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

PROTOCOL IMT-002
CLINICAL REPORT

Formatted: French (France)

AUGUST 30, 2005

VISIONCARE OPHTHALMIC TECHNOLOGIES, INC.
14395 SARATOGA AVENUE, SUITE 150
SARATOGA, CA 95070

Formatted: French (France)

VISIONCARE OPHTHALMIC TECHNOLOGIES
IMPLANTABLE MINIATURE TELESCOPE (IMT)

PROTOCOL IMT-002
CLINICAL REPORT

TABLE OF CONTENTS

	VOLUME	PAGE
PERSONNEL AND FACILITIES	I	24
DEFINITIONS AND ABBREVIATIONS	I	27
1.0 INTRODUCTION & RATIONALE	I	28
2.0 STUDY OBJECTIVE	I	31
3.0 STUDY DESIGN	I	31
4.0 SAFETY & EFFECTIVENESS PARAMETERS	I	32
4.1 EFFECTIVENESS	I	32
4.2 SAFETY	I	32
5.0 PATIENT POPULATION	I	33
5.1 INCLUSION CRITERIA	I	33
5.2 EXCLUSION CRITERIA	I	33
6.0 DEVICE DESCRIPTION	I	35
6.1 DESCRIPTION OF THE INVESTIGATIONAL DEVICE	I	35
6.2 DEVICE COMPONENTS	I	36
7.0 STUDY PROCEDURES	I	38
7.1 SUBJECT ENTRY	I	38
7.2 PREOPERATIVE PROCEDURES	I	38
7.3 SURGICAL PROCEDURE	I	41
7.4 POSTOPERATIVE TREATMENT REGIMEN	I	43
7.5 EXAMINATION SCHEDULE	I	44
7.6 CLINICAL PARAMETERS	I	44
7.7 SPECULAR MICROSCOPY	I	45
7.8 DATA REPORTING	I	46
7.9 STUDY COMPLETION PROCEDURES	I	46

		VOLUME	PAGE
8.0	**STATISTICAL METHODS**	**I**	**47**
8.1	**SAMPLE SIZE**	**I**	**47**
8.2	**STATISTICAL ANALYSES**	**I**	**48**
8.2.1	**General Data Handling**	**I**	**48**
8.2.2	**Primary Effectiveness Endpoint Analysis**	**I**	**48**
8.2.3	**Primary Safety Endpoints**	**I**	**51**
8.2.4	**Secondary Effectiveness Endpoint Quality of Life**	**I**	**52**
8.2.5	**Other Clinical Parameters**	**I**	**52**
8.2.6	**Additional Statistical Analyses**	**I**	**52**
9.0	**REPORTING OF ADVERSE EVENTS AND DEVICE MALFUNCTIONS**	**I**	**57**
10.0	**STUDY MONITORING**	**I**	**59**
11.0	**STUDY RESULTS**	**I**	**60**
12.0	**ENROLLMENT AND ACCOUNTABILITY**	**I**	**61**
13.0	**DEMOGRAPHIC AND BASELINE CHARACTERISTICS**	**I**	**65**
14.0	**PREOPERATIVE PARAMETERS**	**I**	**66**
15.0	**OPERATIVE AND INTRAOPERATIVE PARAMETERS**	**I**	**67**
16.0	**SUMMARY OF VISUAL ACUITY EFFECTIVENESS AND SAFETY ENDPOINTS**	**I**	**69**
17.0	**EFFECTIVENESS OUTCOMES**	**I**	**75**
17.1	**IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCNVA)**	**I**	**75**
17.2	**IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8 INCHES**	**I**	**80**
17.3	**IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 16 INCHES**	**I**	**83**
17.4	**IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8 OR 16 INCHES**	**I**	**85**
17.5	**IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY CROSS-CORRELATED WITH IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY**	**I**	**91**
17.6	**QUALITY OF LIFE**	**I**	**96**

VOLUME PAGE

18.0 SAFETY OUTCOMES ..... I 108

18.1 PRESERVATION OF VISUAL ACUITY ..... I 108
18.2 SLIT LAMP FINDINGS ..... I 114
18.3 INTRAOCULAR PRESSURE ..... I 116
18.4 ENDOTHELIAL CELL DENSITY (ECD) ..... I 118
18.4.1 Accountability for Endothelial Cell Density Analysis ..... I 119
18.4.2 Endothelial Cell Density and Percent Change in ECD ..... I 120
18.4.3 Percent Change in ECD between Visits for IMT-Implanted Eyes and Pseudophakic Fellow Eyes ..... I 123
18.4.4 Analysis of Images Graded as "Good" ..... I 126
18.4.5 Stability of Endothelial Cell Density Stability ..... I 129
18.4.6 Annualized Percent Change in IMT Implanted Eyes and Pseudophakic Fellow Eyes ..... I 130
18.4.7 Factors Contributing to Endothelial Cell Loss at 3 Months ..... I 132
18.4.8 Effect of 3-month ECD Loss on Overall Loss of ECD ..... I 136
18.4.9 ECD < 1,000 cells/mm^2 ..... I 139
18.4.10 Additional Analyses of ECD ..... I 141
18.5 OCULAR COMPLICATIONS ..... I 142
18.6 OCULAR ADVERSE EVENTS ..... I 147
18.7 DEVICE FAILURES ..... I 153
18.8 NON-OCULAR ADVERSE EVENTS ..... I 154

19.0 SUMMARY & CONCLUSIONS- ..... I 158

19.1 EFFECTIVENESS OUTCOMES ..... I 158
19.2 SAFETY OUTCOMES ..... I 161
19.3 CONCLUSIONS ..... I 167

20.0 REFERENCES ..... I 169

APPENDICES

		VOLUME	PAGE
APPENDIX A	**COMPLETE DATA TABLES**	**II**	**172**
APPENDIX B	**INDIVIDUAL CASE HISTORIES**	**III**	**450**
APPENDIX B.1	CHOROIDAL DETACHMENT	III	451
APPENDIX B.2	CHOROIDAL HEMORRHAGE	III	452
APPENDIX B.3	CORNEAL DECOMPENSATION	III	453
APPENDIX B.4	CYCLITIC MEMBRANE & CYCLODIALYSIS CLEFT	III	456
APPENDIX B.5	EYES WITH >2 LINE LOSS OF BCDVA AND BCNVA	III	457
APPENDIX B.6	IMT DISLOCATION	III	463
APPENDIX B.7	INTRAOPERATIVE IMT EXCHANGE	III	464
APPENDIX B.8	INTRAOPERATIVE IMT REMOVAL AND ABORTED SURGERIES	III	471
APPENDIX B.9	POSTOPERATIVE IMT REMOVAL	III	472
APPENDIX B10	SIGNIFICANT ANTERIOR CHAMBER BLEEDING	III	482
APPENDIX B.11	SUBRETINAL HEMORRHAGE	III	483
APPENDIX B.12	VITREOUS HEMORRHAGE	III	484
APPENDIX B.13	DEATHS	III	485
APPENDIX C	**PATIENT PROFILES**	**III**	**494**
APPENDIX D	**PROTOCOL DEVIATIONS**	**III**	**610**
APPENDIX E	**PROTOCOL IMT-002 A PROSPECTIVE, MULTICENTER CLINICAL TRIAL OF THE IMPLANTABLE MINIATURE TELESCOPE (IMT™) IN PATIENTS WITH CENTRAL VISION IMPAIRMENT ASSOCIATED WITH AGE RELATED MACULAR DEGENERATION OR STARGARDT'S MACULAR DYSTROPHY**	**III**	**615**
APPENDIX F:	**QUALITY OF LIFE QUESTIONNAIRES**	**III**	**616**
APPENDIX F.1	VFQ-25	III	617
APPENDIX F.2	ACTIVITIES OF DAILY LIVING (ADL)	III	618

Formatted: French (France)

Formatted: French (France)

LISTING OF IN-TEXT TABLES

IMT INFORMATION

Table I Overall dimensions and physical characteristics of the IMT models

Table II Telescope optical features for the IMT

Table III Preoperative External Telescope Evaluation

STUDY METHODS

Table IV M-value with corresponding LogMAR at 8” and 16”

STUDY ADMINISTRATION

Table 1 Enrollment

Table 2 Accountability

Table 2A Protocol Deviations

Table 3 Demographic Information

Table 4 Preoperative Parameters

Table 5 Operative & Intraoperative Parameters

Formatted: French (France)

SUMMARY OF VISUAL ACUITY OUTCOMES

Table 6 Summary of Visual Acuity Effectiveness and Safety Endpoints

IMPROVEMENT IN BCDVA

Table 7 Improvement in Best Corrected Distance Visual Acuity (BCDVA)

Table 7.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) (Cumulative Frequency)

Table 7.2 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 12 Months Stratified by Preoperative BCDVA

Table 7.3 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by Preoperative BCDVA

Table 7.4 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA

Table 8 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8"

Table 8.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" (Cumulative Frequency)

Table 9 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16"

Table 9.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" (Cumulative Frequency)

Table 10 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16"

Table 10.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" (Cumulative Frequency)

Table 10.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 12 Months Stratified by Preoperative BCDVA

Table 10.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 18 Months Stratified by Preoperative BCDVA

Table 10.4 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA CROSS-CORRELATED WITH BCDVA

Table 11 Improvement in BCNVA versus Improvement in BCDVA at 12 Months
N = 193 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table 12 Improvement in BCNVA versus Improvement in BCDVA at 18 Months
N = 179 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table 13 Improvement in BCNVA versus Improvement in BCDVA at 24 Months
N = 147 Eyes Implanted with IMT with Either BCDVA or BCNVA

QUALITY OF LIFE QUESTIONNAIRES

Table 14 VFQ-25 Score

Table 15 Change in VFQ-25 Score from Baseline

Table 16 ADL Score

Table 17 Change in ADL Score from Baseline

Table 18 Correlation Between Change in VFQ-25 Overall Composite Score and Change in ADL Total Score
All Eyes Implanted with IMT and With Both VFQ & ADL Scores

SUMMARY OF VISUAL ACUITY SAFETY ENDPOINTS

Table 19 Summary of Visual Acuity Safety Endpoints

PRESERVATION OF VISUAL ACUITY

Table 20 Loss of Best Corrected Distance Visual Acuity (BCDVA)

Table 21 Loss of BCNVA versus Loss of BCDVA at 12 Months
N = 193 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table 22 Loss of BCNVA versus Loss of BCDVA at 18 Months
N = 179 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table 23 Loss of BCNVA versus Loss of BCDVA at 24 Months
N = 147 Eyes Implanted with IMT with Either BCDVA or BCNVA

SLIT LAMP AND IOP

Table 24 IMT Positioning

Table 25 Intraocular Pressure (IOP) and Change in IOP from Baseline

ENDOTHELIAL CELL LOSS

Table 26 Endothelial Cell Density Accountability

Table 27 Endothelial Cell Density (ECD)

Table 28 Endothelial Cell Density (ECD)
24-Month Consistent Cohort of Eyes Implanted with IMT

Table 29 Percentage Change in Endothelial Cell Density (ECD) from Baseline

Table 30 Percentage Change in Endothelial Cell Density (ECD) from Baseline
24-Month Consistent Cohort of Eyes Implanted with IMT

Table 31 Percentage Change in ECD Between Consecutive Postoperative Visits
All Eyes Implanted with IMT Versus All Pseudophakic Fellow Eyes

Table 32 Proportion of Eyes with Specular Images Graded as "Good"

Table 33 Percentage Change in ECD Between Consecutive Postoperative Visits
Based on Specular Images Graded as "Good"

Table 34 Endothelial Cell Density Stratified by Specular Image Quality

Table 35 Generalized Estimating Equation Analysis on
Percentage Change in Endothelial Cell Density Between Visits

Table 36 Generalized Estimating Equation Analysis on
Percentage Change in Endothelial Cell Density Between Visits
24-Month Consistent Cohort of Eyes Implanted with IMT

Table 37 Annual ECD Percentage Change Estimated Based on Records Between
9 to 24 Months

Table 38 Annual ECD Percentage Change Estimated Based on Records Between
9 to 24 Months
24-Month Consistent Cohort of Eyes Implanted with IMT

Table 39 ECD Percentage Change at 3 Months from Baseline
Modeling Analyses
All Eyes Implanted with IMT &ECD Change at 3 Months

Table 40 ECD Percentage Change at 3 Months from Baseline
Modeling Analyses - Final Model
All Eyes Implanted with IMT &ECD Change at 3 Months

Table 41 Percentage Change in ECD Between Consecutive Postoperative Visits
Stratified by ECD Percent Loss from Baseline at 3 Months

of ≤ 20% vs > 20%

Table 42 Percentage Change in ECD Between Consecutive Postoperative Visits Stratified by ECD at 3 Months of ≤ 1000 cells/mm^2 vs >1000 cells/mm^2

Table 43 Day 1 Cornea of Normeal/1+ Edema and ≥ 2+ Edema Versus IMT Implanted Eyes with ECD < 1000 cells/mm^2 and IMT Implanted Eyes Without ECD < 1000 cells/mm^2

Table 44 Flat Anterior Chamber or Iris Related Safety Events Versus IMT Implanted Eyes with ECD < 1000 cells/mm^2 and IMT Implanted Eyes Without ECD < 1000 cells/mm^2

COMPLICATIONS AND ADVERSE EVENTS

Table 45 Reported Ocular Complications Eyes with IMT not Successfully Implanted

Table 46 Reported Ocular Complications All Eyes Implanted with IMT

Table 47 Reported Ocular Adverse Events Eyes with IMT not Successfully Implanted

Table 48 Reported Ocular Adverse Events All Eyes Implanted with IMT

Table 49 Reported Non-Ocular Events All Study Subjects

Table 50 Summary of Improvement in Visual Acuity

LISTING OF IN-TEXT FIGURES

Figure 1 VisionCare Wide Angle Implantable Miniature Telescope

Figure 2 Image Distribution with the IMT

Figure 3 WA 3.0X IMT and IMT Components

Figure 4 Primary Efficacy Endpoint: ≥ 2 line gain in BCDVA or BCNVA

Figure 5 Efficacy: ≥ 2 line gain in BCDVA and BCNVA

Figure 6 Safety – Preservation Visual Acuity
> 2 lines loss in BCDVA and no change/loss in BCNVA or
> 2 lines loss in BCNVA and no change/loss in BCDVA

Figure 7 Improvement in Best Corrected Distance Visual Acuity

Figure 8 Improvement in Best Corrected Near Visual Acuity at 8” or 16”

Figure 9 Quality of Life VFQ-25
Change in Quality of Vision Subscales

Figure 10 Quality of Life VFQ-25
Change in Vision Specific Activities Subscales

Figure 11 Endothelial Cell Density in IMT-Implanted Eyes

Figure 12 Mean and Standard Deviation of ECD Percentage Change Between
Consecutive Postoperative Visits
Eyes Implanted with IMT Versus Pseudophakic Fellow Eyes

LISTING OF ALL TABLES

APPENDIX A

STUDY ADMINISTRATION

Table A1 Enrollment
(N = 218 Enrolled, 217 Operated, 206 Successfully Implanted)

Table A2 Accountability
(N = 206 Eyes Successfully Implanted with IMT)

Table A2.1 Accountability
(N = 115 Eyes Successfully Implanted with WA 2.2X)

Table A2.2 Accountability
(N = 91 Eyes Successfully Implanted with WA 3.0X)

Table A3 Demographic Information

Table A4 Preoperative Parameters

Table A5 Operative & Intraoperative Parameters

SUMMARY OF VISUAL ACUITY OUTCOMES

Table A6 Summary of Visual Acuity Effectiveness and Safety Endpoints

Table A6A.1 Summary of Visual Acuity Effectiveness and Safety Endpoints at 12 Months Stratified by Age

Table A6A.2 Summary of Visual Acuity Effectiveness and Safety Endpoints at 18 Months Stratified by Age

Table A6A.3 Summary of Visual Acuity Effectiveness and Safety Endpoints at 24 Months Stratified by Age

