Implantable Miniature Telescope™ (IMT by Dr. Isaac Lipshitz) for End-Stage AMD

- **Introduction**
  - Judy F Gordon, DVM – Clinical and Regulatory Consultant

- **Background and Device Description**
  - Jeffrey S Heier, MD – Medical Monitor Retina, Clinical Investigator

- **Surgical Procedure and Study Design**
  - Stephen S Lane, MD – Medical Monitor Anterior Segment, Clinical Investigator

- **Effectiveness Outcomes**
  - Jeffrey S Heier, MD - Clinical Investigator

- **Safety Outcomes**
  - Doyle Stulting, MD, PhD - Clinical Investigator

- **Discussion and Questions from Panel**
  - Drs. Gordon, Lane, Heier, Stulting
  - Mark Bullimore, MCOptom, PhD – Low Vision, Vision Science Consultant
  - Yi-Jing Duh, PhD - Statistician
  - Henry Edelhauser, PhD – Specular Microscopy Reading Center
Implantable Miniature Telescope™ (by Dr. Isaac Lipshitz)

The IMT is indicated for use in adult patients with bilateral, stable moderate to profound central vision impairment (20/80 to 20/800) due to macular degeneration.

Patients selected for implantation should meet the following criteria:

- 55 years of age or older with bilateral, stable central vision deficit resulting from AMD as determined by fluorescein angiography, and evidence of cataract.
- Distance BCVA between 20/80 and 20/800, and adequate peripheral vision in one eye (the non-implemented eye) to allow for orientation and mobility.
- Achieve at least a five-letter improvement on the ETDRS chart in the eye scheduled for surgery using an external telescope.
- Show interest in participating in a postoperative visual rehabilitation program.
Background and Device Description

Jeffrey Heier, MD
Medical Monitor, Retina
Clinical Investigator
End-Stage Age Related Macular Degeneration

- Approximately 60,000 to 80,000 cases per year in the U.S.\(^1,2\)
- Majority of patients are legally blind as a result of central vision loss in both eyes due to:
  - Dry AMD (geographic atrophy)
    - No treatment available
  - Stable wet AMD (disciform scar)
    - Completed all laser and drug treatments for exudation in and around the macula

\(^1\) AREDS Report No. 11. Arch Ophthalmol 2003;121:1621-1624
Vision with and without Scotoma

Normal Central Vision

End-Stage AMD
Effect on Functional Status

- End-stage AMD has a profound effect on Activities of Daily Living (ADL)

- Patients have extreme difficulty with:

  - **Household Activities/Self-Care**: Preparing tea, shaving, make-up
  - **Social Interaction**: Recognizing friends, facial expressions
  - **Reading or TV/Computer**: News, leisure reading
  - **Consumer Interaction**: Identifying products and paying
Current Options for Patient Management in End-Stage AMD

- Visual rehabilitation and training in the use of low vision aids, including external telescopes, loupes, hand-held magnifiers for reading, illumination

- Limitations of current treatment
  - Only 30% of visually impaired adults use optical devices per Lighthouse National Survey on Vision Loss (1995)
  - Low utilization of rehabilitation services
  - Limited psychosocial benefits
  - Difficulty using low vision aids in both static and dynamic activities
The Implantable Miniature Telescope (IMT™ by Dr. Isaac Lipshitz)

- Optical prosthesis
- Two models - WA2.2X, WA3.0X
- Improves central vision
- Distance/near vision refined with spectacles
- Quartz tube housing with two wide angle microlenses
- Diameter 3.6 mm
  Length 4.4 mm
- Carrier haptic 13.5 mm diameter
Projection on Retina

- Designed to improve vision by magnifying the retinal image
- Key differences from external telescopes
  - Wide visual field
  - Natural eye movements
  - Normal cosmetic appearance
Enlargement of Retinal Image

- Enlarges retinal image 2.2x or 2.7x
- Reduces relative size of scotoma
- Enlarges and positions relevant information on seeing retina
### Field of View

**External vs Implantable Telescopes**

<table>
<thead>
<tr>
<th>Magnification</th>
<th>External Telescope on Spectacles</th>
<th>Wide Angle Implantable Telescope</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2x</td>
<td>13°</td>
<td>24°</td>
</tr>
<tr>
<td>3.0x, 2.7x</td>
<td>5-6°</td>
<td>20°</td>
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</table>

- 3.0x External Telescope
- WA 3.0x Implantable Telescope
Preoperative Measurement of Scotoma and Simulation of Effect in Study Subject

Measurement of Scotoma at Baseline

Eli Peli, OD
Schepens Eye Institute

Simulation
Preoperative of the Field of View and Scotoma through an External Telescope in Study Subject

10° Field of View, Restricted Superiorly by Scotoma

Measurement of Magnified Field of View and Scotoma through a 2.2X External Telescope

Eli Peli, OD
Schepens Eye Institute
Postoperative View Through the Implanted Telescope in Study Subject

