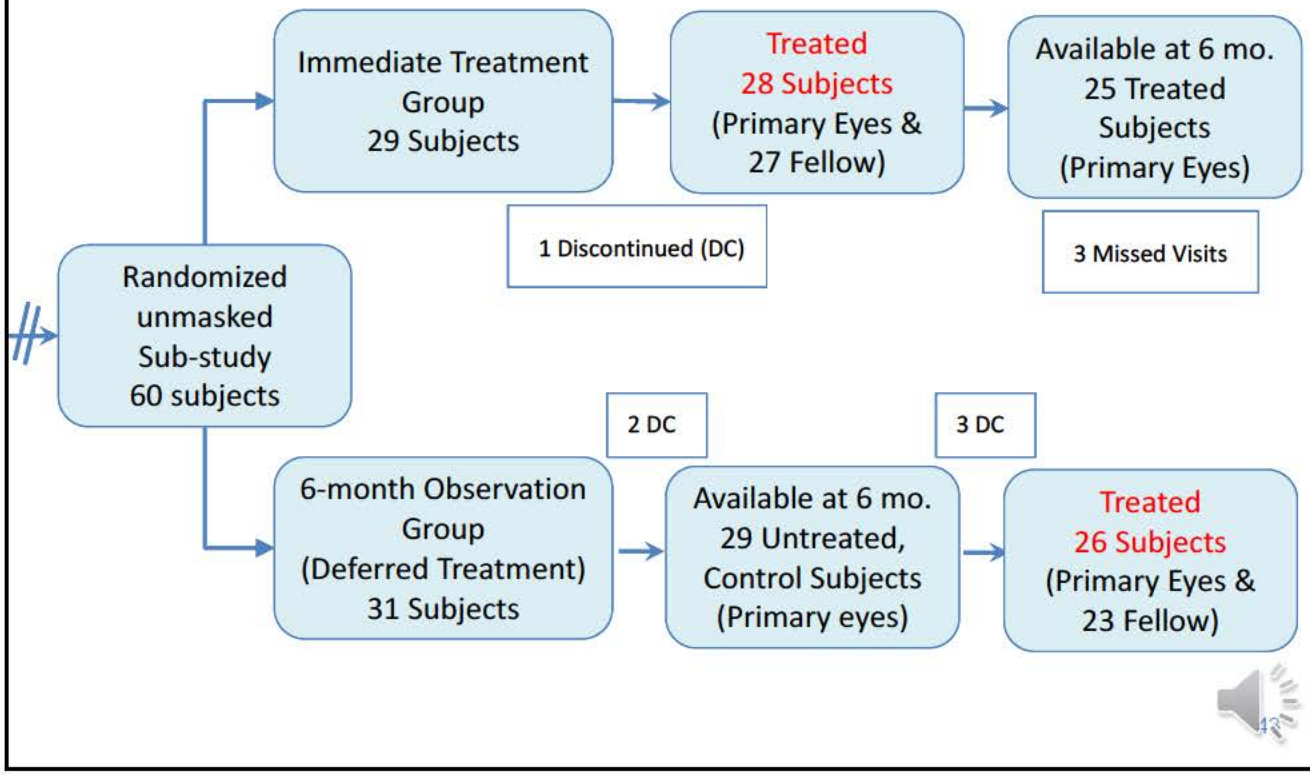
Enrollment

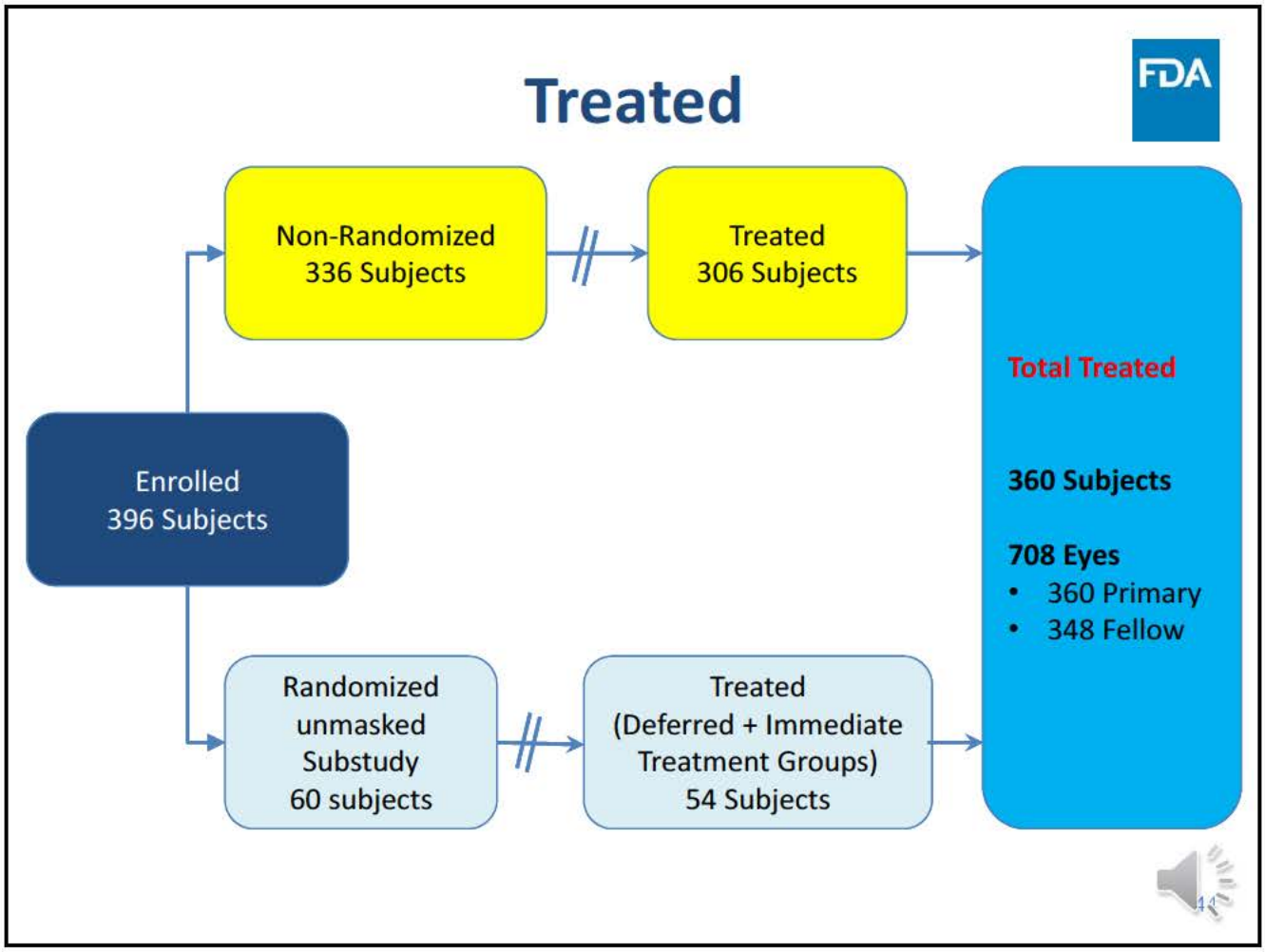

Non-Randomized
336 Subjects
Enrolled
396 Subjects
Immediate Treatment
Group
29 Subjects
Randomized unmasked
Sub-study
60 subjects
6-month Observation
Group
(Deferred Treatment)
31 subjects

Treated
Non-Randomized Cohort

306 Primary Eyes
298 Fellow Eyes

Treated Randomized Cohort




Treated
FDA
Non-Randomized
336 Subjects
Treated
306 Subjects
Total Treated
360 Subjects
708 Eyes
• 360 Primary
• 348 Fellow
Enrolled
396 Subjects
Randomized
unmasked
Substudy
60 subjects
Treated
(Deferred + Immediate
Treatment Groups)
54 Subjects

Accountability

	708 Treated Eyes			
	360 Primary Eyes (Total Treated Subjects)		348 Fellow Eyes	
	12 months	24 months	12 months	24 months
Available Eyes	346 (96.1%)	337 (93.6%)	341	331
Explants	4	8	1	5
Missed Visit	6	--	3	--
Lost to Follow-up	4	15	3	12

Safety Analysis Cohort Definition Pre-specified

- **Safety Cohort**: All eyes (both primary and fellow eyes) that have undergone surgical preparation of the ocular surface.
  - 708 eyes

Trial Success Definition Required Meeting Both Endpoints

- First co-primary Effectiveness Endpoint
  - Achievement of DCNVA 20/40 or better and gain ≥ 10 letters DCNVA in 75% of the primary eyes of implanted subjects at 12-months.
    - the lower limit of the one-sided 97.5% confidence interval (CI) should be at least 75% (equivalent to the lower bound of the two-sided 95% CI).
- Second co-primary Effectiveness Endpoint
  - Achievement of a statistically significant (one-sided $p<0.025$) difference in the proportion of primary eyes with DCNVA 20/40 or better and gain of ≥ 10 letters in subjects randomized to treatment versus deferred surgery as part of the randomized controlled sub-study at 6-months.