Table A6B.1 Summary of Visual Acuity Effectiveness and Safety Endpoints at 12 Months Stratified by Gender

Table A6B.2 Summary of Visual Acuity Effectiveness and Safety Endpoints at 18 Months Stratified by Gender

Table A6B.3 Summary of Visual Acuity Effectiveness and Safety Endpoints at 24 Months Stratified by Gender

Table A6C.1 Summary of Visual Acuity Effectiveness and Safety Endpoints at 12 Months Stratified by IMT Model

Table A6C.2 Summary of Visual Acuity Effectiveness and Safety Endpoints at18 Months Stratified by IMT Model

Table A6C.3 Summary of Visual Acuity Effectiveness and Safety Endpoints at 24 Months Stratified by IMT Model

Table A6D.1 Summary of Visual Acuity Effectiveness and Safety Endpoints at 12 Months Stratified by Preoperative BCDVA

Table A6D.2 Summary of Visual Acuity Effectiveness and Safety Endpoints at 18 Months Stratified by Preoperative BCDVA

Table A6D.3 Summary of Visual Acuity Effectiveness and Safety Endpoints at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCDVA

Table A7 Improvement in Best Corrected Distance Visual Acuity (BCDVA)

Table A7.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) Cumulative Frequency

Table A7A.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 12 Months Stratified by Age

Table A7A.2 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 18 Months Stratified by Age

Table A7A.3 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by Age

Table A7B.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 12 Months Stratified by Gender

Table A7B.2 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 18 Months Stratified by Gender

Table A7B.3 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by Gender

Table A7C.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 12 Months Stratified by IMT Model

Table A7C.2 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 18 Months Stratified by IMT Model

Table A7C.3 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by IMT Model

Table A7D.1 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 12 Months Stratified by Preoperative BCDVA

Table A7D.2 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 18 Months Stratified by Preoperative BCDVA

Table A7D.3 Improvement in Best Corrected Distance Visual Acuity (BCDVA) at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA AT 8 INCHES

Table A8 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8"

Table A8.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" Cumulative Frequency

Table A8A.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 12 Months Stratified by Age

Table A8A.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 18 Months Stratified by Age

Table A8A.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 24 Months Stratified by Age

Table A8B.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 12 Months Stratified by Gender

Table A8B.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at18 Months Stratified by Gender

Table A8B.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 24 Months Stratified by Gender

Table A8C.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 12 Months Stratified by IMT Model

Table A8C.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 18 Months Stratified by IMT Model

Table A8C.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 24 Months Stratified by IMT Model

Table A8D.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 12 Months Stratified by Preoperative BCDVA

Table A8D.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 18 Months Stratified by Preoperative BCDVA

Table A8D.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA AT 16 INCHES

Table A9 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16"

Table A9.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" Cumulative Frequency

Table A9A.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 12 Months Stratified by Age

Table A9A.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 18 Months Stratified by Age

Table A9A.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 24 Months Stratified by Age

Table A9B.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 12 Months Stratified by Gender

Table A9B.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 18 Months Stratified by Gender

Table A9B.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 24 Months Stratified by Gender

Table A9C.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 12 Months Stratified by IMT Model

Table A9C.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 18 Months Stratified by IMT Model

Table A9C.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 24 Months Stratified by IMT Model

Table A9D.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 12 Months Stratified by Preoperative BCDVA

Table A9D.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" at 18 Months Stratified by Preoperative BCDVA

Table A9D.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 16" `at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA AT 8 OR 16 INCHES

Table A10 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16"

Table A10.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" Cumulative Frequency

Table A10A.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 12 Months Stratified by Age

Table A10A.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 18 Months Stratified by Age

Table A10A.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 24 Months Stratified by Age

Table A10B.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 12 Months Stratified by Gender

Table A10B.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 18 Months Stratified by Gender

Table A10B.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 24 Months Stratified by Gender

Table A10C.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 12 Months Stratified by IMT Model

Table A10C.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 18 Months Stratified by IMT Model

Table A10C.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 24 Months Stratified by IMT Model

Table A10D.1 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 12 Months Stratified by Preoperative BCDVA

Table A10D.2 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 18 Months Stratified by Preoperative BCDVA

Table A10D.3 Improvement in Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" at 24 Months Stratified by Preoperative BCDVA

IMPROVEMENT IN BCNVA CROSS-CORRELATED WITH IMPROVEMENT IN BCDVA, GEE TABLES

Table A11 Improvement in BCNVA versus Improvement in BCDVA at 12 Months N = 193 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table A12 Improvement in BCNVA versus Improvement in BCDVA at 18 Months N = 179 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table A13 Improvement in BCNVA versus Improvement in BCDVA at 24 Months N = 147 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table AGEE1 Generalized Estimating Equation Analysis on Effectiveness Endpoint from 12 to 24 Months

Table AGEE2 Effectiveness Endpoint by Patient's Age and IMT Model

QUALITY OF LIFE QUESTIONNAIRES

Table A14 VFQ-25 Score

Table A15 Change in VFQ-25 Score from Baseline

Table A15A Change in VFQ-25 Overall Composite Score from Baseline at 12 Months Stratified by Age

Table A15B Change in VFQ-25 Overall Composite Score from Baseline at 12 Months Stratified by Gender

Table A15C Change in VFQ-25 Overall Composite Score from Baseline at 12 Months Stratified by IMT Model

Table A15D Change in VFQ-25 Overall Composite Score from Baseline at 12 Months Stratified by Preoperative BCDVA

Table A15E Change in VFQ-25 Overall Composite Score from Baseline at 12 Months Stratified by 12-Month Visual Acuity Improvement

Table A15F Subjects with VFQ-25 Overall Composite Score 15 Points worse at the Last Available Visit than at Baseline

Table A16 ADL Score

Table A17 Change in ADL Score from Baseline

Table A17A Change in ADL Total Score from Baseline at 12 Months Stratified by Age

Table A17B Change in ADL Total Score from Baseline at 12 Months Stratified by Gender

Table A17C Change in ADL Total Score from Baseline at 12 Months Stratified by IMT Model

Table A17D Change in ADL Total Score from Baseline at 12 Months Stratified by Preoperative BCDVA

Table A17E Change in ADL Total Score from Baseline at 12 Months Stratified by 12-Month Visual Acuity Improvement

Table A18 Correlation Between Change in VFQ-25 Overall Composite Score and Change in ADL Total Score
All Eyes Implanted with IMT and With Both VFQ & ADL Scores

SUMMARY OF VISUAL ACUITY SAFETY ENDPOINTS

Table A19 Summary of Visual Acuity Safety Endpoints

Table A19A Subjects Reported with More Than 2 Lines Loss of BCDVA Without at Least 2 Lines Gain in BCNVA at Last Available Visit

Table A19B Subjects Reported with More Than 2 Lines Loss of BCNVA Without at Least 2 Lines Gain in BCDVA at Last Available Visit

PRESERVATION OF VISUAL ACUITY

Table A20 Loss of Best Corrected Distance Visual Acuity (BCDVA)

Table A20A Loss of Best Corrected Near Visual Acuity (BCNVA) at 8"

Table A20B Loss of Best Corrected Near Visual Acuity (BCNVA) at 16"

Table A20C Loss of Best Corrected Near Visual Acuity (BCNVA) at 8" or 16" with no Gain of ≥2 lines at the Other Near Distance

Table A21 Loss of BCNVA versus Loss of BCDVA at 12 Months
N = 193 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table A22 Loss of BCNVA versus Loss of BCDVA at 18 Months
N = 179 Eyes Implanted with IMT with Either BCDVA or BCNVA

Table A23 Loss of BCNVA versus Loss of BCDVA at 24 Months
N = 147 Eyes Implanted with IMT with Either BCDVA or BCNVA

SLIT LAMP AND IOP

Table A24 IMT Positioning

Table A24A Slit Lamp Examination — Cornea

Table A24B Slit Lamp Examination — Endothelium

Table A24C Slit Lamp Examination — Anterior Chamber Cells

Table A24D Slit Lamp Examination — Anterior Chamber Flare

Table A24E Slit Lamp Examination — Iris

Table A24F Posterior Capsular Opacification

Table A25 Intraocular Pressure (IOP) and Change in IOP from Baseline

ENDOTHELIAL CELL LOSS

Table A26 Endothelial Cell Density Accountability

Table A27 Endothelial Cell Density (Mean, SD)

Table A27A Endothelial Cell Density (Mean, SD Stratified by Day-1 Corneal Edema

Table A27B Endothelial Cell Density (Mean, SD) Stratified by ACD

Table A27C Endothelial Cell Density (Mean, SD) Stratified by Surgical Order

Table A27D Endothelial Cell Density (Mean, SD) Stratified by Incision Type

Table A27E Endothelial Cell Density (Mean, SD) Stratified by Incision Size

Table A27F Endothelial Cell Density (Mean, SD) Stratified by Surgeon’s Specialty

Table A27G Endothelial Cell Density (Mean, SD) Stratified by Subject's Age at Implant

Table A27H Endothelial Cell Density (Mean, SD) Stratified by Preoperative ECD

Table A27I Endothelial Cell Density ((Mean, SD) Stratified by Surgeon

Table A27J Endothelial Cell Density (Mean, SD) Stratified by Axial Length

Table A27K Endothelial Cell Density (Mean, SD) Stratified by Use of Healon V

Table A28 Endothelial Cell Density (Mean, SD)
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A28A Change in ECD from Baseline (Mean, SD)

Table A28B Change in ECD from Baseline (Mean, SD)
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A29 Percentage Change in ECD from Baseline (Mean, SD)

Table A29A Percentage Change in ECD from Baseline (Mean, SD) Stratified by Day-1 Corneal Edema

Table A29B Percentage Change in ECD from Baseline (Mean, SD) Stratified by ACD

Table A29C Percentage Change in ECD from Baseline (Mean, SD) Stratified by Surgical Order

Table A29D Percentage Change in ECD from Baseline (Mean, SD) Stratified by Incision Type

Table A29E Percentage Change in ECD from Baseline (Mean, SD) Stratified by Incision Size

Table A29F Percentage Change in ECD from Baseline (Mean, SD) Stratified by Surgeon's Specialty

Table A29G Percentage Change in ECD from Baseline (Mean, SD) Stratified by Subject's Age at Implant

Table A29H Percentage Change in ECD from Baseline (Mean, SD) Stratified by Preoperative ECD

Table A.29I Percentage Change in ECD from Baseline (Mean, SD) Stratified by Surgeon

Table A29J Percentage Change in ECD from Baseline (Mean, SD) Stratified by Axial Length

Table A29K Percentage Change in ECD from Baseline (Mean, SD) Stratified by Use of Healon V

Table A30 Percentage Change in ECD from Baseline (Mean, SD)
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A31 Percentage Change in ECD Between Consecutive Postoperative Visits
All Eyes Implanted with IMT Versus All Pseudophakic Fellow Eyes

Table A31A Percentage Change in ECD Between Consecutive Postoperative Visits
All Eyes Implanted with IMT

Table A31B Percentage Change in ECD Between Consecutive Postoperative Visits
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A31C Percentage Change in ECD Between Consecutive Postoperative Visits
Fellow Eyes of Subjects Implanted with IMT

Table A31D Percentage Change in ECD Between Consecutive Postoperative Visits
Pseudophakic Fellow Eyes of Subjects Implanted with IMT

Table A32 Proportion of Eyes with Specular Microscopy Images Graded as “Good”
Subjects Implanted with IMT

Table A33 Percentage Change in ECD Between Consecutive Postoperative Visits
Based on Specular Images Graded as “Good”
All Eyes Implanted with IMT

Table A34 Endothelial Cell Density Stratified by Specular Image Quality
All Eyes Implanted with IMT

Table A35 Generalized Estimating Equation Analysis on Percentage Change in Endothelial Cell Density Between Visits

Table A36 Generalized Estimating Equation Analysis on Percentage Change in Endothelial Cell Density Between Visits
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A36A Generalized Estimating Equation Analysis on Endothelial Cell Density from 3 to 24 Months

Table A36B Generalized Estimating Equation Analysis on
Endothelial Cell Density from 3 to 24 Months
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A37 Annual ECD Percentage Change Estimated Based on Records Between 9 to 24 Months

Table A37A Annual ECD Percentage Change Estimated Based on Records Between 9 to 24 Months
Fellow Eyes of Subjects Implanted with IMT

Table A37B Annual ECD Percentage Change Estimated Based on Records Between 9 to 24 Months
Pseudophakic Fellow Eyes of Subjects Implanted with IMT

Table A38 Annual ECD Percentage Change Estimated Based on Records Between 9 to 24 Months
24-Month Consistent Cohort of Eyes Implanted with IMT

Table A38A Annual ECD Percentage Change Estimated Based on Records Between 9 to 24 Months Stratified by Clinically Important Factors

Table A39 ECD Percentage Change at 3 Months from Baseline
Modeling Analyses
All Eyes Implanted with IMT & ECD Change at 3 Months

Table A40 ECD Percentage Change at 3 Months from Baseline
Modeling Analyses – Final Model
All Eyes Implanted with IMT & ECD Change at 3 Months

Table A40A 3-Month ECD Loss More Than 20% from Baseline
Logistic Regression Analyses
All Eyes Implanted with IMT & ECD Change at 3 Months

Table A41 Percentage Change in ECD Between Consecutive Postoperative Visits
Stratified by ECD Percent Loss from Baseline at 3 Months of $\leq$20% vs >20%

Table A42 Percentage Change in ECD between Consecutive Postoperative Visits
Stratified by ECD at 3 Months of $\leq$1000 cells/mm^2 vs >1000 cells/mm^2

Table A42A Eyes with Postoperative ECD < 1000 at Any Visit
(Prior to IMT Removal for Subjects with IMT Removal)
Data Line Listing

Table A43 Day 1 Corneal Status of Normal/1+ Edema and $\geq$2+ Edema versus IMT Implanted Eyes with ECD <1000 cells/mm^2 and IMT Implanted Eyes without ECD <1000 cells/mm^2

Table A44 Flat Anterior Chamber or Iris Related Safety Events versus IMT Implanted Eyes with ECD <1000 cells/mm^2 and IMT Implanted Eyes without ECD <1000 cells/mm^2

COMPLICATIONS AND ADVERSE EVENTS

Table A45 Reported Ocular Complications
Eyes with IMT Not Successfully Implanted

Table A46 Reported Ocular Complications
All Eyes Implanted with IMT

Table A47 Reported Ocular Adverse Events
Eyes with IMT Not Successfully Implanted

Table A47A Subject IDs for Reported Ocular Adverse Events
Eyes with IMT Not Successfully Implanted

Table A47B Reported Ocular Adverse Events Data Line Listing
Eyes with IMT Not Successfully Implanted

Table A48 Reported Ocular Adverse Events
All Eyes Implanted with IMT

Table A48A Subject IDs for Reported Ocular Adverse Events
All Eyes Implanted with IMT

Table A48B Reported Ocular Adverse Events Data Line Listing
All Eyes Implanted with IMT

Table A49 Reported Non-Ocular Events
All Eyes Implanted with IMT

VISIONCARE OPHTHALMIC TECHNOLOGIES, INC.