25° Field of View and Relative Reduction in Scotoma

Measurement of Magnified Field of View and Scotoma through IMT

Eli Peli, OD
Schepens Eye Institute

Simulation
Surgical Procedure

Stephen Lane, MD
Medical Monitor, Anterior Segment
Clinical Investigator
Unique Geometrical and Surgical Considerations for the Implantable Telescope

Standard IOL

- ECCE represented an improvement over ICCE, with decreased endothelial cell loss
- Phacoemulsification and small incision surgery further reduced surgical trauma, loss of ECD

Implantable Telescope

- Requires large incision, results in greater endothelial cell loss
- Careful handling of the cornea and adequate use of ophthalmic viscosurgical devices (OVD) are key
Avoid Corneal Touch
Both Loops in the Capsular Bag
Corneal Clearance

Ultrasound indicates good postoperative clearance to cornea

- Images obtained for 7 eyes implanted at Kellogg Eye Center, University of Michigan
- Average 2.54 mm clearance between anterior surface of telescope and cornea
- Well centered in capsular bag

Source: not in PMA
Appearance of Implantable Telescope in the Eye
6 Weeks Postoperative
Visualization of Retina through the Implantable Telescope
Protocol IMT-002

A Prospective, Multicenter Clinical Trial of the Implantable Miniature Telescope (IMT™ by Dr. Isaac Lipshitz) in Patients with Central Vision Impairment Associated with Age Related Macular Degeneration

Study Design

Stephen Lane, MD
**Clinical Study Investigators**

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carl Baker, MD</td>
<td>Paducah, KY</td>
</tr>
<tr>
<td>Daniel Berinstein, MD</td>
<td>Chevy Chase, MD</td>
</tr>
<tr>
<td>David Chang, MD</td>
<td>Los Altos, CA</td>
</tr>
<tr>
<td>Brian Connolly, MD</td>
<td>Wills Eye Institute</td>
</tr>
<tr>
<td>Doug Dehning, MD</td>
<td>Independence, MO</td>
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<tr>
<td>Sharon Fekrat, MD</td>
<td>Duke University Eye Center</td>
</tr>
<tr>
<td>Howard Fine, MD</td>
<td>Eugene, OR</td>
</tr>
<tr>
<td>Stephen Fisher, MD</td>
<td>San Antonio, TX</td>
</tr>
<tr>
<td>M. Bowes Hamill, MD</td>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>Dennis Han, MD</td>
<td>Medical College of Wisconsin</td>
</tr>
<tr>
<td>Jeffrey Heier, MD</td>
<td>Boston, MA</td>
</tr>
<tr>
<td>Henry Hudson, MD</td>
<td>Tucson, AZ</td>
</tr>
<tr>
<td>Manus Kraff, MD</td>
<td>Chicago, IL</td>
</tr>
<tr>
<td>Baruch Kuppermann, MD</td>
<td>University of California, Irvine</td>
</tr>
<tr>
<td>Stephen S. Lane, MD</td>
<td>Stillwater, MN</td>
</tr>
<tr>
<td>Robert Leonard, MD</td>
<td>Dean A. McGee Eye Institute</td>
</tr>
<tr>
<td>Paul R. Lichter, MD</td>
<td>Kellogg Eye Center</td>
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<tr>
<td>Dan Martin, MD</td>
<td>Emory University Eye Center</td>
</tr>
<tr>
<td>Joan Miller, MD/Kathryn Colby, MD</td>
<td>Massachusetts Eye &amp; Ear Infirmary</td>
</tr>
<tr>
<td>Srinivas Reddy Sadda, MD</td>
<td>Doheny Retina Institute</td>
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<tr>
<td>Oliver D. Schein, MD</td>
<td>Wilmer Eye Institute</td>
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<tr>
<td>Lawrence J. Singerman, MD</td>
<td>Beachwood, OH</td>
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<tr>
<td>Jason S. Slakter, MD</td>
<td>Manhattan Eye &amp; Ear</td>
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<tr>
<td>Paul Sternberg, MD</td>
<td>Vanderbilt University</td>
</tr>
<tr>
<td>Donald Stewart, MD</td>
<td>Charlotte, NC</td>
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<tr>
<td>Michael T. Trese, MD</td>
<td>Royal Oak, MI</td>
</tr>
<tr>
<td>Keye Wong, MD</td>
<td>Sarasota, FL</td>
</tr>
<tr>
<td>Seth Yoser, MD</td>
<td>Memphis, TN</td>
</tr>
</tbody>
</table>
Protocol IMT-002 - Study Design

- Patients screened using external telescope in office and home environment
  - Gain >5 letters BCDVA with telescope was required to qualify for enrollment

- Monocular implantation
  - In worse seeing eye if one or both eyes better than 20/200
  - Doctor/patient select if both eyes less than 20/200