Effectiveness Cohorts

- **1st Co-Primary Endpoint: Primary eyes of all subjects that underwent surgical implantation -**
  - Includes randomized and non-randomized arms of the study.
- **2nd Co-Primary Endpoint:**
  - **Immediate Treatment Group - Primary eyes of all subjects that underwent surgical implantation**
  - **Untreated Control Group – Primary eyes of subjects eligible for treatment at the 6-mo. observation visit**

First Co-Primary Effectiveness Endpoint

- Not Met
  - ➢ 79.1% (277 of 350) treated primary eyes with DCNVA ≥20/40 and gain ≥10 letters
    - o 4 primary eyes with removal of all segments prior to 12-months counted as failures
  - ➢ Lower bound of the 95% CI was 74.5%
    - o lower than target value of 75%.

Second Co-Primary Effectiveness Endpoint

- Met
  - 2/29 (6.9%) Deferred Treatment Group vs. 18/28 (64.3%) Immediate Treatment Group
  - Statistically significant difference ($p < 0.001$) in the percentage of sub-study subjects with DCNVA ≥ 20/40 & gain ≥ 10 letters

Large Variability in Effectiveness across Sites

- 1st co-primary endpoint - results at 12 months mostly driven by 3 sites.
- 2nd co-primary endpoint - difference in outcomes between treatment and control varied among the three sites.
- Generalizability may be an issue.

Additional Analyses: Patient Preferred Distance

- Measured at near:
  - in centimeters
  - Pre-op & 3-, 6-, 12-, 18-, and 24-mo. post-op
  - Uncorrected – binocularly
  - Distance-corrected – binocularly & monocularly
  - "SLOAN threshold VA charts" with 250-284 lux
- No additional testing methodology in protocol:
  - line on chart, starting distance, or endpoint for testing
- Results challenging to interpret
  - Non-standardized methodology used
  - Did not meaningfully contribute to FDA's benefit-risk assessment

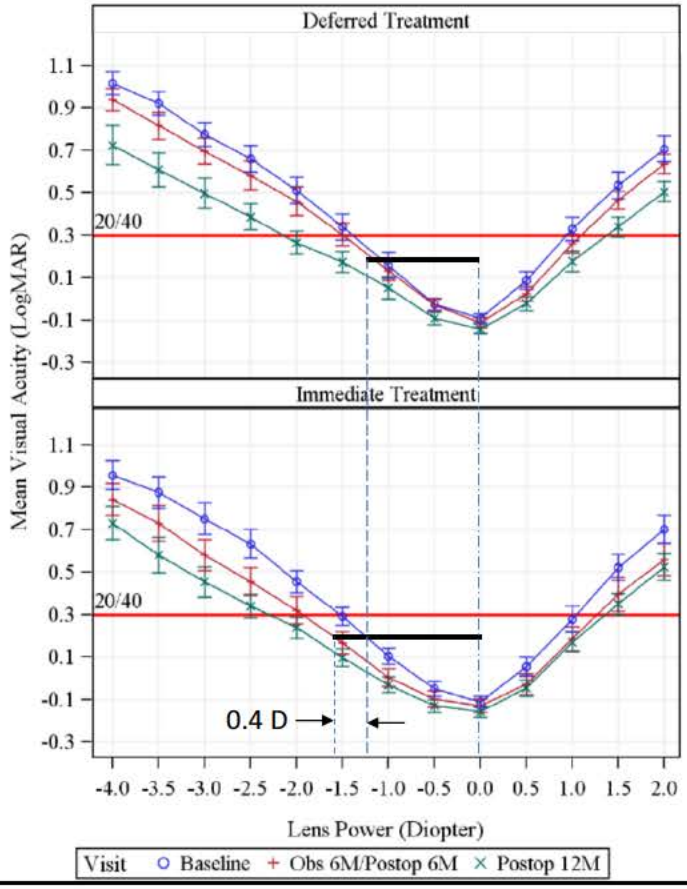
Additional Analyses: Defocus Curve Testing