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 (AMD)

CLINICAL REPORT

PERSONNEL AND FACILITIES

STUDY SPONSOR

VisionCare Ophthalmic Technologies, Inc.
14395 Saratoga, Ave., Suite 150
Saratoga, CA 95070
(408) 872-9393 Phone
(408) 872-9395 Fax

Formatted: French (France)

MEDICAL MONITOR

Stephen S. Lane, MD
Associated Eye Care
232 North Main Street
Stillwater, MN 55082

SPECULAR MICROSCOPY READING CENTER

Bernard E. McCarey, PhD
Professor, Ophthalmology
Emory University
1380 Oxford Road, NE
Atlanta, GA 30322

PRINCIPAL INVESTIGATORS/SITES

Carl Baker, MD
Paducah Retinal Center
1900 Broadway, Suite 2
Paducah, KY 42001

Daniel Berinstein, MD
Retina Group of Washington
5454 Wisconsin Ave., Suite 1540
Chevy Chase, MD 20815

Formatted: French (France)

David Chang, MD
Altos Eye Physician
762 Altos Oaks Drive, Suite 1
Los Altos, CA 94024

Brian Connolly, MD
Wills Eye Hospital, Retina Research
840 Walnut Street, Suite 1020
Philadelphia, PA 19107

Formatted: Spanish (Argentina)

PRINCIPAL INVESTIGATORS/SITES (CONTINUED)

Doug Dehning, MD
Discover Vision Centers
4741 South Cochise Drive
Independence, MO 64055

Sharon Fekrat, MD
Duke University Eye Center
Box 3802, Erwin Rd.
Room 304
Durham, NC 27710

Howard Fine, MD
Fine Hoffman & Packer
1550 Oak Street, Suite 5
Eugene, OR 97401

Stephen Fisher, MD
Medical Center Ophthalmology
9157 Huebner Road
San Antonio, TX 78240

Formatted: Spanish (Argentina)

M. Bowes Hamill, MD
Baylor College of Medicine
6565 Fannin, NC205
Houston, TX 77030

Dennis Han, MD
Medical College of Wisconsin
Eye Institute
925 N. 87th Street
Milwaukee, WI 53226

Jeffrey Heier, MD
OCB Boston
50 Staniford Street, Suite 600
Boston, MA 02114

Henry Hudson, MD
Retina Centers P.C.
6585N. Oracle Road, Suite A
Tucson, AZ 85704

Manus Kraff, MD
Kraff Eye Institute
3115 North Harlem, Suite 300
Chicago, IL 60634

Baruch D. Kuppermann, MD
University of California at Irvine
118 Med Surge I
Irvine, CA 92697

Formatted: Norwegian (Bokmål)

Stephen S. Lane, MD
Associated Eye Care
232 North Main Street
Stillwater, MN 55082

Robert Leonard, MD
Dean A. McGee Eye Institute
608 Stanton L. Young Blvd.,
Suite 554
Oklahoma City, OK 73104

Paul R. Lichter MD
University of Michigan
W.K. Kellogg Eye Center
1000 Wall Street
Ann Arbor, MI 48105

Dan Martin, MD
Emory Eye center
1365B Clifton Road N.E.
Atlanta, GA 30322

PRINCIPAL INVESTIGATORS/SITES (CONTINUED)

Joan Miller, MD
Kathryn Colby, MD
Massachusetts Eye & Ear Infirmary
Schepens Eye Research Institute
243 Charles Street, Suite 808
Boston, MA 02114

Srinivas Reddy Sadda, MD
Doheny Retina Institute
University of Southern California
1450 San Pablo Street, DEI 3615
Los Angeles, CA 90033

Formatted: Norwegian (Bokmål)
Formatted: Spanish (Argentina)
Formatted: French (France)

Oliver D. Schein, MD, MPH
Wilmer Ophthalmological Institute
Johns Hopkins University School of Medicine
116 Wilmer Building
600 North Wolfe St.
Baltimore, MD 21287-9277

Lawrence J. Singerman, MD
Retina Associates of Cleveland
3401 Enterprise Pkwy., Suite 300
Beachwood, OH 44122

Formatted: German (Germany)

Jason S. Slakter, MD
Manhattan Eye & Ear
210 E. 64th St., 8th floor
New York, NY 10021

Paul Sternberg, MD
Vanderbilt University
Department of Ophthalmology & Visual Sciences
8000 Medical Center East-8808
Nashville, TN 37232

Donald Stewart, MD
Southeast Clinical Research
6035 Fairview Road
Charlotte, NC 28210

Michael T. Trese, MD
Associated Retinal Consultants
3535 W. 13th Mile Road, Suite 636
Royal Oak, MI 48073

Keye Wong, MD
Sarasota Retinal Institute
3400 Bee Ridge Road, Suite 200
Sarasota, FL 34239

Seth Yoser, MD
Vitreoretinal Foundation
825 Ridgelake Blvd.
Memphis, TN 38120

Formatted: English (U.S.)

DEFINITIONS AND ABBREVIATIONS

ACD	Anterior Chamber Depth
AMD	Age-related Macular Degeneration
ANOVA	Analysis of Variance
BCDVA	Best Corrected Distance Visual Acuity
BCNVA	Best Corrected Near Visual Acuity
BCVA	Best Corrected Visual Acuity
CCI	Clear Corneal Incision
CFR	Code of Federal Regulations
CNV	Choroidal Neovascularization
CRF	Case Report Form
ECCE	Extra-Capsular Cataract Extraction
ECD	Endothelial Cell Density
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GEE	Generalized Estimating Equation
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IMT	Implantable Miniature Telescope
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
NA	Not applicable
ND	Not done
NAV	Missing or not available
OVD	Ophthalmic Viscosurgical Device
PKP	Penetrating Keratoplasty
PMA	Pre-Market Approval
PMMA	Polymethyl Methacrylate
SD	Standard Deviation
WA	Wide Angle

Formatted: French (France)

Formatted: French (France)

1.0 INTRODUCTION AND RATIONALE

1.1 MACULAR DYSTROPHIES AND DEGENERATIONS

Acquired and hereditary macular dystrophies and degenerations are a leading cause of central vision impairment and blindness. Age-related macular degeneration (AMD) is the most common form of macular dystrophy.

Macular degeneration refers to the breakdown of cells in the macula (the center of the retina). Some degeneration is an inevitable consequence of the aging process. However, when it is coupled with the loss of sight in the central part of the field of vision, an underlying pathology is considered present. It is estimated that in the US, AMD affects 1% of all 55-year-olds, and the incidence increases with age, reaching approximately 15% among those aged 80 and over.[1] With increasing longevity, it is anticipated that the incidence of AMD will increase significantly.[1]

AMD often reduces the ability of affected individuals to engage in everyday activities that require detailed central vision, resulting in elevated risk of depression, increased levels of dependency, and an overall decrease in the quality of life.[2-4] Currently there is no effective treatment for the majority of patients. For a minority of patients (i.e., those with wet AMD resulting from choroidal neovascularization [CNV]) advances in therapies have led to improvements in the management of the rate of vision loss. These treatments include biopharmaceutical therapy, photodynamic therapy, submacular surgery and photocoagulation. However, no viable treatments are available for the several hundred thousand individuals with moderate to profound central vision loss due to late-stage dry, atrophic AMD (geographic atrophy), end stage CNV with disciform scar and other maculopathies.

The only corrective interventions currently available to patients with geographic atrophy or disciform scar AMD are vision aids such as special spectacles and head-mounted or hand-held telescopes, which magnify images on the retina. While these aids are widely available, they are of limited utility, difficult to use, bulky, uncomfortable and unattractive. In addition, use of external telescopes requires suppression of natural eye movements. Instead, the patient has to learn to scan the visual field by moving his/her entire head. If not properly adapted to this behavioral change requirement, a conflict between the visual and vestibular systems may arise, resulting in nausea.

Formatted: English (U.S.)

1.2 THE WIDE ANGLE IMPLANTABLE MINIATURE TELESCOPE

VisionCare's Wide Angle Implantable Miniature Telescope (IMT™ by Dr. Isaac Lipshitz) is a visual prosthetic device (Figure 1). The IMT, which functions as a fixed focus telephoto device in conjunction with the cornea, contains two micro lenses that magnify objects in the central visual field. A magnified image is projected by the IMT onto approximately 55° of the retina (Figure 2), enabling the patient to recognize

and respond to objects that could not otherwise be seen. The optical component is embedded in a carrier, which is intended to be implanted in the capsular bag in the posterior chamber of the eye, in place of the eye's crystalline lens. The implant procedure is performed by an ophthalmologist specializing in anterior segment surgery.

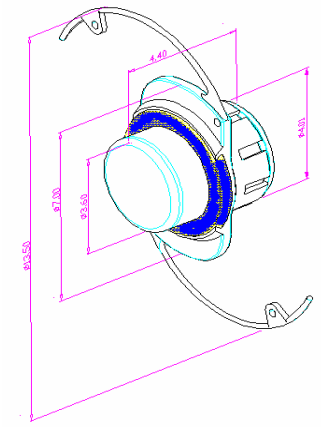


FIGURE 1. THE IMT

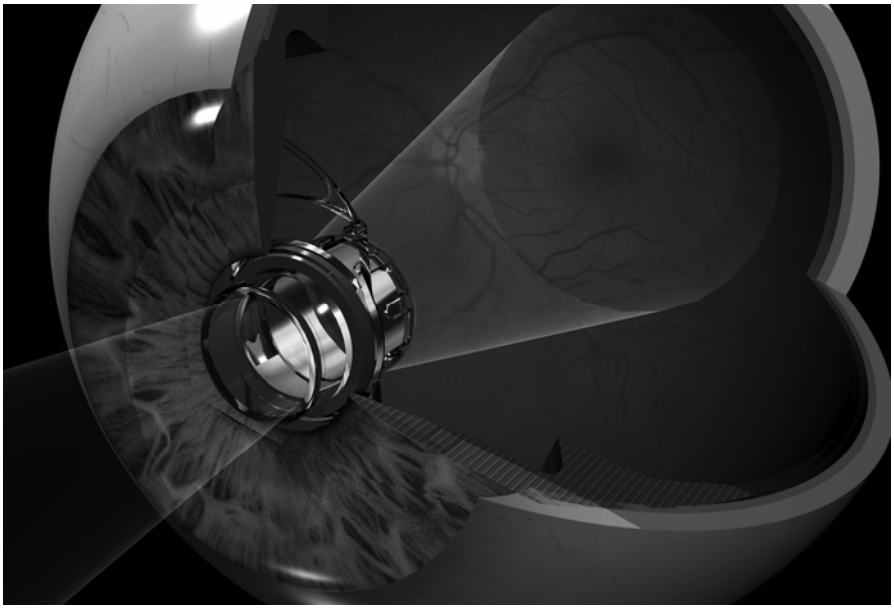


FIGURE 2. IMAGE DISTRIBUTION WITH THE IMT

The IMT is indicated for use in patients with bilateral, stable macular degeneration. Vision loss must be sufficiently advanced to have caused moderate to profound central vision loss, but adequate peripheral vision must be retained. The IMT is implanted in one of the patient's eyes. In this way, the implanted eye provides a magnified view of the central visual field while the non-implanted eye provides peripheral vision.

1.3 ADVANTAGES OF THE IMT

The primary advantage of the IMT over alternative treatments for impaired central vision is that the IMT allows scanning of reading materials and other images using natural eye movements, rather than head movements. Since there is no relative movement between the eye and the telescope, there are no induced optical aberrations. The wide angle micro lens optics also provide a wide view (20° or more) of the central visual field (retinal image of approximately 55°). The placement of the magnifying device entirely inside the eye eliminates vertex distance (to cornea) issues, increased perceived speed of motion and vestibular conflict. The IMT can be used for both distance and, with the use of a low plus spectacle lens, near vision activities. Furthermore, unlike hand-held or hand operated magnifiers, IMT implanted patients have both hands available to perform daily activities for self-care, hobbies, and other activities of daily living.

Results from a U.S. feasibility study of the IMT provided initial evidence of safety and effectiveness. The majority of patients experienced an improvement in best corrected distance and/or near visual acuity, and all but one of the complications and adverse events resolved without sequelae.

Data generated in the feasibility study supported initiation of a definitive PMA clinical trial under protocol IMT-002, in which 206 eyes from 206 subjects underwent implantation of IMT. The purpose of this clinical report is to describe the safety and effectiveness of IMT implantation in patients with moderate to profound bilateral vision impairment due to AMD, in support of this marketing application (PMA) for the IMT.

2.0 STUDY OBJECTIVE

The primary objective of IMT-002 study is to evaluate the safety and effectiveness of the Implantable Miniature Telescope (IMT) for the improvement of visual acuity in patients with bilateral moderate to profound central vision impairment due to age-related macular degeneration.

3.0 STUDY DESIGN

This is a prospective multicenter clinical trial. All investigators secured Institutional Review Board (IRB) approval prior to subject enrollment, provided financial disclosure as required by FDA regulation, and signed investigator's agreements that identified their responsibilities with regard to study conduct per Good Clinical Practices (GCP) and the IDE regulations. None of the study investigators, including the medical monitor, had a financial interest in VisionCare during the course of the study or received stock options as part of their compensation.

Twenty-eight (28) clinical sites enrolled a total of 218 consecutive patients and 206 patients have been implanted and are being followed over a 24-month period. No patient was allowed to be enrolled in this study without prior written enrollment authorization approval from the Sponsor or its designee. An Enrollment Authorization Section on the preoperative CRF was completed and approved by the Sponsor or designee for each patient prior to treatment.

This study is conducted in compliance with the Code of Federal Regulations (CFR) for institutional review boards (U.S. 21 CFR, Part 56), sponsor and investigator obligations (U.S. 21 CFR, Part 812), and informed consent (U.S. 21 CFR, Part 50). This study is conducted in compliance with the Declaration of Helsinki.

Signed and dated informed consent was obtained from each patient prior to any study-specific procedure and device implantation in accordance with ICH and GDA Good Clinical Practices (GCP) and local regulatory and legal requirements.

4.0 SAFETY & EFFECTIVENESS PARAMETERS

Safety and effectiveness parameters are defined as follows:

4.1 EFFECTIVENESS

4.1.1 The primary effectiveness endpoint is defined as an improvement of 2 lines or greater in either near or distance best corrected acuity in 50% of the implanted eyes at 12 months post-implantation.

4.1.2 Quality of Life surveys (ADL and VFQ-25) are secondary measurements of procedure success.

4.2 SAFETY

4.2.1 Endothelial cell loss: Mean percentage endothelial cell loss less than or equal to 17% at one year post IMT implantation, the average endothelial cell loss reported in a survey of published literature on large-incision cataract surgery.

4.2.2 Preservation of best corrected visual acuity, i.e., no more than 10% of implanted eyes were to experience a loss of more than 2 lines of either near or distance BCVA without a corresponding improvement (gain of 2 lines or more) in BCVA (a gain of 2 or more lines of near BCVA in eyes with loss of more than 2 lines distance BCVA, and vice versa).

4.2.3 Adverse events and complications.

5.0 PATIENT POPULATION

A total of two hundred eighteen (218) consecutive patients who provided informed consent, were capable of comprehending the nature of the study, and were likely to comply with the visit schedule, were entered into the study. The following inclusion and exclusion criteria were identified in the study protocol.

5.1 INCLUSION CRITERIA

- Bilateral, stable, untreatable central vision disorders (untreatable AMD or Stargardt's macular dystrophy) as determined by fluorescein angiography, and cataract.
- Distance BCVA between 20/80 and 20/800, and adequate peripheral vision in one eye (the non-implanted eye) to allow navigation.
- Achievement of at least a five-letter improvement on the ETDRS chart in the eye scheduled for surgery, with the external telescope.
- Anterior chamber depth of ≥ 2.5mm in the operative eye.
- Available for the study duration of approximately 24 months and willing to return for all visits for training and evaluation.
- Alert, mentally competent, and able to understand and comply with the requirements of the clinical trial, and be personally motivated to abide by the requirements and restrictions of the clinical trial.
- At least 55 years of age.
- Provide written informed consent.

5.2 EXCLUSION CRITERIA

- Evidence of active CNV on fluorescein angiography or treatment for CNV within the past six months.
- Anticipated need for cataract extraction and intraocular lens implantation during the first 12 months following IMT implantation in the fellow eye. If cataract extraction was anticipated, this procedure had to be performed at least 30 days prior to enrollment in the clinical study.
- Ophthalmic related surgery within the 30 days preceding implantation of the IMT.
- Any of the following conditions in the operative eye:
  - Myopia > 6.0 D
  - Hyperopia > 4.0 D
  - Axial length < 21 mm

- Endothelial cell density < 1600 cells/mm^2
- Narrow angle, i.e., less than Shaffer grade 2
- Cornea stromal or endothelial dystrophies or disorders
- Inflammatory ocular disease
- Zonular weakness/instability of crystalline lens
- Pseudoexfoliation
- Diabetic retinopathy
- Untreated retinal tears
- Retinal vascular disease
- Optic nerve disease
- History of retinal detachment
- Retinitis pigmentosa
- Any intraocular tumor and medical or ophthalmic condition that in the opinion of the Investigator rendered the subject unsuitable for participation in the study.