- Visit schedule
  - Day 1, Week 1, Months 1, 3, 6, 9, 12, 18, 24

- Vision training
  - Weeks 1, 2, 4, 6, 10 and 12
Key Eligibility Criteria

- Bilateral, stable, untreatable AMD on fluorescein angiography
- Distance BCVA of 20/80 to 20/800
- Adequate peripheral vision in fellow eye to allow for navigation
- Improvement in BCDVA of ≥ 5 letters on ETDRS chart with the external telescope in the eye scheduled for surgery
- Anterior chamber depth of ≥ 2.5mm on A-scan
- Endothelial cell density ≥ 1600 cells/mm²
- Manifest sphere between +4.0 to -6.0 D
- Axial length ≥ 21 mm
- Schaffer grade ≥ 2
- Controlled glaucoma
- No corneal stromal or endothelial dystrophies or disorders, inflammatory ocular disease, zonular weakness, pseudoexfoliation, retinal pathology other than stable end-stage AMD
Study Methods

- Distance visual acuity (BCDVA) – all study visits
  - Measured with standard ETDRS charts (C110 and C105) with retro-illuminated box; LogMAR computed

- Near visual acuity (BCNVA) – all study visits
  - Measured with ETDRS chart (Precision Vision Chart 2000); LogMAR computed

- VFQ-25 and Activities of Daily Living (ADL) Questionnaires – baseline through 12 months
  - Administered by trained study personnel

- Specular microscopy – baseline through 24 months
  - Images analyzed by central reading center (H. Edelhauser, B. McCarey, Emory University)
Vision Training/Rehabilitation Protocol

- Goal to provide patients with the skills to adjust to the IMT and achieve optimal functionality
- Conducted by low vision professionals at each clinical site
- Five fundamental skills
  - Localizing - locating an object of interest in the IMT field of view. If difficult, the patient first looked at the object with both eyes, then obscured the fellow eye and tried again with implanted eye
  - Fixating – performed by the implanted eye to enable object identification
  - Scanning – natural eye movement performed by the implanted eye
  - Tracing – following a path between objects of interest
  - Tracking - ability to follow a moving object
- Training for distance activities, intermediate distance, reading and writing, static and dynamic environments
- IMT bi-ocular function: initial training performed with the fellow eye patched to promote use of the IMT
  - Fellow eye patched for training in static vision
  - Implanted eye patched for motility training
Protocol IMT-002
Safety and Effectiveness Endpoints

Effectiveness Parameters
- Change in lines of best corrected visual acuity
- Quality of life - VFQ-25 and ADL questionnaires

Safety Parameters
- Preservation of best corrected visual acuity
- Endothelial cell loss
- Adverse events and complications
Protocol IMT-002

Baseline Information and Effectiveness Data

Jeffrey Heier, MD
Patient Accountability

Enrolled  N = 218

IMT Surgery  N = 217

Implanted  N = 206

1 patient withdrawal

11 eyes not implanted
7 eyes with posterior capsular rupture
2 eyes with choroidal detachment (increased posterior pressure)
1 eye with choroidal hemorrhage
1 eye with loss of zonular support

Accountability

Original PMA

6 Months  100.0% (202/202)
12 Months  97.5% (194/199)
18 Months  91.4% (180/197)
24 Months  95.5% (148/155)

Model WA2.2X – 115 patients
Model WA3.0X – 91 patients

Complete 24-Month Safety Data  92.6% (N = 174/188)

Source: PMA Table A2
# Demographic and Baseline Information

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>75.4 (7.2)</td>
<td>55 - 93</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>Female 98</th>
<th>47.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male 108</td>
<td>52.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Caucasian 198</th>
<th>96.1%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Black 3</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>Hispanic 4</td>
<td>1.9%</td>
</tr>
<tr>
<td></td>
<td>Asian 1</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best Corrected Visual Acuity (mean, range)</th>
<th>Mean BCDVA</th>
<th>Range</th>
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<tbody>
<tr>
<td></td>
<td>20/312</td>
<td>20/80 to 20/800</td>
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</table>

Source: PMA Table A3
Effectiveness Outcomes

Visual Acuity

NEI VFQ-25, ADL
Improvement in Distance or Near Vision at 12 Months (N = 193)

89.6% gain ≥ 2 lines

Source: PMA Table A11
Improvement in Distance or Near Vision at 24 Months (N = 147)

85.7% gain ≥2 lines

72.8% ≤-3
6.1% -2
12.9% +2
6.8% No change
40%
20%
0%

Source: PMA Table A13
Improvement in Distance Vision

<table>
<thead>
<tr>
<th>Time</th>
<th>≥ 2 lines</th>
<th>≥ 3 lines</th>
<th>≥ 4 lines</th>
<th>≥ 5 lines</th>
<th>≥ 6 lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>80%</td>
<td>66%</td>
<td>45%</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>18 Months</td>
<td>79%</td>
<td>63%</td>
<td>41%</td>
<td>24%</td>
<td>10%</td>
</tr>
<tr>
<td>24 Months</td>
<td>74%</td>
<td>59%</td>
<td>42%</td>
<td>20%</td>
<td>9%</td>
</tr>
</tbody>
</table>

N=193 N=179 N=147

Source: PMA Table A7
Improvement in Near Vision at 8” (20 cm)