- Performed in Randomized Substudy
  - All subjects at baseline x 2 (avg.) & 3, 6, 12, 18, and 24 mo. post-op
  - + at 3- and 6-mo. observation timepoints for Deferred Treatment group (no control at 12 and 24 months)
- Method
  - Without masking
  - Monocularly
  - Phoropter
  - Best distance correction
  - Viewing smallest line on ETDRS chart at 6 m based on BCDVA
  - -4.00 D added to the distance correction
  - Lens power changed in +0.50-D increments through +2.00 D
  - Visual acuity (VA) recorded at each step

Defocus Curve Testing - Results

- Exploratory
- Primary eyes
- Mean change in monocular VA from baseline to 6 months at -2.50 D (stimulus demand = near testing distance of 40 cm):
- Control group: -0.070 logMAR
  - Treatment group: -0.169 logMAR
  - *Difference = -0.099 logMAR = 1 line (5 letters on the ETDRS) in favor of the treatment group.*
    - ***Not consistent with*** *difference in the mean change from baseline to 6 months of DCNVA between the two groups: 2.40 lines in favor of the treatment group.*

Defocus Curve Testing – Results (cont.)



Additional Analyses: Wavefront Aberrometry

- Performed in Randomized Substudy
- Method
  - ➢ iTrace Wavefront Aberrometer (Tracey Technologies Corp.)
    - o Initially submitted analyses (A003) all over a pupil diameter of 2 mm = Zone 1 (Z1)
  - ➢ Distance target at 6 m
  - ➢ Near targets at five different testing distances
  - ➢ Repeated 3X at each distance
- One would anticipate that improvements in near acuity would be associated with optical changes in wavefront of either induced multifocality or consistent with attempted accommodation.

Wavefront Aberrometry

- Method cont.
  - Static Testing
    - Monocularly
    - Without refractive correction
    - Viewing 6-meter distance target
    - To determine whether the treatment may alter the aberrations of the eye to improve near vision

Wavefront Aberrometry

- Method cont.
  - ➢ Dynamic Testing
    - o To determine whether the treatment may improve accommodation or result in a pseudo-accommodative change
    - o Monocular
    - o Corrected for distance with soft contact lens
    - o Change from the distance (6m) to each consecutive near target stimulus (1 m, 66 cm, 50 cm, 40 cm, and 33 cm)
  - ➢ Only objective measure of optical change

Wavefront Aberrometry Results

- Exploratory – statistical hypothesis testing ("pairwise") was performed, but was not pre-specified in the IDE protocol and no accounting for multiplicity
- Primary eyes of Control and Treatment groups at baseline and the 6-month visits

Wavefront Aberrometry Results

- Static Testing
  - Some statistically significant differences (based on "nominal p-values") within (from baseline to 6 months) and between arms (at 6 months) for some of the Zernike wavefront parameters
  - No clinically significant difference (per the applicant's evaluation).

Wavefront Aberrometry Results

- Dynamic Testing
  - Some statically significant differences (based on "nominal p-values")
  - No clinically significant differences for any of the testing distances (per the applicant's evaluation).
- No indication of an accommodative or pseudo-accommodative change.

Additional Analyses: Near Activity Visual Questionnaire (NAVQ)

- Measure of near visual function (not Quality of Life)
- Evidence lacking to verify validity & reliability in pivotal trial is limited:
  - Not all items clearly assess near vision
  - No known criteria for success or improvement
  - Satisfaction item
    - no published evidence
    - response options positively biased with 4 of 5 referencing satisfied and only one unsatisfied
- Results of the questionnaire challenging to interpret
  - Post-op – still little or moderate difficulty with activities & majority only moderately satisfied or worse
  - Did not meaningfully contribute to FDA's benefit-risk assessment

Summary of Effectiveness

- **Success of the trial as defined in the protocol was not achieved.**
- **Variability raises questions about generalizability of effectiveness outcomes.**
  - Significant variability in the effectiveness outcomes across sites. Outcomes may not be generalizable to the broader US intended users and patient population.
- **Exploratory analyses not consistent with the primary endpoint parameter results.**
  - Defocus curve testing
    - Mean change difference in logMAR VA (baseline - 6month) - 1 line on the ETDRS chart.
      - ✓ Using the 2.50 D lens power equivalent to a near testing distance of 40 cm
  - Wavefront measurements
    - Per applicant, no clinically significant differences with static testing or dynamic testing.
    - No indication of an accommodative or pseudo-accommodative change.