- Any ophthalmic pathology that compromised the patient's peripheral vision in the fellow eye.
- Any ocular condition that predisposed the patient to eye rubbing.
- Significant communication impairments or severe neurological disorders that prevented or interfered with the study requirements.
- Previous intraocular or corneal surgery of any kind in the operative eye(s), including any type of surgery for either refractive or therapeutic purposes.
- History of steroid-responsive rise in intraocular pressure, uncontrolled glaucoma, or preoperative IOP >22 mm Hg.
- Known sensitivity to planned study concomitant medications.
- Participation in any other ophthalmic drug or device clinical trial during the time of this clinical investigation.

6.0 DEVICE DESCRIPTION

6.1 DESCRIPTION OF THE INVESTIGATIONAL DEVICE

Two magnifications (or models) of the Wide Angle (WA) IMT were available for study patients:

- WA 2.2X
- WA 3.0X.

Both models of the visual prosthetic device are designed with an optimal focusing distance of 3 meters to help enhance or restore intermediate to distance central vision (e.g., watching TV, recognizing people, reading signs). The device also enhances near vision (i.e., reading distance) with focus provided by standard spectacles. Device configuration and components are shown in Figure 3 and described below.

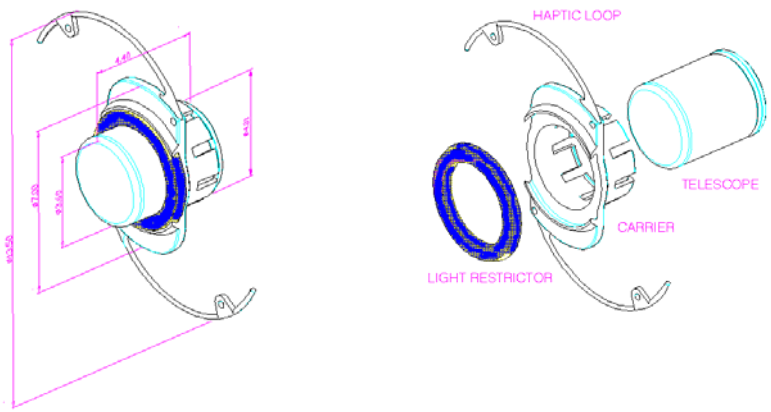


FIGURE 3. WA 3.0X IMT AND IMT COMPONENTS

The IMT is composed of three primary components; a fused silica capsule containing an optical doublet lens and three air spaces, a clear polymethyl methacrylate (PMMA) carrier, and a blue PMMA light restrictor. The capsule with the optical component is snap-fit into the carrier. All external surface materials are biocompatible for long-term ocular implantation per ISO 10993. The IMT is assembled and packaged in a controlled environment and is sterilized by ethylene oxide. The overall dimensions and physical characteristics of the two IMT models used in this study are shown in Table I, below.

TABLE I
OVERALL DIMENSIONS AND PHYSICAL CHARACTERISTICS OF THE IMT MODELS

FEATURE	WA 2.2X IMT	WA 3.0X IMT
Dimensions		
$Ø_T$	13.5 mm	13.5 mm
$Ø_B$	Max: 7.0 mm Min: 4.50 mm	Max: 7.0 mm Min: 4.50 mm
Length	4.4 mm	4.4 mm
Weight (± 10%)		
Air	115 mg ± 10%	115 mg ± 10%
Aqueous	60 mg ± 10%	60 mg ± 10%

6.2 DEVICE COMPONENTS

6.2.1 TELESCOPE

The IMT provides sufficient image resolution for a variety of tasks such as face recognition, TV viewing, and reading at graded visual fields of up to a maximum of 6º (16.2º on the retina) for the WA 3.0X model and 9º (20º on the retina) for the WA 2.2X model. The IMT provides the patient (for detection) nominal visual abilities at a angle of 20º (54º on the retina) for the WA3.0X model and 24º (52.8º on the retina) for the WA 2.2X model.

The optic features for the IMT models used in this study are summarized in Table II.

TABLE II
TELESCOPE OPTICAL FEATURES FOR THE IMT

FEATURE	WA 2.2X IMT	WA 3.0X IMT
OVERALL DIMENSIONS		
DIAMETER	3.6 mm	3.6 mm
LENGTH	4.4 mm	4.4 mm
OPTIC DIAMETER	3.2 mm	3.2 mm
NOMINAL MAGNIFICATION RELATIVE TO SCHEMATIC EYE	2.2X	2.7X
OPTIMAL FOCUSING DISTANCE	3 m	3 m
DEPTH OF FIELD	1.5 m – 10 m	1.5 m – 10 m
RELATIVE BRIGHTNESS	0.3	0.1

6.2.2 CARRIER & LOOPS

In the WA 2.2X and WA 3.0X models, the telescope capsule is snap-fit into a transparent, medical grade PMMA carrier with loops. The loops range in thickness from 0.18 mm – 0.20 mm and are positioned at a 12.7º angulation from planar and have two sets of positioning holes, one set on the carrier body and another on the loops.

6.2.3 RESTRICTOR

A blue PMMA light restrictor, which is snap-fit on the anterior surface of the carrier, reduces the amount of light penetrating around the device optic to the retina.

7.0 STUDY PROCEDURES

7.1 SUBJECT ENTRY

7.1.1 PATIENT SCREENING

Prior to enrollment in the study, interested patients were evaluated to determine eligibility. The Investigator or a designee explained the study purpose, procedures, and patient responsibilities to the potential participant. The patient's willingness and ability to meet the follow-up requirements were determined. No patient was allowed to be implanted in this study without prior written enrollment authorization approval from the Sponsor or its designee. The Enrollment Authorization on the preoperative CRF was completed and approved by the Sponsor or its designee for each patient prior to treatment.

7.1.2 INFORMED CONSENT

When it was established that the patient might be eligible, written informed consent was obtained. The patient signed and dated the consent form. The Investigator also signed and dated the consent form. One copy of the informed consent form was retained with the patient records and a copy was provided to the patient. A screening identification number was assigned and preoperative screening was performed. When preoperative screening established that the patient was eligible and the Sponsor or its designee approved enrollment, a patient identification number was assigned and the patient was considered enrolled in the trial.

7.2 PREOPERATIVE PROCEDURES

7.2.1 EXTERNAL TELESCOPE EVALUATION

Visual acuity with an external telescope was performed using ETDRS (Early Treatment Diabetic Retinopathy Study) charts. Testing was performed in accordance with standard methods defined in the study protocol.

VisionCare provided two or more sets of 2.2X and 3.0X Galilean external telescopes with reading caps to each site for use in the trial. These Galilean telescopes were used for all in-office testing and a 2.2X Galilean external telescope was given to potential patients to try at home for a period of at least three days.

Patients had to achieve at least a five-letter improvement (minimal one line) on the ETDRS chart in the eye scheduled for surgery with at least one of the external telescopes in order to proceed with the surgery. Patients who did not

meet this criterion were excluded from the trial. This exclusion was noted in the screening log at each site.

Table III details the required steps for patient evaluation with the external telescope models.

TABLE III. PREOPERATIVE EXTERNAL TELESCOPE EVALUATION

STEP	ACTION
1	With the patient sitting in a chair, the external 3.0X telescope was placed over the patient's distance correction in a trial frame. It was communicated to the patient that the external telescope was intended to provide the patient with a simulated experience of the magnification, clarity and visual field (slightly less than the corresponding WA 2.2X or 3.0X IMT) expected with the IMT.
2	Each eye was tested individually. The fellow eye was covered with a paddle, and then uncovered and the patient was questioned on preference for one eye over the other. It was important to gauge the patient's ability to use the telescope with the fellow eye not covered. The patient should have been able to use the telescope with the fellow eye uncovered. Failure to do so may indicate strong dominance of the second eye; this was considered in the determination of the eye to be selected for surgery.
3	At a distance of approximately 3 meters, the patient was asked to look at another person's face while an assistant repeatedly put on and removed the telescopes. The patient was asked to compare vision with each telescope. It was important to determine what the patient hoped to achieve through implantation of the IMT and to ensure that these goals were within the anticipated improvement in vision that may be provided by the device.
4	This testing was repeated for the 2.2X external telescope.
5	If the patient achieved a 5-letter improvement (minimal one line) in visual acuity with either or both of the external telescopes, he/she was a candidate for implantation, and was given the 2.2X external telescope to take home and use in practice sessions for at least three days. Patients were instructed to attempt daily tasks and activities such as watching television (from 2-3 meters), making coffee, reading, washing hands, etc., while wearing the external telescope in order to provide the patient with a simulation of the visual acuity that may be achieved with the IMT.

STEP	ACTION
6	For safety reasons, the patient was trained in the use of the telescope while practicing walking. Patients were NOT allowed to walk about unassisted until they had grown accustomed to the use of the telescope.
7	The patient returned for examination following this in-home trial with the external telescopes. If it was determined that the patient was interested in participating in the study, ETDRS visual acuity was measured using both external telescopes. The patient had to achieve a five-letter or greater (minimal one line) improvement in distance visual acuity with at least one of the telescopes in order to be a candidate for IMT implant. Data were collected and recorded on the use of both external telescopes regardless of which was preferred by the patient.
8	If the patient had BCDVA better than 20/200 in either eye, the eye with worse visual acuity was designated for implantation.
9	If BCDVA was equal to or worse than 20/200, or if visual acuity was the same in both eyes, the choice of the eye to be implanted was left to the discretion of the physician and patient. (Patients with an IOL in one eye were allowed to have the IMT implanted only in the other eye).

7.2.2 SCREENING FOR ELIGIBILITY AND BASELINE EVALUATION

Once it was determined that the patient experienced improvement in visual acuity during the trial period of use of external telescope(s), the patient was further evaluated for eligibility, with the following measurements:

- Distance best spectacle corrected visual acuity
- Near best spectacle corrected visual acuity
- Manifest refraction
- Intraocular pressure by applanation tonometry
- Slit lamp exam
- Fluorescein angiography
- Dilated fundus examination and photography
- Specular microscopy

- Pachymetry
- A-scan

Results of these procedures were used for the baseline evaluation if they were obtained no more than 90 days before IMT implantation; distance VA without the external telescope was required to be obtained within 45 days before IMT implantation. Detailed methods of examination were specified in the study protocol.

7.3 SURGICAL PROCEDURE

The IMT procedure was performed on Day 0 of the study by the Investigator or a Co-Investigator, as described below.

7.3.1 PATIENT PREPARATION

1. Anesthesia was induced by retrobulbar or peribulbar injection.
2. Mydriatic agents were administered to ensure adequate pupil dilation during surgery.
3. A lid speculum was placed on the eye to be implanted to provide the maximum corneal exposure.
4. The operating microscope was positioned over or in front of the eye to be treated. Illumination from the operating microscope provided adequate visualization during the procedure.

7.3.2 IMT IMPLANTATION

The IMT procedure was performed using either a limbal insertion technique or a scleral tunneling procedure. Both surgical approaches are described below.

7.3.2.1 Limbal Insertion

1. A 10 mm – 11 mm limbal incision was made at 120º to 160º degrees arc length.
2. A paracentesis was performed and ophthalmic viscosurgical device (Healon V or equivalent) was injected into the anterior chamber.
3. After the incisions were made, a continuous curvilinear capsulorhexis of approximately 6.5 mm was made in the lens capsule.
4. Phacoemulsification was performed to remove the lens.

5. Ophthalmic viscosurgical devices (Healon V or equivalent) were injected into the anterior chamber and the capsular bag, and used to coat the IMT.
6. The IMT was implanted in the capsular bag:
    a. Both loops were placed inside the capsular bag;
    b. The cornea was sutured; and
    c. The loops of the IMT were rotated to the 12:6 o'clock position.
7. The ophthalmic viscosurgical device (OVD) agents were removed.
8. The pupil was constricted.
9. A peripheral iridectomy was performed.
10. The incision was tested for leakage.

7.3.2.2 Scleral Tunnel Implantation

1. The conjunctiva and Tenon's fascia were opened from the 10 o'clock to the 2 o'clock position.
2. A paracentesis was performed and ophthalmic viscosurgical devices (Healon V or equivalent) were injected into the anterior chamber and the capsular bag, and used to coat the IMT.
3. A continuous curvilinear capsulorhexis of approximately 6.5 mm was created in the lens capsule.
4. A minimum 10 mm scleral incision was performed 2.5 mm – 3 mm posterior to the limbus. A tunnel was then created which opened into the anterior chamber at the limbus.
5. Phacoemulsification was performed to remove the lens.
6. The IMT was implanted in the capsular bag:
    a. The IMT was inserted through the scleral tunnel into the capsular bag;
    b. Both loops were placed inside the capsular bag;
    c. The scleral tunnel was sutured; and
    d. The loops of the IMT were rotated to the 12:6 o'clock position.
7. The ophthalmic viscosurgical device (OVD) agents were removed.
8. The pupil was constricted.
9. A peripheral iridectomy was performed.
10. The incision was tested for leakage.

Irrespective of the surgical technique utilized, a sub-Tenon's injection of betamethasone depot (or appropriate substitute) was administered at the end of surgery.

7.4 POSTOPERATIVE TREATMENT REGIMEN

Following surgery, the study Sponsor encouraged Investigators to adhere to the following standardized regimen of topical ophthalmic medications, taking into account individual patient considerations:

1. One drop of a topical ophthalmic antibiotic solution was to be administered following surgery, and then continued per product labeling for at least two days.

2. One drop of Voltaren Ophthalmic (diclofenac sodium 0.1%, CIBA Vision Ophthalmics) or equivalent was to be administered following surgery, and then continued per product labeling for at least two days.

3. Prednisolone acetate (1%) or equivalent was to be administered every 2 waking hours for the first two weeks post-implantation, followed by administration every 4 waking hours for 2-4 weeks.

4. The prednisolone acetate (1%) was to be gradually tapered over the next 4 to 6 weeks for a total duration of postoperative steroid treatment of approximately 3 months.

5. Homatropine 5% or a similar drug was to be administered twice daily for 4 to 6 weeks postoperatively. If homatropine was inadequate to maintain cycloplegia, the use of atropine was allowed.

The Investigator exercised clinical judgment in deciding if a more moderate or rapid tapering of the topical steroid regimen was indicated for some patients, particularly in eyes with signs of medicamentosa.

7.5 EXAMINATION SCHEDULE

Subjects were examined and evaluated according to the following schedule of visits:

- Preoperative Evaluation (Day -90 to Day 0)
- Operative Evaluation Day 0
- Day 1 (24 to 36 hours postoperative)
- Day 7 (4 to 10 days postoperative)
- 1 month (2 to 6 weeks postoperative)
- 3 months (6 to 18 weeks postoperative)
- Vision training (Week 1, 2, 4, 6, 10 and 12, +/- 4 days)
- 6 months (18 to 32 weeks postoperative)
- 9 months (32 to 44 weeks postoperative)
- 12 months (44 to 56 weeks postoperative)
- 18 months (66 to 78 weeks postoperative)
- 24 months (84 to 102 weeks postoperative)

7.6 CLINICAL PARAMETERS

The clinical parameters evaluated at study examinations were:

- Pinhole acuity (safety assessment): Day 1
- Best spectacle-corrected distance acuity, using ETDRS VA charts: preoperative, Day 7, months 1, 3, 6, 9, 12, 18, 24 and any interim visits
- Best spectacle-corrected near visual acuity, using MN charts: preoperative, months 1, 3, 6, 9, 12, 18, 24 and any interim visits
- Manifest refraction (no auto-refraction); preoperative, Day 7, months 1, 3, 6, 9, 12, 18, 24 and any interim visits
- Intraocular pressure (applanation): all visits
- Slit lamp examination: all visits
- Fundus examination (dilated) and photography: preoperative
- Fluorescein angiography: preoperative
- Specular microscopy of the central cornea: preoperative, 3, 6, 9, 12, 18 and 24 months
- Activities of Daily Life (ADL) & VFQ-25 questionnaire: preoperative, 3, 6, 9, and 12 months

Postoperative visual examinations were performed by the Investigator or his/her designee such as ophthalmic technicians, optometrists and/or ophthalmologists under the supervision of the Investigator using methods described in the study protocol. All preoperative and postoperative examinations were performed using comparable pieces of equipment at each site.