% of IMT-Implanted Eyes

- ≥ 2 lines
- ≥ 3 lines
- ≥ 4 lines
- ≥ 5 lines
- ≥ 6 lines

<table>
<thead>
<tr>
<th>Time</th>
<th>≥ 2 lines</th>
<th>≥ 3 lines</th>
<th>≥ 4 lines</th>
<th>≥ 5 lines</th>
<th>≥ 6 lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 Months</td>
<td>69%</td>
<td>54%</td>
<td>18%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>N=192</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Months</td>
<td>67%</td>
<td>51%</td>
<td>18%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>N=179</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 Months</td>
<td>67%</td>
<td>52%</td>
<td>35%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>N=147</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Source: PMA Table A8
Improvement in Near Vision at 16” (40 cm)

Source: PMA Table A9
Improvement in Distance and Near Vision

% of IMT-Implanted Eyes

12 Months: 73% Gain ≥ 2 lines, 53% Gain ≥ 3 lines
18 Months: 71% Gain ≥ 2 lines, 50% Gain ≥ 3 lines
24 Months: 67% Gain ≥ 2 lines, 51% Gain ≥ 3 lines

N=194, N=180, N=148

Source: PMA Table A11, A12, A13
Gain ≥ 2 Lines in Distance Vision at 12 Months Stratified by Age, Gender, Baseline Visual Impairment, Model

Source: PMA Table A7a.1, A7b.1, A7c.1, A7d.1
Mean Gain in Distance Vision at 12 Months vs Expected Benefit from Magnification

Model 2.2X
51.8% Achieved > Predicted Gain in Vision

Model 3.0X
50.6% Achieved > Predicted Gain in Vision

Source: not in PMA
Mean Gain in Distance Vision at Baseline vs Expected Benefit from Magnification with External Telescope

<table>
<thead>
<tr>
<th>Magnification</th>
<th>Predicted Gain</th>
<th>Achieved Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2X ET</td>
<td>3.4 Lines</td>
<td>3.0 Lines</td>
</tr>
<tr>
<td>3.0X ET</td>
<td>4.8 Lines</td>
<td>3.5 Lines</td>
</tr>
</tbody>
</table>

Source: not in PMA

- 34.8% Achieved ≥ Predicted Gain in Vision
- 18.7% Achieved ≥ Predicted Gain in Vision
National Eye Institute VFQ-25

- Validated quality of life questionnaire developed by Mangione et al\(^1,2\) sponsored by NEI
- Assesses vision-targeted functioning\(^3\) by measuring impact of vision problems on health-related QOL in many eye diseases
- Patient reported outcomes, reflects effect of improvement in vision on functionality, quality of life
- Validated instrument, employed in numerous clinical trials
- DHHS, Agency for Healthcare Research and Quality, Technology Assessment Program, Vision Rehabilitation for Elderly Individuals with Low Vision or Blindness, Oct. 2004, pg 58, QOL

“This outcome measure may be the most meaningful of all measures. This is because an individual’s ability to perform activities of daily living, mood, psychological status, and any adverse events associated with the intervention should – if these changes are meaningful – be reflected by changes in the individual’s quality of life.”

NEI VFQ-25

- A total of 25 items representing 12 subscales
  - General vision - 1 item
  - Near activities - 3 items (newsprint, up close, objects on shelf)
  - Distance activities - 3 items (movies, stairs, street signs)
- 100 point scale, 0 = worst, 100 = best
- Clinical relevance established - 5-10 point change corresponds to a 2 to 3 line change in vision\(^1\)
- Defined scoring algorithm

\(^1\) Globe et al. Ophthalmol 2004;111:1141-9
Change from Baseline on VFQ-25 Subscales at 12 Months

Source: PMA Table A15; A002 Table Q29
Relationship between Visual Acuity and VFQ

Mean change in VFQ score from baseline on 8 relevant subscales:

- +7.7 for ≥ 2 lines (N=141)
- +2.4 for < 2 lines (N=52)

Distance and Near Vision in IMT-Implanted Eye

Source: not in PMA
Change from Baseline on VFQ-25 Subscales
IMT vs Low Vision Services

Scott et al. AJO 1999*
- 156 patients
- Bascom Palmer
- 55% AMD patients
- BCVA 20/200 (mean)
- 1 ‘device or service’ per patient
- VFQ measured at 3 months

*Scott IU, et al. Quality of life of low-vision patients and the impact of low-vision services. AJO 1999;128:54-62

Source: not in PMA
# Distribution of Outcomes on VFQ-25 at 12 Months for Subjects Reporting Extreme Difficulty at Baseline Questions 5 through 9

<table>
<thead>
<tr>
<th></th>
<th>VFQ5 Reading Newspaper</th>
<th>VFQ6 Hobbies</th>
<th>VFQ7 Finding on Crowded Shelf</th>
<th>VFQ8 Street Signs and Stores</th>
<th>VFQ9 Stairs, or Curbs in Dim Light</th>
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<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients who stopped activity or had extreme difficulty</td>
<td>N = 185</td>
<td>N = 112</td>
<td>N = 101</td>
<td>N = 144</td>
<td>N = 71</td>
</tr>
<tr>
<td><strong>12 MONTHS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stopped activity</td>
<td>59%</td>
<td>17%</td>
<td>2%</td>
<td>23%</td>
<td>12%</td>
</tr>
<tr>
<td>Had extreme difficulty</td>
<td>26%</td>
<td>27%</td>
<td>37%</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Moderate difficulty</td>
<td>9%</td>
<td>41%</td>
<td>43%</td>
<td>29%</td>
<td>41%</td>
</tr>
<tr>
<td>No or little difficulty</td>
<td>5%</td>
<td>15%</td>
<td>18%</td>
<td>19%</td>
<td>18%</td>
</tr>
</tbody>
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Source: not in PMA
Activities of Daily Living
Change in Subscales from Baseline