Question

- Do the results provide reasonable assurance of the effectiveness of the device for the proposed indications?

Safety

- No pre-specified safety endpoints
- Descriptive statistics of the following safety parameters:
  - Best corrected distance visual acuity (BCDVA)
  - Intraocular pressure (IOP)
  - Slit Lamp findings
  - Fundus exam findings
  - Rate of adverse events (AEs)
    - list of anticipated AEs included in the protocol

Anterior Segment Ischemia (ASI)

- Grade 1 - Delayed iris perfusion on angiography
  - Not assessed
- Grade 2 - Acute decrease in pupil reactivity
- Grade 3: Decreased pupil reactivity + anterior chamber (AC) reaction
- Grade 4 - Decreased pupil reactivity + AC reaction + corneal edema

ASI AE Reporting (per protocol)

- Grade 4 ASI at ≥ post-op day 1
  - Reported as Anticipated AE
- Grade 2 or 3 ASI persisting 6 hours postop
  - Immediate removal
  - Reported as "Secondary Surgical Intervention: Implant segment removal'
- Persistent pupillary abnormalities due to reduced iris vascular perfusion
  - Reported as Anticipated AE

Safety Cohort Surgical Complications

- Total: 1.8% (15/708) eyes; 3.6% (13/360) subjects
  - **Scleral perforations** — 8 eyes of 8 subjects
  - **Decreased IOP** — 2 eyes of 2 subjects
  - **Shallow tunnels** in 1 quadrant — 2 eyes of 2 subjects
  - **Nausea and vomiting** (due to medications) — 1 subject/eye
  - **Pupil abnormalities** (within first 6 hrs. after surgery resulting in Micro Insert segment removals) — 2 eyes of 2 subjects

Scleral Perforations

- Total: 1.1% (8/708) eyes ; 2.2% (8/360) subjects
  - 5 eyes with vitreous prolapse
  - 3 eyes with sequelae
    - 3 quadrants of **posterior synechiae**.
    - vitreous prolapse – **hypotony, anterior segment inflammation, corneal edema,** and **constricted pupil** at Day 1, posterior vitreous detachment (**PVD**) and **retinal hemorrhage** at Week 1.
    - **conjunctival bleb, IOP 6 mmHg, 3+ posterior subcapsular, 3+ anterior subcapsular cataract, and 3-4+ nuclear sclerotic cataract with decrease in BCDVA of ≥ 2 lines (≥ 10 letters)** at Month 6.

Postoperative AEs

- Total: 365 ocular AEs:
  - 36.7% (260/708) eyes
  - 47.2% (170/360) subjects
- AE Types
  - Anterior Segment Ischemia (ASI)
  - Secondary Surgical Interventions
    - Implant segment removal
    - Exposed implant segments or conjunctival retraction requiring conjunctival re-approximation

Postoperative AEs: ASI

- Total reported - 5 subjects (1.4%, 5/360):
  - 1 subject - **Grade 4 ASI**
  - 1 subject – Grade 3 ASI
    - Peaked pupil & **AC reaction** on Day 1 postop
    - **AC reaction until Month 3**
  - 2 subjects – Grade 2 ASI
    - **Pupil abnormalities & implant segment removals Op Day**
  - 1 subject - **Persistent iris atrophy** at Month 24
    - Pupil abnormalities with symptoms (glare & reduced distance vision) at Month 1

Postoperative AEs: Secondary Surgical Interventions (during 24-mo. Pivotal Trial)

- Total: 4% (28/708) eyes; 6.4 % (23/360) subjects
  - **Conjunctival re-approximation** - 2.1% (15/708) eyes; 4.2% (15/360) subjects
  - **Removals** (all segments) - 1.8 % (13/708) eyes; 2.2% (8/708) subjects

Reasons for Removals (all segments)