7.7 SPECULAR MICROSCOPY

To evaluate change in endothelial cell density over time, specular microscopy was performed preoperatively and at the Month 3, 6, 9, 12, 18 and 24 examinations in both the operated eyes and fellow eyes using the non-contact Konan or Topcon Specular Microscope. Three images were obtained at each visit. Specular micrographs were sent to a central reading center (B. McCarey, Ph.D., Emory University) for analysis and the mean density from all three images was used for statistical analyses.

The following common sources of variability in specular microscopy were identified in the study protocol :

- difficulty in returning to same location on the cornea at each visit;
- poor image quality (less than 100 countable cells); and
- technician error.

To address differences in location of the image within a given area of the cornea, sites were instructed to take three acceptable images at each visit. The mean density from the three images has been used for analyses. Problems due to poor image quality and/or technician error were minimized by using appropriate equipment (non-contact specular microscopes) and trained, experienced clinical sites. Training (or retraining) was performed as necessary. Instructions provided to the site emphasized patient factors (related to the shape of the patient's face, the ability for the patient to fixate on the target [or to hold still and look in one place], the patient's level of alertness or tiredness, dryness of the patient's corneas) and position, i.e., the angle of the patient's face, brow, forehead, cheek and chin to the specular microscope.

A central reading center was retained for analyzing the specular images and conducting ECD counts. The reading center performing the image analysis used the following methodology:

- A minimum of 100 cells, when available, in a contiguous area were identified as the criteria for accurate ECD measurements. The center method for counting cells was recommended.
- The quality of cells in an image was assessed. Since the presence of disease can increase variability (e.g., polymegathism/pleomorphism post-contact lens wear), the area with the fewest distortions (not in shadow, washed-out, or blurred) were to be used for the image analysis.

Furthermore, the central laboratory rated all images using the following scale: good, fair, poor and indistinct. For analyses purposes, a score of 3 was assigned to good, 2 to fair, 1 to poor and 0 to indistinct images. However, all three images for each eye were used in the analysis of endothelial cell density.

7.8 DATA REPORTING

A Case Report Form (CRF) booklet was provided by the Sponsor or its designee for each patient enrolled in the study. The appropriate Case Report Form was completed by the Investigator or his/her designee and signed by the Investigator at each examination. All Case Report Forms were completed in a legible manner in black ink. Any corrections were made by drawing a single line through the incorrect entry, entering the correct information, and initialing and dating the change. Data entries boxes or spaces should not have been left blank, but instead should have indicated: NA = not applicable, ND=not done or NAV= missing or not available data. The original signed forms, not copies, were returned to the Sponsor.

All clinical data generated in the study were submitted to the Sponsor or its designee for quality assurance review, data entry, and statistical analysis. All forms were reviewed for completeness and evident recording errors were rectified by contact with the appropriate clinical site. Double-entry routines were utilized to reduce data entry errors, and computerized editing routines were used to identify unusual data entries for verification prior to statistical analysis.

7.9 STUDY COMPLETION PROCEDURES

7.9.1 PATIENT COMPLETION

Patients were considered to have completed the study if they completed all follow-up examinations through 24 months.

7.9.2 PATIENT TERMINATION

Patients may have been terminated from the study at the discretion of the Investigator only if continuation of the treatment regimen would jeopardize the patients' health and/or welfare. Terminated patients were considered to have completed the study and were not replaced. However, every effort was made to follow terminated patients for safety reasons using the appropriate case report forms until the planned end of the study period. Notification of a patient termination was made immediately to the Sponsor or its designee.

7.9.3 PATIENT EXIT

A patient exit form had to be completed for all patients who either completed, were discontinued, were considered lost to follow-up, or were terminated from the study. Before a patient was considered "lost to follow-up", at least three documented attempts to reach the patient were required. At least one of these attempts was required to be in writing by certified / return receipt mail, a copy of which was included in the patient's medical / clinic chart.

8.0 STATISTICAL METHODS

8.1 SAMPLE SIZE

The sample size for this study was calculated based on the following criteria:

- The significance level was 0.05.
- The primary effectiveness endpoint was the proportion of eyes with an improvement of 2 lines or more in either distance or near BCVA at 12 months postoperatively, P_t.
- The statistical hypotheses for the primary effectiveness endpoint were:

  H_0: $P_t \leq 0.5$ (50%) versus H_a: $P_t > 0.5$.
- The statistical power was 80% at the expected rate of 0.6 (60%). The expectation of 60% of the eyes achieving improvement was based on results in the feasibility clinical study in which ten of thirteen eyes that reached 12 months had an improvement of 2 lines or greater in either the distance or near BCVA from baseline.
- Binomial distribution was used to calculate the sample size for the effectiveness endpoint.
- One of the primary safety endpoints was the percentage loss in the endothelial cell density (ECD) from baseline at 12 months postoperatively. A review of published literature on mean endothelial cell density suggests an average loss of 10-17% within one year after large incision surgery. Therefore, the statistical objective was to prove that the mean percentage of cell loss was no more than 17% and the corresponding statistical hypotheses for the primary safety endpoint H_0: $\mu_t \geq 0.17$ (17%) versus H_a: $\mu_t < 0.17$, where μ_t is the mean percentage loss from baseline at 12 months postoperatively.
- The statistical power was 80% at the expected mean loss of 0.135 (13.5%), which is the middle point of the literature's range of 10% to 17%.
- The standard deviation of percentage loss in the endothelial cell density was assumed to be 0.175 (17.5%), which was estimated based on the feasibility clinical study.
- Normal distribution was used to calculate the sample size for the safety endpoint.

The sample size for the primary effectiveness endpoint was 158 implanted eyes. If 90 or more eyes had an improvement of 2 lines or greater in either distance or near BCVA at 12 months postoperative, the null hypothesis (H_0) was rejected. Due to the advanced age of the study population, and potential problems with compliance with the visit schedule for patients who may not be independent due to impaired central vision, a dropout rate of 20% was considered, resulting in the sample size for the primary effectiveness endpoint of 198 eyes.

The sample size for the primary safety endpoint of ECD was 156 implanted eyes. If a dropout rate of 20% was considered, the sample size for the primary safety endpoint was 195 eyes.

Therefore, the planned population for this study was at least 198 eyes to fulfill the sample size required for the primary effectiveness endpoint. With this sample size, there was a 95% confidence level to observe at least one adverse event at a rate of 1.5%.

8.2 STATISTICAL ANALYSES

8.2.1 GENERAL DATA HANDLING

The primary cohort for the data analyses is the group of subjects who underwent a successful IMT implantation at surgery. Records from subject follow-up after IMT removal were excluded from the effectiveness analyses. However, all the complications and adverse events reported after IMT removal were included in the tables of complications and adverse events presented in this report. These post-IMT-removal records were also included in the data listings and patient profiles.

All available data for subjects who did not have a successful IMT implant (surgery canceled, IMT implant was aborted during the surgery, or IMT was implanted but removed immediately due to intraoperative complications) are also presented and discussed in this clinical study report.

Missing data were treated as missing and no imputation of missing data was performed. Data from unscheduled visits are presented in the patient profiles and data listings, but are not included in the data tables. However, all reported complications and adverse events from unscheduled visits are included in the tables presenting complications and adverse events.

8.2.2 PRIMARY EFFECTIVENESS ENDPOINT ANALYSES

The primary effectiveness endpoint in this study consisted of the proportion of eyes with at least a 2-line improvement in either BCNVA or BCDVA at 12 months. The change in the best corrected distance visual acuity (BCDVA) was calculated for each eye by subtracting the baseline LogMAR value from the postoperative LogMAR value. A difference in the LogMAR value of -0.1 means a one-line improvement in visual acuity and a difference in the LogMAR value of 0.1 means a one-line decrease in visual acuity. A LogMAR value of 1.7 was assumed for the subjects that could not read any ETDRS letters.

The change in the best corrected near visual acuity (BCNVA) was calculated for each eye based on the M-value. For example, a change from 8.0M to 6.3M means a one-line improvement in visual acuity and a change from 2.5M to 3.2M means a one-line decrease in visual acuity. For simplicity of the calculation, the M-values were converted to the corresponding LogMAR value based on the following mapping. The change in BCNVA for each eye was then calculated in the same way for the change in BCDVA. If the M-value was not assigned but the number of letters read correctly was not zero, an M-value of 10.0M was assumed. Otherwise an M-value of 12.5M was assumed for the subjects that could not read any ETDRS letters.

TABLE IV. M-VALUE WITH CORRESPONDING LOGMAR AT 8" AND 16"

M-value	logMAR at 8"	logMAR at 16"
0.32 M	0.2	-0.1
0.40 M	0.3	0
0.50 M	0.4	0.1
0.63 M	0.5	0.2
0.80 M	0.6	0.3
1.00 M	0.7	0.4
1.25 M	0.8	0.5
1.60 M	0.9	0.6
2.00 M	1.0	0.7
2.50 M	1.1	0.8
3.20 M	1.2	0.9
4.00 M	1.3	1.0
5.00 M	1.4	1.1
6.30 M	1.5	1.2
8.00 M	1.6	1.3
10.00 M	1.7	1.4
12.50 M	1.8	1.5

An exact binomial test with a binomial parameter of 0.5 has been utilized for analysis of the primary effectiveness endpoint, i.e., the proportion of eyes with at least a 2-line improvement in either BCNVA or BCDVA at 12 months. The corresponding 90% confidence interval of the success rate based on the Clopper Pearson method was provided. Although the p-value was calculated for all postoperative visits, the primary effectiveness endpoint was at 12 months postoperative and no adjustment for multiplicity was performed. It should be noted that, since BCNVA was measured at both 8 and 16 inches, the "at least a 2-line improvement in BCNVA" means either BCNVA at 8 inches or BCNVA at 16 inches gained ≥ 2 lines.

In addition to the overall success rate, the success rate was stratified by age, gender, preoperative visual acuity status and IMT model. Fisher's exact test was used to compare the success rates among different age groups, genders,

IMT models, and preoperative visual acuity statuses. The success rates from 12 to 24 months were also analyzed by the Generalized Estimation Equation (GEE). The covariates considered in the GEE were visit, baseline parameters such as age, gender, IMT model, and preoperative visual acuity status, and two-factor interaction effects. The GEE analyses were based on the following approach:

- Visit and one of the baseline parameters along with their interaction effect were considered in the GEE. This stage served to identify the possible interaction effect between visit and baseline parameters. Any interaction effect with a p-value of ≤ 0.15 was considered in the later Backward Procedure to select the final model. The significance level of 0.15 was chosen to include any potential interaction effects for these exploratory analyses.

- Visit, two of the baseline parameters, and the interaction effect between the two selected baseline parameters were then considered in the GEE. This stage served to identify the possible two-factor interaction effect between baseline parameters. Any interaction effect with a p-value of ≤ 0.15 was considered in the later Backward Procedure to select the final model.

- All the main effects and the interaction effects identified from Stages one and two were considered in the final model selection based on the Backward Procedure. Interaction effects were evaluated first. The interaction with the largest p-value of > 0.15 was dropped from the model. The procedure was iterated until all the interaction effects in the model were ≤ 0.15. Then the main effects that were not associated with the interaction effects in the model were evaluated. The main effect with the largest p-value of > 0.10 was dropped from the model. A significance level of 0.1 was chosen to include any potential main effects for these exploratory analyses. The procedure was iterated until all the main effects in the model were ≤ 0.10. The final model was then identified.

Since a total of 28 investigational sites were involved in the study and the enrollment ranged from 1 to 26 subjects, the possible site effect on the success rate was not evaluated.

The improvement in visual acuity was also summarized separately for BCDVA, BCNVA at 8 inches, and BCNVA at 16 inches.

8.2.3 PRIMARY SAFETY ENDPOINTS

Primary endpoints were defined as endothelial cell loss and preservation of best corrected visual acuity.

The average of ECD measurements taken at the same visit for the same eye was calculated and treated as the ECD value of the eye at the visit. The percentage change in the ECD from baseline was calculated as follows for each eye.

% Change in ECD from baseline

= (Postoperative ECD – Baseline ECD) ÷ Baseline ECD × 100%

Descriptive statistics such as mean, standard deviation, median, and range, and the 90% confidence interval for the mean were calculated for percentage change in the ECD from baseline at each postoperative visit.

During the conduct of this study, it was identified in the interim reports that the mean loss in ECD at 12 months was larger than the expected 17% and the standard deviation of the loss in ECD was also larger than the expected 17.5%. Therefore, no t-test was performed for testing the mean percentage ECD loss against the target value of 17%. Several ad hoc analyses were performed and communicated with FDA regarding the loss in ECD. These ad hoc analyses are described in Section 8.2.6.

The percentages and the corresponding binomial 90% confidence intervals (based on the Clopper Pearson method) were calculated for the percentage of eyes experiencing a loss of more than 2 lines of BCNVA (or BCDVA) without a corresponding improvement (gain of 2 lines or more) in BCDVA (or BCNVA). This safety incidence was compared to the expected rate of 10% by using the one-sided exact binomial test.

Since BCNVA was measured at both 8 and 16 inches, a loss of more than 2 lines of BCNVA means that one BCNVA lost > 2 lines without the other BCNVA gaining ≥ 2 lines.

Similar to the primary effectiveness endpoint, this secondary safety endpoint was stratified by age, gender, preoperative visual acuity and IMT model. Fisher's exact test was used to compare safety based on loss of lines of visual acuity at near or distance among different age groups, genders, IMT models, and preoperative visual acuity statuses. The loss in visual acuity was also summarized separately for BCDVA, BCNVA at 8 inches, and BCNVA at 16 inches.

8.2.4 SECONDARY EFFECTIVENESS ENDPOINT: QUALITY OF LIFE

VFQ-25 and ADL scores were summarized by descriptive statistics such as mean, standard deviation, median, and range. The 95% confidence interval for the mean was also provided. The change in VFQ-25 and ADL scores from baseline were calculated for each subject by subtracting the baseline score from the postoperative score. The percentage change in VFQ-25 and ADL scores from baseline were also calculated by dividing the change in the score by the baseline score and multiplying by 100%. Descriptive statistics were used to summarize the change and the percentage change in VFQ-25 and ADL score. It should be noted that some subjects were reported with a zero baseline score and the percentage change from baseline could not be calculated. These subjects were not included in the analyses for percentage change from baseline.

In addition to the standard descriptive statistics, the percentage of subjects reported with an increase of ≥ 5 points in VFQ-25 overall composite score was calculated and the corresponding 95% confidence interval was calculated based on the Clopper Pearson method. The same approaches were used to summarize the percentage of subjects reported with an increase of ≥ 10 points in ADL total score.

The Pearson correlation between VFQ-25 overall composite score and ADL total score at each visit was calculated. These correlations were tested against zero. This was to evaluate if the responses to quality of life questionnaires were consistent.

8.2.5 OTHER CLINICAL PARAMETERS

For continuous or ordinal measures such as age or IOP, the number of observations, mean, standard deviation, median, minimum, and maximum values were presented. If necessary, the 95% confidence interval for the mean value was provided. For categorical variables such as slit lamp findings or adverse events, the proportion with the characteristic was presented. If it was necessary, the corresponding exact 95% confidence limits were provided.

8.2.6 ADDITIONAL STATISTICAL ANALYSES

Additional statistical analyses were performed to assess the pattern of the ECD loss and to evaluate possible clinical parameters that could impact loss in endothelial cell density (ECD).