<table>
<thead>
<tr>
<th>Subscale</th>
<th>6 Months N=200</th>
<th>9 Months N=196</th>
<th>12 Months N=193</th>
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<tbody>
<tr>
<td>Mobility</td>
<td>+14.0</td>
<td>+15.3</td>
<td>+12.0</td>
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<tr>
<td>Distance Activities</td>
<td>+15.3</td>
<td>+15.3</td>
<td>+13.4</td>
</tr>
<tr>
<td>Near Activities</td>
<td>+20.9</td>
<td>+18.3</td>
<td>+17.0</td>
</tr>
<tr>
<td>Total</td>
<td>+17.0</td>
<td>+15.8</td>
<td>+19.6</td>
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</table>

Source: PMA Table A17
Summary of Effectiveness

- Protocol target for effectiveness significantly exceeded
  - 85% gain ≥ 2 lines distance or near
  - 60% gain ≥ 3 lines distance or near
  - 50% gain ≥ 3 lines distance and near

- IMT performed as intended, with study subjects on average achieving the predicted gain in vision based on magnification

- Significant relationship between gain in BCVA and improvement in VFQ-25
Safety Outcomes

Doyle Stulting, MD, PhD
Safety Parameters

- Loss of lines of acuity
- Intraocular pressure
- Complications
- Adverse events
- Endothelial cell density (ECD)
Change in Distance Vision
Baseline to Last Available Visit

% of IMT-Implanted Eyes

Source: not in PMA
Mean Gain in BSCVA

Expected Change from Magnification

12 Month Line Change in BCDVA

- Model 2.2X: 3.4 lines Predicted, 3.0 lines Achieved
  - 51.8% Achieved ≥ Predicted Gain in Vision

- Model 3.0X: 4.3 lines Predicted, 4.0 lines Achieved
  - 50.6% Achieved ≥ Predicted Gain in Vision

Source: not in PMA
Mean Gain in BSCVA

Expected Change from Magnification

Change in Lines of BSCVA

- **Model 2.2X**
  - Predicted: 3.4 lines
  - Achieved: 3.0 lines
  - 51.8% Achieved Predicted Gain

- **Model 3.0X**
  - Predicted: 4.3 lines
  - Achieved: 4.0 lines
  - 50.6% Achieved Predicted Gain

- **2.2X External Telescope**
  - Predicted: 3.4 lines
  - Achieved: 3.0 lines
  - 34.8% Achieved Predicted Gain

- **3.0X External Telescope**
  - Predicted: 4.8 lines
  - Achieved: 3.6 lines
  - 18.7% Achieved Predicted Gain

Source: not in PMA
Intraocular Pressure
Mean, Change from Baseline

Mean IOP
Mean Change from Baseline

Source: PMA Table A25
<table>
<thead>
<tr>
<th>Complication</th>
<th>Count</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Corneal abrasion</td>
<td>11</td>
<td>5.1%</td>
</tr>
<tr>
<td>Corneal edema</td>
<td>14</td>
<td>6.5%</td>
</tr>
<tr>
<td>Descemet’s membrane separation</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>Hyphema</td>
<td>14</td>
<td>6.5%</td>
</tr>
<tr>
<td>Increased IOP</td>
<td>62</td>
<td>28.6%</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>4</td>
<td>1.8%</td>
</tr>
<tr>
<td>Iris damage</td>
<td>8</td>
<td>3.7%</td>
</tr>
<tr>
<td>Iris incarceration</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>Iris prolapse</td>
<td>12</td>
<td>5.5%</td>
</tr>
<tr>
<td>Posterior capsule rupture</td>
<td>10</td>
<td>4.6%</td>
</tr>
<tr>
<td>Posterior capsule opacification</td>
<td>8</td>
<td>3.7%</td>
</tr>
<tr>
<td>Vitreous in anterior chamber</td>
<td>3</td>
<td>1.4%</td>
</tr>
<tr>
<td>Wound leak</td>
<td>3</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

Source: A004 Table 46, 48; A003 Table 46 rev., 14.2-14.6
## Ocular Adverse Events