Subj.	Eye	Abnormal Pupil	FB* Sensation	Dry Eye	Redness/ Cosmetic	Lack of Effect	Refractive Error
1	Primary	1					
2	Primary	1					
3	Primary		1		1		
3	Fellow		1		1		
4	Primary		1	1			
4	Fellow		1	1			
5	Primary			1		1	
5	Fellow			1		1	
6	Primary				1		
7	Primary				1	1	
7	Fellow				1	1	
8	Primary					1	1
8	Fellow					1	1
Total	13	2	4	4	5	6	2

*FB = Foreign Body

Removals after 24-mo. Pivotal Trial

- Denominator unknown – can't accurately calculate rates
  - 4.4% Minimum 4-yr. cumulative rate (additional reports for 16 eyes of 8 subjects)
- All segments – 18 eyes of 9 subjects for:
  - foreign body (FB) sensation in 4 eyes of 2 subject
  - ocular surface dryness &/or lid margin disease in 4 eyes of 2 subjects
  - combination of dry eye, redness, cosmesis and/or perceived lack of effect in 8 eyes of 4 subjects
  - the "patient's systemic health issues that could exacerbate ocular symptoms" in 2 eyes of 1 subject.
- Partial explants (1 or 2 segments) – 6 eyes of 5 subjects for:
  - FB sensation
  - Dry eye
  - Redness

Other SSIs

- During 24-mo Trial:
  - Laser retinopexy – 2 eyes of 2 subjects (1 for retinal hole and 1 for retinal tear)
  - Cataract extraction (posterior subcapsular) - 3 eyes of 2 subjects
  - Conjunctival cyst removal - 2 eyes of 2 subjects
  - LASIK – 1 eye of 1 subject
- During VIS-2014-5YR (reported in IDE annual report)
  - Additional refractive surgery for near vision complaints
    - Clear lens extraction with multifocal intraocular lens implantation - 2 eyes of 1 subject
    - Monovision photorefractive keratectomy (PRK) – 1 eye of 1 subject

Summary of Safety

- Scleral perforations - 1.1% (8/708) eyes ; 2.2% (8/360) subjects
- ASI – 0.7% (5/708) eyes; 1.4% (5/360) subjects
- Removals
  - During 24-mo. pivotal trial
    - All segments - 1.8% (13/708) eyes ; 2.2% (8/360) subjects
  - After 24 mo.
    - All segments – 18 eyes of 9 subjects
    - Partial explants - 6 eyes of 5 subjects
  - 4-yr. minimum cumulative
    - 4.1% (29/708) eyes; 4.4% (16/360) subjects

Question

Has the applicant provided reasonable assurance of the safety of the device for the proposed indications for use?

Benefit-Risk Assessment[1]

- Proposed Indications for Use:
  - The VisAbility™ Micro Insert is indicated for bilateral scleral implantation to improve unaided near vision in phakic, presbyopic patients between the ages of 45 and 60 years of age, who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to 1.00 D of refractive cylinder in both eyes, and require a minimum near correction of at least +1.25 D reading add.
- Alternatives:
  - Glasses, contact lenses, corneal inlays, and conductive keratoplasty

1 - FDA Guidance: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Benefits

- 79.1% (277/350) treated primary eyes with DCNVA ≥ 20/40 and ≥ 10-letter gain
- Benefit Uncertainty:
  - pre-specified success criterion not met
  - significant variability across sites
  - defocus curve (at 2.5 D) - 1-line difference from control
  - wavefront - no clinically significant change

Risks: Adverse Events

- During 24-mo. pivotal trial:
  - Total: 36.7% (260/708) eyes, 47.2% (170/360) subjects
    - Scleral perforations: 1.1% (8/708) eyes, 2.2% (8/360) subjects
    - ASI: 0.7% (5/708) eyes, 1.4% (5/360) subjects
    - Removals: 1.8% (13/708) eyes, 2.2% (8/360) subjects
- After 24 mo., included but not limited to:
  - 18 eyes of 9 subjects with removal of all segments
  - 6 eyes of 5 subjects with partial explants

Risks

- Impact of Risk Mitigation Strategies Unclear:
  - No sub-population
  - No modifications to the surgical technique and/or training
- Risk Uncertainty:
  - Scleral perforations – tunnel floor not visualized during surgery
  - ASI – Grades 2 & 3 not explicitly listed as anticipated AEs in protocol

Question

- Based on the totality of evidence, do the benefits outweigh the risks for the proposed indications for use?