8.2.6.1 Possible Factors Affecting ECD

The clinical parameters possibly affecting ECD that were considered in the additional analyses included postoperative Day 1 corneal status, anterior

chamber depth (ACD), surgical order, incision type, incision size, surgeon's specialty, subject's age at implant, preoperative ECD, surgeon, axial length, and use of Healon V. Categorization (levels) of these clinical parameters were as follows:

- **Corneal status on postoperative Day 1**
  - Normal
  - 1+ edema
  - 2+ edema
  - 3+ or 4+ edema
- **ACD**
  - ≤ 3.00 mm
  - > 3.00 to 3.50 mm
  - > 3.50 mm
- **Surgical order**
  - First, second and third IMT implant by the surgeon
  - Fourth IMT implant and beyond by the surgeon

If the surgeon was an experienced IMT surgeon, i.e., participation in the feasibility study, and had implanted *n* IMTs in the feasibility study and *m* IMTs in this trial, then the surgical order for this surgeon's *mth* IMT implant in this study would be $n + m$.

- **Incision type**
  - Limbal incision
  - Scleral tunneling
- **Incision Size**
  - < 12 mm
  - ≥ 12 mm
- **Surgeon's specialty**
  - Corneal trained
  - Non-corneal trained
- **Subject's age at implant**
  - < 71 years
  - 71 to 75 years
  - 76 to 80 years
  - > 80 years
- **Preoperative ECD**
  - < 2400
  - ≥ 2400
- **Surgeon**

Due to the small sample size for most of the surgeons, their data were pooled so that each combined "surgeon" would have a sample size of at least 10 subjects at 3 months postoperative. They were pooled based on their assigned

site number in the study, not based on the outcomes. The combined "surgeons" are as follows:

- 001-Lane
- 002-Hamill, 003-Chao, 004-Fine, 004-Hoffman, 004-Packer
- 005-Lichter
- 006-Dehning, 008-Clinch, 008-Martin
- 009-Mandelbaum, 010-Raizman
- 011-Colby, 012-Carter, 012-Kerschner
- 013-Bradford, 014-Stulting
- 015-Fisher, 016-Kraff, 017-Linn
- 019-Gillespie, 020-Chang, 021-Koenig, 022-Levy
- 023-Rotberg, 023-Stewart
- 025-Irvine, 026-Markowitz
- 027-Horn, 028-Dugan, 029-Lesser, 031-Kim, 032-Schein

- **Axial Length**
  - ≤ 23 mm
  - > 23 mm
- **Use of Healon V**
  - Using Healon V
  - Without Healon V

ECD analyses were stratified by these outlined clinical parameters. The 2-sample Wilcoxon or Kruskal-Wallis test was used to compare the differences in the mean ECD outcomes among different levels of these clinical parameters at each visit. The sample sizes for some levels of the clinical parameters are small and therefore the nonparametric approach was used, and the Central Limit Theory may not be suitable.

8.2.6.2 Modeling ECD And ECD Change from Baseline

The GEE analysis with visit as the only factor in the model was performed on the mean ECD from 3 months to 24 months to evaluate the ECD pattern over time. The same analysis was performed for the consistent cohort that consists of the subjects with ECD measurements at all postoperative visits (3, 6, 9, 12, 18 and 24 months).

To evaluate how the clinical parameters discussed above affect the ECD loss due to surgery, the generalized linear model analysis was performed on the 3-month percentage change in ECD from baseline based on the following steps:

- Univariate one-way ANOVA involving the outlined clinical parameter was performed first to statistically identify the potential significant factors for multivariate analyses. Any parameter with a p-value ≤ 0.15 was considered a potential factor in the multivariate analyses.

The significance level of 0.15 was chosen to include any potential effects.

- Once the potential factors were identified, the two-factor ANOVA (Type III) was performed on every pair of the potential factors to examine the potential two-factor interaction effects on the 3-month ECD percentage change from baseline. Any interaction effect with a p-value of 0.15 or less was considered a potential factor in the next multivariate analyses step. It should be noted that due to the small sample size for some levels of "Day 1 corneal status," the levels of this clinical parameter were grouped as "Normal/1+ edema" and "≥ 2+ edema" in the multivariate analyses.
- Once the potential main effects and interaction effects were identified, the Backward Procedure in the multivariate analyses was used to select the final model for the 3-month ECD percentage change from baseline. A significance level of 0.10 was used to remove a main factor (effect) from the model and a significance level of 0.15 was used to remove an interaction effect from the Backward Procedure.
- Interaction terms were examined first. The interaction effect with the largest p-value of > 0.15 was removed and a reduced model (i.e., the model without the interaction effect) was fitted. This procedure was repeated until all interaction effects in the model were ≤ 0.15.
- Main effects associated with significant interaction effects in the model were not removed. However, main effects without interaction effects in the model were examined. The main effect that had the largest p-value of > 0.10 was removed and a reduced model was fitted. This procedure was repeated until all main effects that were examined were ≤ 0.10.
- After several iterations, the final model for the 3-month ECD percentage change from baseline on the significant factors was then identified.

Similar steps with logistic regression analyses were used to evaluate the effects of these clinical parameters on the incidence of eyes reported with an ECD loss of >20% from baseline at 3 month.

8.2.6.3 Change in ECD Between Consecutive Postoperative Visits

In addition to the ECD change from baseline, the change in ECD between two consecutive postoperative visits was calculated for each eye as follows.

% Change in ECD between two consecutive postoperative visits
= (Visit-2 ECD – Visit-1 ECD) ÷ Visit-1 ECD × 100%

The descriptive statistics such as mean, standard deviation, median, and range, and the 90% confidence interval for the mean was calculated for percentage change in the ECD between two consecutive postoperative visits.

The GEE analyses with Visit Period (from 3-month to 6-month, from 6-month to 12-month, from 12-month to 18-month, and from 18-month to 24-month) as the only factor in the model were performed on the mean percentage change in ECD between two consecutive postoperative visits to evaluate the ECD change pattern between two postoperative visits from 3 months to 24 months.

The percentage change in ECD between two postoperative visits was also calculated for the non-IMT fellow eyes. The percentage change in ECD between two postoperative visits was compared between IMT and non-IMT fellow eyes by using a paired-t test at each period for the cohort and the subset of subjects with a pseudophakic fellow eye. Additionally, the outcomes were compared between all IMT eyes and the pseudophakic fellow eyes by using a GEE analysis, which had the eye as the only factor and treated the ECD outcomes from the same subjects as the repeated measurements.

8.2.6.4 Estimated Annual Percentage Change in ECD

The annual percentage change in ECD was estimated based on the ECD measurements at 9, 12, 18 and 24 months. For each eye, the percent change in ECD between each pair of visits from 9 months to 24 months (i.e. 9-month to 12-month, 9-month to 18-month, 9-month to 24-month, etc.) was calculated. An estimated annual percentage change based on a between-visit percentage change was then calculated as the between-visit percentage change divided by the interval in months and multiplied by 12. For example, the estimated annual percentage change based on the 12-to-18-month change is the 12-to-18-month percentage change divided by 6 and multiplied by 12. If an IMT-implanted eye had ECD data at 9, 12, 18 and 24 months, then it had six estimated annual ECD percentage changes. An overall estimation of the annual ECD percentage change from 9 to 24 months for this eye consists of the average of these six available estimated annual percent changes. This calculation averages out the possible up-and-down ECD evaluations due to inter-interval variation.

The percentage change in ECD between each pair of visits and the estimated annual percentage change in ECD for each eye were summarized by the mean, standard deviation, median, range and the 90% confidence intervals for mean.

9.0 REPORTING OF ADVERSE EVENTS AND DEVICE MALFUNCTIONS

9.1 ADVERSE EVENTS

Throughout the course of the study, all efforts were made to remain alert to possible adverse events or untoward findings. If adverse events occurred, the first concern was the safety and welfare of the patient. Appropriate medical intervention was undertaken. Any adverse events or complications observed by the Investigator or reported by the patients, whether or not ascribed to the IMT, were recorded in the appropriate section of the patient's Case Report Form.

Any serious adverse events and unanticipated adverse device effects, whether or not ascribed to the IMT were communicated promptly to the Sponsor and to the IRB. These reports had to be confirmed in writing within five days of the occurrence. Any patient who was terminated from the study due to adverse events was followed until their medical outcome was determined, and written reports were provided to VisionCare Ophthalmic Technologies by the investigator.

Below is a list of anticipated adverse events and complications identified in the study protocol, based on prior IMT clinical trials or known to be potentially associated with similar types of anterior segment surgery:

- Acute corneal decompensation
- Anterior segment neovascularization
- Choroidal detachment
- Corneal edema
- Cortical remnants
- Cystoid macular edema
- Endophthalmitis
- Fibrin in the anterior chamber
- Hyphema
- IMT dislocation
- Inflammatory deposits on IMT
- Intraocular inflammation
- Iris transillumination defects
- Optic atrophy
- Posterior synechiae
- Removal of IMT
- Repositioning of IMT
- Retinal vascular occlusion
- Secondary surgical intervention
- Vitrectomy/vitreous aspiration
- Vitreous in anterior chamber
- Anterior chamber cells
- Anterior synechiae
- Closure of a peripheral iridotomy (with or without pigment)
- Corneal transplant
- Cyclitic membrane
- Distorted pupil
- Epithelial heaping
- Flat anterior chamber
- Hypopyon
- Increased IOP requiring treatment
- Intraocular infection
- Iris atrophy
- Iritis
- Pigment deposits on IMT
- Pupillary block
- Repeat iridectomy
- Retinal detachment
- Secondary glaucoma
- Uveitis/Vitritis
- Vitreous incarceration in incision
- Wound leak

9.2 DEVICE MALFUNCTIONS

A device malfunction was defined as a failure of the IMT to meet its performance specifications or otherwise perform as intended. Performance specifications included all claims made in the study protocol or the product associated labeling included with the device. Examples of malfunctions include:

- Missing product components
- IMTs which appeared malformed or disfigured
- Compromised packaging
- Broken haptic loops
- Scratches to the IMT device surfaces.
- Condensation
- Window separation.

All device malfunctions were recorded as an adverse event on the patient Case Report Forms.

10.0 STUDY MONITORING

VisionCare personnel or its designee monitored all clinical studies in a manner consistent with applicable health authority regulations and the clinical research standards adopted by the Sponsor. Study monitoring involved the following elements:

A. VisionCare personnel or designee met with Investigator(s) prior to the enrollment in order to review the adequacy of the patient population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol.

B. VisionCare personnel or designee met with the Investigator(s) at the time study patients began to be enrolled or shortly thereafter in order to ensure that patients were being properly selected and that study data were being correctly recorded.

C. VisionCare personnel or designee visited the clinical site during the study to review and/or collect the Case Report Forms.

D. Interim monitoring visits and telephone consultation occurred as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

11.0 STUDY RESULTS

A total of 28 sites actively participated in this multicenter clinical trial. The database for this clinical report was locked on July 18, 2005 for purposes of data analysis and preparation of this clinical report. At the time of database lock, 194 eyes had reached the 12-month follow-up, 180 eyes had reached the 18-month follow-up examination and 148 eyes had reached 24-month follow-up. It should be noted that the timing of this PMA submission, relative to the number of eyes at the 24-month visit, was discussed with FDA, to determine whether the PMA for the IMT be could be submitted with complete 18-month data and at least 50% of the 24-month data. Based on statistical modeling, (generalized estimating equation [GEE] and regression methods), a determination was made by FDA that the PMA could be submitted at this time. This was particularly important given the age of the study population and the associated increasing numbers of hospitalizations and deaths that have occurred during the second year of patient follow-up.

It should be noted that a full set of data tables is provided in Appendix A. Appendix A includes all tables found in the text of this report as well as tables showing additional analyses that may be of interest, such as subgroup analyses and stratifications of in-text tables. Tables found in the body of this report, i.e., those tables found in the body of this report, have the same number in Appendix A as in this report, and additional tables are identified by additional numeric or alphanumeric notation.

12.0 ENROLLMENT, ACCOUNTABILITY AND PROTOCOL DEVIATIONS

Subject enrollment by site is summarized in Table 1. A total of 218 consecutive subjects were enrolled at 28 participating US clinical sites. Retina Centers PC (Tucson, AZ) enrolled the largest number of subjects (n=26), followed by Southeast Clinical Research, (Charlotte, NC) with 18 patients and Emory Eye Center, (Atlanta, GA) with 15 patients.

TABLE 1
ENROLLMENT
(N = 218 ENROLLED, 217 OPERATED, 206 SUCCESSFULLY IMPLANTED)

Site Name	Enrolled Subjects		2.2X IMT Implants		3.0X IMT Implants		No Implant*	
	N	%	N	%	N	%	N	%
Associated Eye Care	13	6.0%	8	7.0%	5	5.5%	0	0.0%
Baylor College of Medicine	1	0.5%	1	0.9%	0	0.0%	0	0.0%
University of California at Irvine	4	1.8%	0	0.0%	3	3.3%	1	8.3%
Fine, Hoffman & Packer	7	3.2%	2	1.7%	5	5.5%	0	0.0%
University of Michigan/Kellogg Eye Ctr.	12	5.5%	2	1.7%	10	11.0%	0	0.0%
Discover Vision Centers	9	4.1%	7	6.1%	2	2.2%	0	0.0%
Retina Group of Washington	13	6.0%	6	5.2%	6	6.6%	1	8.3%
Manhattan Eye & Ear	2	0.9%	1	0.9%	1	1.1%	0	0.0%
OCB Boston	9	4.1%	8	7.0%	1	1.1%	0	0.0%
Massachusetts Eye & Ear	4	1.8%	1	0.9%	3	3.3%	0	0.0%
Retina Centers PC	26	11.9%	5	4.3%	18	19.8%	3	25.0%
Dean A. McGee Eye Inst.	10	4.6%	3	2.6%	7	7.7%	0	0.0%
Emory Eye Center	15	6.9%	14	12.2%	1	1.1%	0	0.0%
Medical Center Ophthalmology	6	2.8%	5	4.3%	1	1.1%	0	0.0%
Kraff Eye Inst.	1	0.5%	1	0.9%	0	0.0%	0	0.0%
Vitreoretinal Foundation	3	1.4%	3	2.6%	0	0.0%	0	0.0%
Paducah Retinal Center	4	1.8%	3	2.6%	0	0.0%	1	8.3%
Altos Eye Physician	10	4.6%	6	5.2%	3	3.3%	1	8.3%
Medical College of Wisconsin Eye Inst.	2	0.9%	1	0.9%	1	1.1%	0	0.0%
Sarasota Retinal Inst.	5	2.3%	5	4.3%	0	0.0%	0	0.0%
Southeast Clinical Research	18	8.3%	11	9.6%	7	7.7%	0	0.0%
Doheny Retina Inst.	5	2.3%	3	2.6%	0	0.0%	2	16.7%
Retina Associates of Cleveland	12	5.5%	6	5.2%	5	5.5%	1	8.3%
Vanderbilt Un. Dept. of Oph. & Visual Sciences	5	2.3%	2	1.7%	2	2.2%	1	8.3%
Wills Eye Hospital, Retina Research	8	3.7%	4	3.5%	4	4.4%	0	0.0%
Associated Retinal Consultants	6	2.8%	5	4.3%	1	1.1%	0	0.0%
Duke University Eye Center	6	2.8%	2	1.7%	3	3.3%	1	8.3%
Johns Hopkins University, Wilmer Ophthalmological Institute	2	0.9%	0	0.0%	2	2.2%	0	0.0%
Total	218	100.0%	115	100.0%	91	100.0%	12	100.0%

* One eye canceled surgery. Five eyes were reported with an aborted implantation. Six eyes were reported with intraoperative IMT removal. These eyes were excluded from analyses, however their safety data will be discussed separately.

Formatted: Norwegian (Bokmål)

Twelve (12) of the 218 enrolled eyes were excluded from further analyses, resulting in a study population of 206 eyes of 206 enrolled subjects; 115 eyes were implanted with the WA 2.2X and 91 eyes were implanted with the WA 3.0X. Of the 12 excluded subjects, one subject canceled surgery, in 5 eyes the IMT was not implanted due to surgical complications, and in 6 eyes the IMT was removed at the time of surgery. Additional information on the 11 subjects whose eyes were not successfully implanted with an IMT is provided in Section 18.5, Ocular Complications, and in Appendix B.