### Cumulative Incidence <5% (N = 206)

<table>
<thead>
<tr>
<th>Event</th>
<th>Cases</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior ischemic optic neuropathy</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td>Choroidal neovascularization</td>
<td>3 eyes</td>
<td>1.5%</td>
</tr>
<tr>
<td>Choroidal hemorrhage</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Corneal edema onset &gt; 30 days postop</strong></td>
<td>6 eyes</td>
<td>2.9%</td>
</tr>
<tr>
<td>Corneal decompensation</td>
<td>2 eyes</td>
<td>1.0%</td>
</tr>
<tr>
<td>Cyclitic membrane/phthisis</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td>Cystoid macular edema</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>Device failure and removal</strong></td>
<td>2 eyes</td>
<td>1.0%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>3 eyes</td>
<td>1.5%</td>
</tr>
<tr>
<td>Distorted pupil</td>
<td>7 eyes</td>
<td>3.4%</td>
</tr>
<tr>
<td>Patient dissatisfaction and removal</td>
<td>4 eyes</td>
<td>1.9%</td>
</tr>
<tr>
<td>IMT dislocation</td>
<td>2 eyes</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>Inflammatory membrane on IMT</strong></td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td>Increased IOP requiring treatment</td>
<td>7 eyes</td>
<td>3.4%</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>7 eyes</td>
<td>3.4%</td>
</tr>
<tr>
<td>Obstructed iridectomy</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td>Subretinal hemorrhage</td>
<td>2 eyes</td>
<td>1.0%</td>
</tr>
<tr>
<td>Synechiae</td>
<td>1 eye</td>
<td>0.5%</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>3 eyes</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Source: A004 Table 46, 48; A003 Table 46 rev., 14.2-14.6
### Ocular Adverse Events with Incidence ≥ 5% (N = 206)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cumulative</th>
<th>Persistent (≥ 1 Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iris transillumination defects</td>
<td>11 eyes (5.3%)</td>
<td>10 eyes (5.1%)</td>
</tr>
<tr>
<td>Iritis</td>
<td>12 eyes (5.8%)</td>
<td>0 eyes (0%)</td>
</tr>
<tr>
<td>Posterior synechiae</td>
<td>15 eyes (7.3%)</td>
<td>9 eyes (5%)</td>
</tr>
<tr>
<td>Guttae</td>
<td>16 eyes (7.8%)</td>
<td>15 eyes (7.6%)</td>
</tr>
<tr>
<td>Pigment deposits on IMT</td>
<td>23 eyes (11.2%)</td>
<td>15 eyes (7.6%)</td>
</tr>
<tr>
<td>Inflammatory deposits on IMT</td>
<td>51 eyes (24.8%)</td>
<td>32 eyes (16.2%)</td>
</tr>
</tbody>
</table>

Source: A004 Table 46, 48; A003 Table 46 rev., 14.2-14.6; persistent AE not in PMA
Inflammatory Deposits on IMT
Inflammatory Deposits on IMT
IMT Removals (N = 8)

- Device failures (N=2)
- Dissatisfaction with outcome (N=4)
- Corneal decompensation (N=2)
IMT Removal Due to Device Failure  
(N = 2)

- Condensation in the telescope
- Cracks in lateral wall of the telescope
- No recurrences after
  - Physician training on handling of the IMT
  - Overall improvement in manufacturing process since early devices were fabricated
IMT Removal Due to Dissatisfaction  
(N = 4)

- Four subjects dissatisfied with outcome
  - Three subjects requested removal of the IMT based on complaints of glare in bright light
  - One subject complained of haze, loss of peripheral vision in implanted eye, loss of depth perception
IMT Removal Due to Corneal Decompensation (N = 2)

- Operative complications
  - In both eyes, positive vitreous pressure during implantation resulted in iris prolapse and shallowing of the anterior chamber, and significant early endothelial cell loss
  - In one of the two cases, one haptic was placed in the capsular bag and the other, in the sulcus
  - Corneal transplantation and IOL exchange was performed
# Major Non-Ocular Adverse Events (N = 206)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>7</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>12</td>
<td>5.8%</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>Death</td>
<td>10</td>
<td>4.9%</td>
</tr>
<tr>
<td>Falls</td>
<td>3</td>
<td>1.5%</td>
</tr>
<tr>
<td>Fractures</td>
<td>5</td>
<td>2.4%</td>
</tr>
<tr>
<td>Infection</td>
<td>19</td>
<td>9.2%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Source: PMA Table A49
## Major Non-Ocular Adverse Events (N = 206)

<table>
<thead>
<tr>
<th>Event</th>
<th>Subjects</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>7 subjects</td>
<td>3.4%</td>
</tr>
<tr>
<td>Cancer</td>
<td>12 subjects</td>
<td>5.8%</td>
</tr>
<tr>
<td>CVA/TIA</td>
<td>5 subjects</td>
<td>2.4%</td>
</tr>
<tr>
<td>Death</td>
<td>10 subjects</td>
<td>4.9%</td>
</tr>
<tr>
<td>Falls</td>
<td>3 subjects</td>
<td>1.5%</td>
</tr>
<tr>
<td>Fractures</td>
<td>5 subjects</td>
<td>2.4%</td>
</tr>
<tr>
<td>Infection</td>
<td>19 subjects</td>
<td>9.2%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>5 subjects</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

Source: PMA Table A49
# Fractures/Falls (N = 8)