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Post-Approval Study (PAS) Considerations

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November 9, 2020

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA has concluded there is a reasonable assurance of safety and effectiveness.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

Proposed Post-Market Plan

- Continued Follow-up of IDE cohort (b) (4) [redacted], VIS-2014-5YR
- New Enrollment PAS, VIS-2014-PAS
- Post-Approval Controlled Access & Training

Continued Follow-up, VIS-2014-5YR

Study Design	5-year (3 additional years) prospective, single-arm, descriptive study comparing to baseline (VIS-2014-5YR)
Primary Endpoints	Descriptive statistics • Explant rate and reason(s) • Rate of Anteiror Segment Ischemia (Grade 2-4) • Rate of segment exposure • Rate of SAEs
Sample Size & Hypothesis	Does NOT include hypotheses testing, success criteria, sample size requirement, or a statistical analysis plan

Question

Is the length of follow-up sufficient to address concerns related to long-term safety and/or effectiveness?

New Enrollment PAS: VIS-2014-PAS

Study Design	1-year multicenter, prospective, single-arm study on 150 subjects per IU Cohort IFU, compared with premarket cohort
Objectives	• To provide additional, prospective, descriptive data on the intended population; • To evaluate device performance stratified by surgeon experience.
Primary Endpoints	Safety: • Rate of occurrence of Anterior Segment Ischemia • Rate of scleral perforations Effectiveness: • Change in DCNVA from baseline
Hypothesis	Does NOT include hypotheses testing, success criteria, or a statistical analysis plan

Question

Is the proposed study design and study endpoints adequate to address safety and effectiveness of the device under real-world conditions?

Post-Approval Controlled Access & Training

Controlled Access	• **Month 0-6: Surgeons involved in clinical trial** • **Month 6-9: expand in clinics in three cities** • **End of First Year: 35-45 surgeons**
Monitoring	All patients will be enrolled in 3rd-party registry, clinical specialist monitoring
Training	Didactic, wet lab, surgery review and proctoring
Certification	Certification list; continuing education; re-certification in event of product update

- Per applicant's presentation today - Thresholds
  - Pivotal study thresholds not submitted to FDA
  - Intent of thresholds driven by "Real-World" performance remain unclear
    - All changes to device design or labeling (including directions for use, e.g., surgical procedure) require FDA approval

Pivotal Trial Training & Monitoring

IDE Investigator Training
• Per the study monitoring plan in the protocol, the applicant or CRO (contract or clinical research organization) personnel were to meet with investigators and clinical staff prior to initiation of the trial in order to "familiarize" them with the protocol, which included the enrollment criteria and postoperative care.
• Per the applicant (P170040/A005), investigators were trained on surgical best practices.
• Wet Lab Training - Demonstration of proficiency
• Minimum 5 eyes for proctoring
Post-Operative Support and Monitoring
• Clinical monitoring by medical monitor and data safety monitoring board
• Clinical trial investigators had to adhere to IDE reporting requirements per 21 CFR 812.
• Collection of safety and effectiveness data (i.e., adverse events) on subjects under IDE (pivotal trial and continued follow-up study) .

Summary: Regulatory History

- PMA:
  - 3 submissions
    - Different follow-up periods
    - 2 different IFUs
  - Currently Proposed
    - IFU:

      ...who have a manifest spherical equivalent between -0.75 D and +0.50 D with less than or equal to **1.00 D of refractive cylinder** in both eyes...
    - Based on:
      - ✓ 12 months - 347 subjects
      - ✓ 24 months - 337 subjects
- IDE:
  - Ongoing 5-year continued follow-up study

Summary

- Effectiveness Uncertainty:
  - Trial success not achieved
  - Significant variability of results across sites
  - Wavefront (objective) and Defocus results not consistent with VA results
- Safety:
  - 47.2% subjects with AEs
    - 1.4% ASI, 2.2% scleral perforations, and 2.2% removals (through 2 yrs.)
  - Uncertainty if true rates greater than reported:
    - Surgical - ASI and Scleral Perforations
    - Post-op Removals – Long-term rate
- Proposed Post-market plan:
  - Unsupported risk mitigation strategies

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Thank You


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