Table 2 summarizes patient availability for analysis and accountability for all successfully implanted subjects at the time of database closure.
Accountability in this study, i.e. the proportion of eyes eligible for the examination window and not discontinued or lost to follow-up, is excellent at $\geq$ 98.5% for visits through 6 months, 97.0% (196/202) at 9 months, 97.5% (194/199) at 12 months, 91.4% (180/197) at 18 months, and 95.5% (148/155) at 24 months.

Seventeen percent (35/206) of implanted subjects are not yet eligible for the 24 months follow-up examination. As of database lock, three subjects (3/206 or 1.5%) missed the 3-month visit, six subjects (6/206 or 2.9%) missed the 9-month visit, four subjects (4/206 or 1.9%) missed the 12-month visit, 14 subjects (14/206 or 6.8%) missed the 18-month visit, and one subject (1/206 or 0.5%) missed the 24-month visit. A total of 16 subjects have been discontinued from the study, including 10 subjects who died during the course of follow-up and 6 subjects who discontinued following removal of the IMT prior to study completion. Data line listings are provided in Table A5 in Appendix A for subjects who died (n=10) during the course of the study.

A total of 8 subjects had the IMT explanted postoperatively, i.e., some time after the initial surgery for implantation; as mentioned above, 6 of these 8 subjects were discontinued from the study before completing required follow-up. These eyes have been included in the efficacy and safety analyses through the time of explantation, and all complications and adverse events, both pre and post-explantation, are included in the summary tables for all visits. Additional information on these eyes is provided in Section 18.6, Ocular Adverse Events, and in Appendix B.

Accountability stratified by the model of IMT implanted, i.e., WA 2.2X or WA 3.0X is summarized in Tables A2.1 and A2.2 located in Appendix A.

TABLE 2
ACCOUNTABILITY
(N = 206 EYES SUCCESSFULLY IMPLANTED WITH IMT)

Total Subjects (N) = 206		1 Month	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Available for Analysis	n/N (%)	206/206 (100.0%)	201/206 (97.6%)	202/206 (98.1%)	196/206 (95.1%)	194/206 (94.2%)	180/206 (87.4%)	148/206 (71.8%)
Discontinued	n/N (%)	0/206 (0.0%)	2/206 (1.0%)	4/206 (1.9%)	4/206 (1.9%)	7/206 (3.4%)	9/206 (4.4%)	16/206 (7.8%)
Deceased	n/N (%)	0/206 (0.0%)	1/206 (0.5%)	3/206 (1.5%)	3/206 (1.5%)	5/206 (2.4%)	7/206 (3.4%)	10/206 (4.9%)
IMT Removed*	n/N (%)	0/206 (0.0%)	1/206 (0.5%)	1/206 (0.5%)	1/206 (0.5%)	2/206 (1.0%)	2/206 (1.0%)	6/206 (2.9%)
Active (Not yet eligible for the interval)	n/N (%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	35/206 (17.0%)
Lost to Follow-up†	n/N (%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	1/206 (0.5%)	3/206 (1.5%)	6/206 (2.9%)
Missed Visit‡	n/N (%)	0/206 (0.0%)	3/206 (1.5%)	0/206 (0.0%)	6/206 (2.9%)	4/206 (1.9%)	14/206 (6.8%)	1/206 (0.5%)
% Accountability = Available for Analysis ÷ (Enrolled - Discontinued - Not yet eligible)		206/206 (100.0%)	201/204 (98.5%)	202/202 (100.0%)	196/202 (97.0%)	194/199 (97.5%)	180/197 (91.4%)	148/155 (95.5%)

DB was locked for data entry on 06/20/2005. However, it was reopened for necessary data revision and was frozen on 07/18/2005 for PMA.
010-202's office chart was lost and no 24-month data could be collected. The subject was included in the "Missed Visit" row.
N = Total number of enrolled eyes with an IMT. One eye canceled surgery. Five eyes were reported with an aborted implantation. Six eyes were reported with IMT removal at surgery. These eyes were excluded from analyses, however their safety data will be discussed separately.
N = Total number of enrolled eyes with an IMT.
* Eight eyes were reported with IMT removal postoperatively at the time of DB closure. Six of these eight eyes have been exited from the study.
† Lost to follow-up: Eyes were not examined at the visit interval, and were not considered active or discontinued.
‡ Missed visit: Eyes were not examined at the scheduled visit, however were examined or may have been examined at a subsequent visit.

Protocol deviations reported in this clinical trial for all subjects implanted with IMT are summarized in Table 2A. The following major protocol deviations were reported: one subject (PtID 23-213) had previous intraocular or corneal surgery and therefore did not meet the protocol exclusion criteria; subject 015-203 received approval for IMT implantation in OD, however the IMT was implanted in OS (the eye with better visual acuity rather than worse visual acuity); in 4 eyes, peripheral iridectomy was not performed following IMT implantation as required by the study protocol (PtID 002-201, 005-201, 005-202 and 013-202); and a total of 28 visits have been missed to date.

The remaining deviations were minor in nature. Missed and/or incomplete ocular examinations and tests involved the fellow eye more often than the IMT implanted eye. A detailed listing of the protocol deviations with patient identification number is provided in Appendix D.

TABLE 2A
PROTOCOL DEVIATIONS

Major Protocol Deviations	n
Did not meet exclusion criteria: Implanted IMT in eye with better baseline BCVA rather than eye with worse baseline BCVA	1
Iridectomy not performed	4
Missed Visits	28
Month 3	3
Month 9	6
Month 12	4
Month 18	14
Month 24	1
Minor Protocol Deviations	**n**
Subtenon injection not administered	21
Incomplete ADL questionnaire	3
Incomplete slit lamp assessment	2
Preoperative	1
Month 3	1
Manifest refraction not performed	5
Day 7	3
Month 1	1
Month 9	1
BCDVA not determined	3
Day 7	3
BCNVA at 8 inches not determined	5
Month 1	4
Month 12	1
BCNVA at 16 inches not determined	9
Month 1	6
Month 3	2
Month 12	1
IOP not measured	6
Month 1	1
Month 3	1
Month 6	3
Month 18	1
Degree of posterior capsular opacification not assessed	1
Month 3	1
No specular microscopy images	12
Month 3	3
Month 6	2
Month 9	2
Month 12	3
Month 18	1
Month 24	1

13.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics for the study cohort are summarized in Table 3. Of the 206 enrolled subjects, 108 (52.4%) are male and 98 (47.6%) are female. The mean age is 75.4 years (S.D. 7.2, range 55 – 93 years). The majority of subjects are Caucasian (198/206 or 96.1%); 1.9% of the study population is Hispanic, 1.5% is black and 0.5% is Asian. The left eye has undergone IMT implantation more frequently than the right eye (52.4% versus 47.6%).

TABLE 3
DEMOGRAPHIC INFORMATION

206 Eyes of 206 Enrolled & Implanted Subjects		
	Number	**Percentage**
Gender		
Female	98	47.6%
Male	108	52.4%
Race		
Caucasian	198	96.1%
Black	3	1.5%
Hispanic	4	1.9%
Asian	1	0.5%
Other	0	0.0%
Eye Implanted		
Right	98	47.6%
Left	108	52.4%
Age (In Years)		
Mean	75.4	
Standard Deviation	7.2	
Minimum	55	
Maximum	93	

One eye canceled surgery. Five eyes were reported with an aborted implantation. Six eyes were reported with IMT removal at surgery. These eyes were excluded from analyses, however their safety data will be discussed separately.

14.0 PREOPERATIVE PARAMETERS

Preoperative parameters are summarized in Table 4. Anterior chamber depth was 3.15 mm (S.D. 0.37 mm, range 2.48 - 4.74 mm). Preoperative axial length, determined by A-scan, was 23.74 mm (S.D. 0.93, range 21.53 – 26.14 mm). In the majority of cases, the type of AMD was described as disciform scar only (n=91 or 44.2%),or geographic atrophy only (n=78 or 37.9%). Cataract type was specified as nuclear in the vast majority of eyes (n=203 or 98.5%). (Note: More than one cataract type could have been observed in the study eye). At baseline, mean BCDVA was 20/312, mean BCNVA at 8 inches was 20/315 and mean BCNVA at 16 inches was 20/262.

TABLE 4
PREOPERATIVE PARAMETERS

206 Eyes of 206 Enrolled & Implanted Subjects		
	Number	**Percentage**
Anterior Chamber Depth		
Mean	3.145	
Standard Deviation	0.374	
1st Quartile, Median, 3rd Quartile	2.89, 3.11, 3.34	
Range	2.48, 4.74	
Axial Length		
Mean	23.739	
Standard Deviation	0.927	
1st Quartile, Median, 3rd Quartile	23.1, 23.6, 24.4	
Range	21.53, 26.14	
Type of AMD		
Geographic atrophy (GA)	78	37.9%
Drusen	3	1.5%
Disciform scar	91	44.2%
GA & Drusen	7	3.4%
GA & Disciform scar	8	3.9%
Drusen & Disciform scar	12	5.8%
GA & Drusen & Disciform scar	7	3.4%
Cataract Type		
Nuclear	147	71.4%
Cortical	1	0.5%
Posterior subcapsular (PSC)	2	1.0%
Nuclear & Cortical	41	19.9%
Nuclear & PSC	12	5.8%
Nuclear & Cortical & PSC	3	1.5%
Best-corrected Visual Acuity		
Mean BCDVA (Range)	20/312 (20/328, 20/120)	
Mean BCNVA @ 8" (Range)	20/315 (20/360, 20/80)	
Mean BCNVA @16" (Range)	20/262 (20/300, 20/100)	

1 eye canceled surgery. 5 eyes were reported with an aborted implantation. 6 eyes were reported with IMT removal at surgery. These eyes were excluded from analyses, but their safety data will be discussed separately.

15.0 OPERATIVE AND INTRAOPERATIVE PARAMETERS

Table 5 summarizes the operative and intraoperative parameters reported during successful IMT implantation. Limbal insertion was performed in 63.6% (131/206) of the study subjects, and the remaining eyes (36.4% or 75/206) underwent scleral tunneling. In 100% of eyes (206/206) the crystalline lens was extracted via conventional phacoemulsification techniques. In 87 eyes (87/206 or 42.2%), Healon V alone or in combination with another viscoelastic was used during the procedure. Mean capsulorhexis size was 6.6 mm (S.D. 0.59 mm; range 5.0 – 8.5 mm. In most eyes (203/206 or 98.5%) the iris position was flat following IMT implantation. The superior loop of the haptic was reported to be in the bag in 96.1% (198/206) of eyes and the inferior loop of the haptic was in the bag in 97.6% (201/206). The IMT position was reportedly centered in 99.5% (205/206) of eyes. As required in the study protocol, iridectomy was performed in all but 4 (1.9%) study eyes. As shown in Table 5, additional other surgical procedures were performed at the time of IMT implantation consisted of pupil stretch and lysis of peripheral anterior synechiae.

TABLE 5
OPERATIVE & INTRAOPERATIVE PARAMETERS

206 Eyes of 206 Enrolled & Implanted Subjects		
	Number	**Percentage**
Incision Type		
Limbal	131	63.6%
Scleral tunnel	75	36.4%
Viscoelastic Used		
Healon V	23	11.2%
Healon V and Amvisc	9	4.4%
Healon V and Amvisc Plus	3	1.5%
Healon V and Healon	2	1.0%
Healon V and Healon GV	4	1.9%
Healon V and Provisc	10	4.9%
Healon V and Viscoat	18	8.7%
Healon V and Viscoat/Provisc or DUOVISC	18	8.7%
Amvisc Plus	1	0.5%
Amvisc Plus/Vitrax	1	0.5%
Healon	2	1.0%
Healon GV	7	3.4%
Occucoat	1	0.5%
Provisc	1	0.5%
Vicair	1	0.5%
Viscoat	46	22.3%
Viscoat/Healon	2	1.0%
Viscoat/Healon GV	1	0.5%
Viscoat/Healon/Healon GV	1	0.5%
Viscoat/Provisc or DUOVISC	50	24.3%
Vitrax	2	1.0%
Vitrax/Occucoat	3	1.5%

TABLE 5 *(CONTINUED)*
OPERATIVE & INTRAOPERATIVE PARAMETERS

206 Eyes of 206 Enrolled & Implanted Subjects			
		Number	**Percentage**
Capsulorhexis Size			
	Mean	6.603	
	Standard Deviation	0.587	
	1st Quartile, Median, 3rd Quartile	6.00, 6.50, 7.00	
	Range	5.00, 8.50	
Iris Position Post Implantation			
	Bulging (convex)	2	1.0%
	Concave	1	0.5%
	Flat	203	98.5%
Haptic Placement			
Superior loop	Bag	198	96.1%
	Sulcus	8	3.9%
Inferior loop	Bag	201	97.6%
	Sulcus	5	2.4%
IMT Positioning			
	Centered	205	99.5%
	Centered & other (small amount condensation inside optics)	1	0.5%
Surgery Time (in minutes)			
	Mean	48.612	
	Standard Deviation	19.25	
	1st Quartile, Median, 3rd Quartile	37.0, 45.0, 60.0	
	Range	6.00, 133.0	
Other Surgical Procedures*			
	Iridectomy	202	98.1%
	Posterior capsulotomy	0	0.0%
	Vitrectomy	1	0.5%
	Other	2	1.0%
Subtenon Injected			
	No	21	10.2%
	Yes	185	89.8%

One eye canceled surgery. Five eyes were reported with an aborted implantation. Six eyes were reported with IMT removal at surgery. These eyes were excluded from analyses, however their safety data will be discussed separately.

* An eye could be reported with multiple other surgical procedures. Other surgical procedures included:
1.Pupil stretch with beehler & perfect pupil
2.Lysis of peripheral anterior synechiae

16.0 SUMMARY OF VISUAL ACUITY EFFECTIVENESS AND SAFETY ENDPOINTS

A summary of visual acuity safety and effectiveness outcomes is shown in Table 6. As identified in the study protocol, effectiveness was defined as an improvement of 2 lines or greater in either near or distance best corrected acuity in 50% of the implanted eyes at 12 months post-implantation. This overall success rate, or effectiveness endpoint, was achieved by 89.1% of eyes at 6 months, by 89.7% at 9 months, and by 90.1% at 12 months, and remained stable at 87.2% at 18 months and 85.7% at 24 months. The binominal exact p-value for alternative hypothesis testing success rate > 50% was < 0.001 at each time point indicating that the results significantly surpassed the effectiveness endpoint defined in the protocol.

The proportion of eyes that showed a gain of at least 2 lines in both BCDVA **and** BCNVA at either 8 inches or 16 inches was 68.7% at 6 and 9 months, 73.4% at 12 months, 70.9% at 18 months and 67.3% at 24 months. These outcomes underscore the effectiveness of the IMT, with approximately 70% of eyes achieving an improvement of 2 or more lines in both near and distance acuity.

The safety parameter of preservation of best corrected visual acuity established in the study protocol consisted of a limit of ≤10% of implanted eyes with a loss of >2 lines of either near (8”and 16”) or distance BCVA without a corresponding improvement or with a loss in the other measure of acuity. Thus, the overall visual acuity safety endpoint consists of the sum of the following three categories:

1) The proportion of eyes with >2 lines loss of BCDVA and no change/loss in BCNVA (8” and 16”)
2) The proportion of eyes with >2 lines loss of BCNVA (8” and 16”) and no change/loss in BCDVA
3) The proportion of eyes with >2 lines loss of BCDVA and BCNVA.

The proportion of eyes with >2 lines loss of BCDVA and no change/loss of BCNVA, or >2 lines loss of BCNVA and no change/loss of BCDVA, was only 4.5% (9/201) at 6 months, 4.6% (9/195) at 9 months, 5.2% (10/193) at 12 months, 4.5% (8/179) at 18 months, and 6.1% (9/147) at 24 months. The binominal exact p-value for the alternative hypothesis testing safety rate of <10% was <0.05 at the 6, 9, 12, and 18 month follow-up visits, and 0.0696 at the 24 month follow-up visit, indicating that the results were well below the 10% limit established in the study protocol.