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Description of Event</th>
<th>Relationship to IMT (Per Investigator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>008-213</td>
<td>Patient slid off ladder and fractured heel bone</td>
<td>Not Related</td>
</tr>
<tr>
<td>010-209</td>
<td>Patient fell 4 weeks after knee replacement, required right knee repair</td>
<td>Not Related</td>
</tr>
<tr>
<td>014-202</td>
<td>Fracture of the femur from a fall from a chair while attempting to pick up an object</td>
<td>Not Related</td>
</tr>
<tr>
<td>014-204</td>
<td>Patient hurriedly stood up to see across the street, tripped, fell, fractured wrist</td>
<td>Not Related</td>
</tr>
<tr>
<td>019-204</td>
<td>Patient fell out of bed</td>
<td>Not Related</td>
</tr>
<tr>
<td>023-204</td>
<td>Patient lost balance and fell</td>
<td>Not Related</td>
</tr>
<tr>
<td>023-212</td>
<td>Patient was sexually assaulted and, in addition to other trauma, fractured toe</td>
<td>Not Related</td>
</tr>
<tr>
<td>026-207</td>
<td>Patient stumbled backwards over her slipper, fell and fractured her hip</td>
<td>Not Related</td>
</tr>
</tbody>
</table>
Falls in the Elderly

Source: Beaver Dam Eye Study
Endothelial Cell Density
Specular Microscopy Methods

- Images analyzed at Emory University Specular Microscopy Reading Center (H Edelhauser, B McCarey)

- Endothelial images were scanned and then analyzed with Konan KSS-300 software

- 3 images per eye (implanted eye and fellow) for each visit were analyzed and the mean was calculated

- Specular images were difficult to obtain in the study population
  - At baseline, some difficulty fixating due to scotoma
  - Glare and reflection from the anterior surface of the IMT
Specular Microscopy
Estimates of Precision

- Best case - 2% SD (47 cells) for a single clinical site, single photographer imaging his own eye, and a single reader\(^1\)

- For multicenter study, precision varies from 8% to 10% with a single reader

\(^1\)Jones SS et al. Effect of laser in situ keratomileusis on the corneal endothelium. AJO 1998;125:465-71
Specular Images from Subject 23-201
Male, 79 Years of Age, Pseudophakic Fellow Eye

OS - IMT-Implanted Eye at 3 Months
1805 cells/mm²

OD - Fellow Eye at 3 Months
1798 cells/mm² (pseudophakic)
Results of Specular Microscopy
Endothelial Cell Density
IMT-Implanted Eyes (mean, SD)

24M: 1808 ± 596 (N=171)

Source: PMA Figure 11
Percentage Change in ECD from Baseline
IMT-Implanted Eyes (mean, SD)

Source: PMA Table A29
ECD In Subjects With Pseudophakic Fellow Eyes

Source: not in PMA
ECD (mean, SD) for IMT-Implanted Eyes, Pseudophakic and Phakic Fellow Eyes

Mean ECD cells/mm²

- IMT
- Pseudophakic
- Phakic

N=170
N=36
N=206

Source: PMA Table A27; (pseudo)phakic not in PMA
Percentage Change (mean, SD) in ECD Between Consecutive Visits
IMT-Implanted Eyes vs Pseudophakic & Phakic Fellow Eyes

-3% ± 15%
-2% ± 15%
0.2% ± 6%
-0.6% ± 7%
0.5% ± 8%
1.0% ± 19%
3% ± 15%
0.1% ± 7%
-2% ± 8%
-3% ± 14%
-3% ± 15%

ECD % Change

Source: PMA Table A31A, A31D; phakic not in PMA
How does the loss in ECD following IMT implantation compare to published data on conventional cataract surgery?
**Percentage ECD Loss Following Cataract Surgery**

<table>
<thead>
<tr>
<th>Publication or Study</th>
<th>3 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol IMT002 - IMT-Implanted Eyes (N=206)</td>
<td>20%</td>
<td>25%</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Protocol IMT002 - Pseudophakic fellow eyes (N=34)</td>
<td></td>
<td>16%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Intracapsular (N=99)</td>
<td>17%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extracapsular (N=99)</td>
<td>14%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracapsular, no IOL (N=20)</td>
<td>13%</td>
<td>16%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Intracapsular, IOL (N=96)</td>
<td>16%</td>
<td>22%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Extracapsular, no IOL (N=83)</td>
<td>11%</td>
<td>9%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>Extracapsular, IOL (N=393)</td>
<td>14%</td>
<td>17%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>N=50</td>
<td>19%</td>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>3.5mm CCI (N=27)</td>
<td>17%</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5mm CCI (N=27)</td>
<td>22%</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scleral Tunnel (N=27)</td>
<td>17%</td>
<td>19%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (N = 433)</td>
<td>7%</td>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Phaco (N=223)</td>
<td></td>
<td></td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>ECCE (N=210)</td>
<td></td>
<td></td>
<td></td>
<td>9%</td>
</tr>
</tbody>
</table>
What factors contributed to the acute and the overall reduction in ECD?
Candidate Predictive Factors

- Day 1 corneal edema
- ACD
- Surgical Order
- Incision Type
- Incision Size
- Age at implantation
- Preoperative ECD
- Surgeon
- Axial Length
- Use of Healon V
Factors Affecting Change in ECD
Final Models

3 Month Change in ECD

Day 1 Corneal Edema <.0001
Surgeon's Specialty 0.0336

Total Change in ECD

Day 1 Corneal Edema <.0001
Surgeon's Specialty 0.0336
Surgical Order 0.0023
Day 1 Corneal Edema and Surgical Order Interaction 0.0679

Source: PMA Table A39; A002 Table Q3.5.9
Percentage Change in ECD Stratified by Surgeon’s Specialty

<table>
<thead>
<tr>
<th>ECD Change %</th>
<th>Cornea</th>
<th>Non-cornea</th>
</tr>
</thead>
<tbody>
<tr>
<td>3M</td>
<td>p=0.005</td>
<td></td>
</tr>
<tr>
<td>6M</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td>9M</td>
<td>p=0.008</td>
<td></td>
</tr>
<tr>
<td>12M</td>
<td>p=0.01</td>
<td></td>
</tr>
<tr>
<td>18M</td>
<td>p=0.07</td>
<td></td>
</tr>
<tr>
<td>24M</td>
<td>p=0.01</td>
<td></td>
</tr>
</tbody>
</table>

Source: PMA Table A29F
Percentage Change in ECD Stratified by Surgeon’s Specialty and Surgical Order

-20.8% for Cornea cases 1-3
-20.1% for Non Cornea cases 1-3

-35.6% for Cornea cases 4+
-27.1% for Non Cornea cases 4+

Source: not in PMA
Effect of Anterior Chamber Depth on Change in ECD

- Linear effect on % change in ECD for surgical order ≤ 3 cases
  - \( p=0.01 \) for baseline to 3 months
  - \( p=0.03 \) for baseline to 24 months

- No effect for surgical order ≥ 4 cases
  - \( p=0.20 \) for baseline to 3 months
  - \( p=0.13 \) for baseline to 24 months

- Predictive power (coefficient of determination or \( R^2 \)) is low
  - 0.05 for baseline to 3 months
  - 0.07 for baseline to 24 months

Source: A003 Table 3.1A, 3.3A
How can we mitigate these contributors to endothelial cell loss?

- **Surgeon training**
  - Extensive training program described in PMA
  - Meticulous attention to surgical detail to avoid iris prolapse, flat anterior chamber and Day 1 corneal edema

- Suggest high ECD and deep ACD for first 5 cases for each surgeon
Following the initial surgical loss, does the rate of ECD loss decrease over time?
Percentage Change (mean, SD) in ECD Between Consecutive Visits
IMT-Implanted Eyes vs Pseudophakic & Phakic Fellow Eyes

Source: PMA Table A31A, A31D; phakic not in PMA
Annual Percentage Change in ECD

Source: PMA Table A37; A002 Table Q6.6
Relationship Between Early Loss of ECD and Later Loss of ECD

- ECD at 3 months is not predictive of the rate of ECD loss at later time points
  - No difference in corneas with 3-month loss of ECD < 20% vs loss of ECD > 20%
  - No difference in corneas with 3-month loss of ECD < 1000 cells/mm² vs ECD > 1000 cells/mm²

Source: PMA Table A37; A002 Table Q6.6
What is the rate of ECD loss more than two years after implantation?
Three-Piece Regression Model

- Change in rate of endothelial cell loss at 3 and 9 months
- Consistent with pathophysiology of endothelial cell loss after intraocular surgery
  - Acute loss at time of surgery
  - Endothelial cell migration
  - Continuing, long-term loss
Chronic Change in ECD
Baseline ECD 1600, 2000 and 2500 cells/mm² and ACD 3.0 mm
Piecewise Regression Model (3-Piece)

Source: A004 Table B
How can the corneal endothelium be protected?
Recommendations

- Establish a minimum endothelial cell density based on age and life expectancy
- High ECD and deep ACD for the first 5 cases
- Comprehensive surgeon training program
How can the loss in ECD be balanced against the significant improvement in vision and quality of life?
Change in ICD-9-CM Categories for Visual Impairment in IMT-Implanted Eyes

Source: not in PMA
Change in ICD-9-CM Categories for Visual Impairment in IMT-Implanted Eyes

Source: not in PMA
Risk vs Benefit Considerations

- Patient benefit: Improvement in vision, VFQ-25
- Patients with AMD place high value on vision
  - Brown et al\(^1\) identified utility value of approximately 0.5 for severe macular degeneration, i.e., patients would give up half of remaining years of life for normal vision

- Endothelial cell loss
  - Acute
  - Not substantially different from that seen after traditional cataract extraction with IOL implantation
  - Can be reduced by training

Implantable Miniature Telescope

- Defined risk, not substantially different from that of routine, modern, cataract surgery

- Risk is manageable by
  - Training
  - Appropriate selection of subjects
  - Informed consent
  - Multidisciplinary approach, including postoperative visual rehabilitation

- Substantial improvement in functional vision for an under-served population with limited treatment options