Only 1.0% of eyes lost >2 lines of both BCDVA and BCNVA at 6 months; this remained relatively stable over the course of follow-up, with 2.1% of eyes at 9 months, 1.0% at 12 months, 1.1% at 18 months and 1.4% at 24 months. The proportion of eyes with >2 lines loss of BCDVA and no change of BCNVA was 0.5% at 6 months, 1.0% at 9 months, 0.5% at 12 months, 0.6% at 18 months and 0.0% at 24 months. Finally, the proportion of eyes with >2 lines loss in BCNVA and no

change in BCDVA was 3.0% at 6 months, 1.5% at 9 months, 3.6% at 12 months, 2.8% at 18 months and 4.8% at 24 months.

In summary, the effectiveness target for the IMT was exceeded in the study population, with approximately 90% of eyes achieving a gain of 2 lines of BCVA at near or distance and approximately 70% of eyes gaining 2 or more lines in both distance and near acuity. This significant improvement in visual acuity was associated with very little loss of lines of visual acuity, with loss of >2 lines of both distance and near acuity reported in approximately 1-2% of eyes.

These outcomes, which are described in more detail in the following sections of this report, clearly establish the clinical benefit of the IMT in improving vision in patients with moderate to profound central vision loss from AMD.

TABLE 6
SUMMARY OF VISUAL ACUITY EFFECTIVENESS AND SAFETY ENDPOINTS

BCVA Endpoints	6 Months n (%) % CI	9 Months n (%) % CI	12 Months n (%) % CI	18 Months n (%) % CI	24 Months n (%) % CI
Effectiveness (N=)	201	195	192	179	147
Overall Effectiveness Endpoint (Success Rate) ≥2 lines gain of BCDVA or BCNVA*	***179 (89.1%) 84.7%, 92.5%***	***175 (89.7%) 85.4%, 93.1%***	***173 (90.1%) 85.8%, 93.4%***	***156 (87.2%) 82.3%, 91.1%***	***126 (85.7%) 80.1%, 90.2%***
Binomial exact p-value for Ha: success rate > 50%	***<.0001***	***<.0001***	***<.0001***	***<.0001***	***<.0001***
≥2 lines gain of BCDVA and BCNVA*	138 (68.7%) 62.8%, 74.1%	134 (68.7%) 62.8%, 74.2%	141 (73.4%) 67.7%, 78.6%	127 (70.9%) 64.9%, 76.5%	99 (67.3%) 60.4%, 73.7%
Not reported/IMT removal	1	1	2	1	1
Total	202	196	194	180	148
Safety (N=)	201	195	193	179	147
Overall Safety Rate >2 lines loss of BCDVA and no change/loss of BCNVA or >2 lines loss of BCNVA and no change/loss of BCDVA†	***9 (4.5%) 2.4%, 7.7%***	***9 (4.6%) 2.4%, 7.9%***	***10 (5.2%) 2.8%, 8.6%***	***8 (4.5%) 2.2%, 7.9%***	***9 (6.1%) 3.2%, 10.4%***
Binomial exact p-value for Ha: safety rate < 10%	***0.0033***	***0.0048***	***0.0120***	***0.0055***	***0.0696***
>2 lines loss of BCDVA and BCNVA‡	2 (1.0%) 0.2%, 3.1%	4 (2.1%) 0.7%, 4.6%	2 (1.0%) 0.2%, 3.2%	2 (1.1%) 0.2%, 3.5%	2 (1.4%) 0.2%, 4.2%
>2 lines loss of BCDVA and no change in BCNVA§	1 (0.5%) 0.0%, 2.3%	2 (1.0%) 0.2%, 3.2%	1 (0.5%) 0.0%, 2.4%	1 (0.6%) 0.0%, 2.6%	0 (0.0%) 0.0%, 2.0%
>2 lines loss of BCNVA and no change of BCDVA§	6 (3.0%) 1.3%, 5.8%	3 (1.5%) 0.4%, 3.9%	7 (3.6%) 1.7%, 6.7%	5 (2.8%) 1.1%, 5.8%	7 (4.8%) 2.3%, 8.8%
Not reported/IMT removal	1	1	1	1	1
Total	202	196	194	180	148

For effectiveness, N = number of records with non-missing BCDVA and BCNVA changes from preop. The records with BCDVA gain ≥2 lines and BCNVA missing and the records with BCNVA gain ≥2 lines and BCDVA missing were counted as successful events.
For safety, N = number of records with non-missing BCDVA and BCNVA changes from preop. The records with BCDVA loss > 2 lines and BCNVA missing and the records with BCNVA loss > 2 lines and BCDVA missing were counted as safety events.
Not reported = number of records with missing BCDVA and/or BCNVA changes from preop.
IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately.
Total = number of treated eyes that returned for the visit.
% = n ÷N ×100. %CI = **90%** confidence interval for %. It was calculated based on Clopper Pearson method.

* BCNVA gain ≥2 lines means that either BCNVA at 8" or BCNVA at 16" gained ≥2 lines.

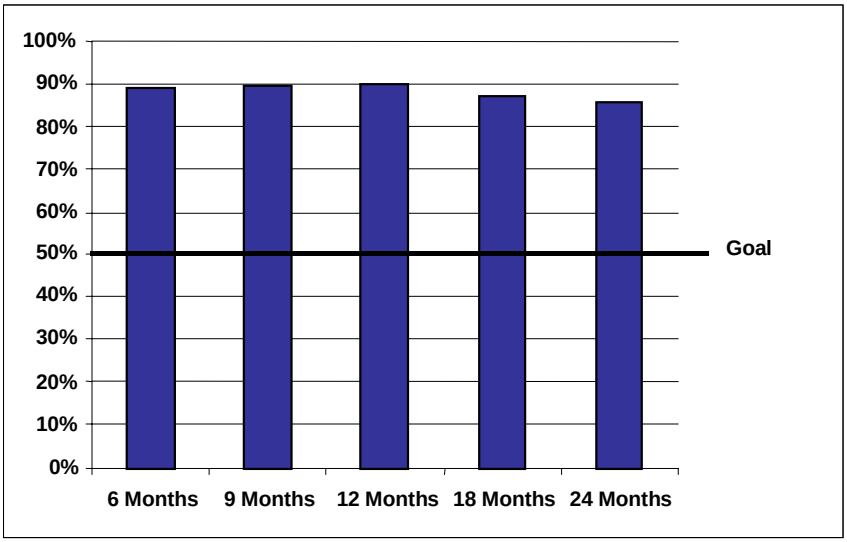
† No gain in BCNVA means that both BCNVA at 8" and BCNVA at 16" did not gain ≥2 lines. No gain in BCDVA means that BCDVA did not gain ≥2 lines.

‡ >2 lines loss in BCNVA means that one BCNVA (8" or 16" lost > 2 lines without the other BCNVA (8" or 16") gaining ≥2 lines.

§ No change = within a loss of 2 lines to a gain of <2 lines. For BCNVA, it means that both BCNVA at 8" and BCNVA at 16" are within a loss of 2 lines to a gain of <2 lines.

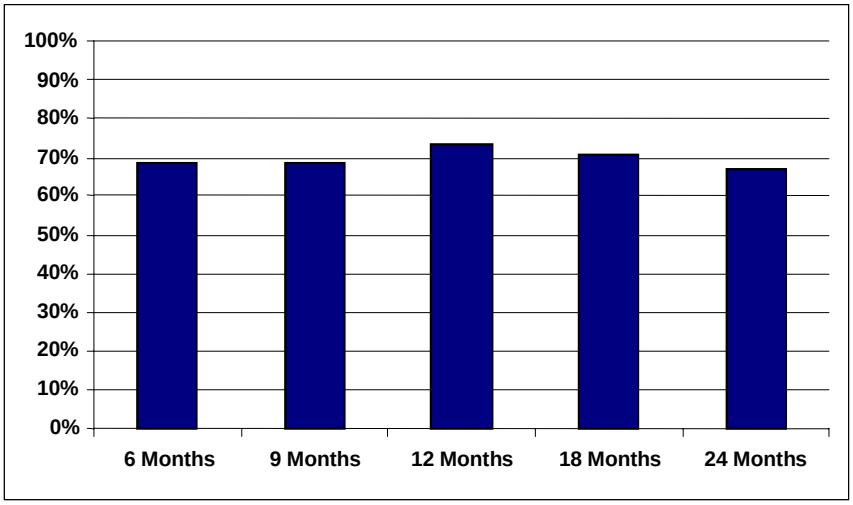
Figure 4 illustrates the primary effectiveness endpoint over time, with approximately 90% of eyes achieving a gain of ≥2 lines of distance or near acuity.

FIGURE 4 PRIMARY EFFECTIVENESS ENDPOINT
2 LINE GAIN IN BCDVA OR BCNVA



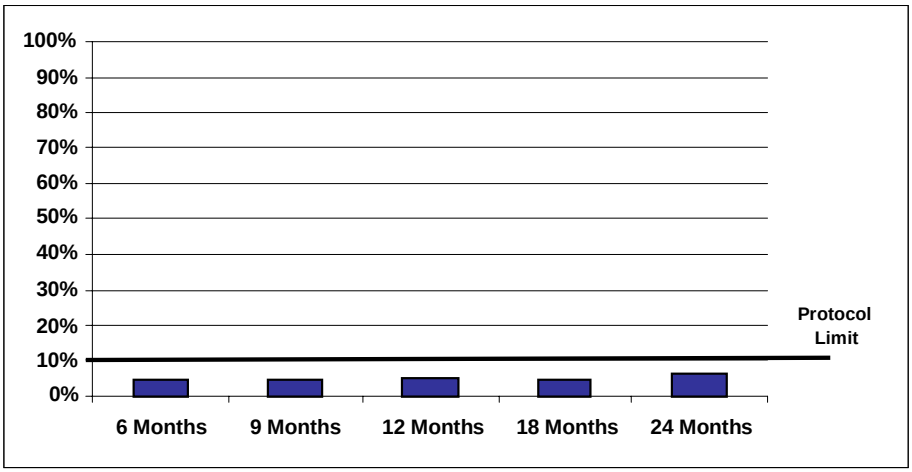
As shown in Figure 5, approximately 70% of eyes achieved a gain of at least 2 lines of BCDVA **and** BCNVA, at either 8 inches or 16 inches.

FIGURE 5 EFFICACY
> 2 LINE GAIN IN BCDVA AND BCNVA



As shown in Figure 6, the number of subjects that experienced a loss of >2 lines of either near or distance BCVA without a corresponding improvement (gain of 2 lines or more) in the other measure of BCVA was well below the safety limit of 10%, establishing excellent preservation of visual acuity in the study population.

FIGURE 6 SAFETY – PRESERVATION OF VISUAL ACUITY
PROPORTION OF EYES WITH
> 2 LINES LOSS OF BCDVA AND NO CHANGE/LOSS OF BCNVA
OR
> 2 LINES LOSS OF BCNVA AND NO CHANGE/LOSS OF BCDVA



Additional analyses of the visual acuity safety and effectiveness endpoints may be found in Appendix A of this report. These analyses of the visual acuity safety and effectiveness endpoints include stratification by patient's age at entry (Tables A6A.1 through A6A.3), by gender (Tables A6B.1 through A6B.3), by IMT model (Tables A6C.1 through A6C.3), and by preoperative BCDVA (Tables A6D.1 through A6D.3).

All age groups significantly ($p < 0.001$) surpassed the overall protocol specified overall effectiveness endpoint, or success rate of 50% at 12, 18 and 24 months. There was no significant difference in overall success rate (gain of 2 or more lines in distance or near acuity) or overall safety rate (loss of more than 2 lines of distance or near acuity with no commensurate gain) when comparing the various age groups at 12, 18 and 24 months. Visual acuity outcomes for both IMT models, WA 2.2X and WA 3.0X, also easily surpassed the overall success rate at each time interval. Stratification by gender did not affect the overall success and safety rates at 12, 18, and 24 months and did not reveal any differences between outcomes for male vs. female subjects.

Preoperative best corrected distance visual acuity was categorized as moderate impairment (20/80 to 20/160), severe impairment (20/161 to 20/400) and profound impairment (worse than 20/400). All three categories easily surpassed the overall protocol specified success rate of 50% at 12, 18 and 24 months. However, as shown in Tables A6D.1 and A6D.2, eyes with profound visual impairment preoperatively showed a significantly higher success rate at 12 and 18 months than eyes with moderate impairment at baseline. This trend continued at 24 months, indicating that eyes with the greatest need experience the greatest benefit from IMT implantation. Associated with this greater benefit to eyes with the most profound visual impairment, a smaller number of these eyes experienced a loss of >2 lines of distance or near acuity without a commensurate gain at 24 months. Thus, at 24 months, more eyes with moderate impairment at baseline than eyes with profound impairment reported with a loss of >2 lines of near or distance vision without a commensurate gain (Table A6D.3).

The following sections of this report describe effectiveness, as measured by improvement in best corrected distance and near acuity, and safety or preservation of best corrected visual acuity, both at distance as well as at near.

17.0 EFFECTIVENESS OUTCOMES

Formatted: English (U.S.)

17.1 IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

Improvement in lines of BCDVA for all implanted eyes is shown in Tables 7 and 7.1 (cumulative percentages for the change in lines of BCDVA). The line change calculation in BCDVA is based on LogMAR values. For example, if the difference between postoperative LogMAR and preoperative LogMAR is -0.1, the line change is a gain in one line; if the difference is -0.2, the line change is a gain in two lines; if the difference was +0.1, the line change is a loss in one line; and if the difference is +0.2, the line change is a loss in 2 lines. If the difference is between -0.21 and -0.29, the line change is a gain of $\geq$ 2 lines but < 3 lines.

As shown in Table 7, a large proportion of eyes gained 3 or more lines of best corrected distance acuity, with an increase in this proportion between 6 month and 9 months and a slight reduction at 18 and 24 months. Specifically at 6 months, 156/201 (77.6%) eyes gained at least two lines of BCDVA, 126/201 (62.7%) gained at least three lines of BCDVA, 79/201 (39.3%) gained at least four lines of BCDVA, 40/201 (19.9%) gained at least five lines of BCDVA, and 14/201 (7.0%) gained at least six lines of BCDVA.

At 12 months, 155/193 (80.3%) eyes gained at least two lines, 128/193 (66.3%) eyes gained at least three lines, 87/193 (45.1%) eyes gained at least four lines, 49/193 (25.4%) eyes gained at least five lines, and 21/193 (10.9%) gained at least 6 lines of BCDVA. Very similar outcomes were reported at 18 and 24 months, with approximately 75% of eyes gaining at least 2 lines, over 60% gaining at least 3 lines, over 40% gaining $\geq$ 4 lines, about 20% with a gain of $\geq$ 5 lines and approximately 10% with a gain o at least 6 lines of BCDVA.

Importantly, the mean increase in lines of BCDVA was 3.3 lines (S.D. 2.1) at 6 months, 3.3 lines (S.D. 2.3) at 9 months, 3.4 lines (S.D. 2.3) at 12 months, 3.3 lines (S.D. 2.2) at 18 months, and 3.1 lines (S.D. 2.2) at 24 months.

Thus, the proportion of eyes with a gain of both 2 lines and 3 lines of best corrected distance acuity was generally stable over time, suggesting no diminution of effect over the 24 months following implantation. Importantly, these gains in BCDVA were both statistically and clinically significant.

TABLE 7
IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

BCDVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	14	7.0%	20	10.3%	21	10.9%	18	10.1%	13	8.8%
Gain ≥5 lines but <6 lines	26	12.9%	20	10.3%	28	14.5%	24	13.4%	16	10.9%
Gain ≥4 lines but <5 lines	39	19.4%	42	21.5%	38	19.7%	32	17.9%	33	22.4%
Gain ≥3 lines but <4 lines	47	23.4%	48	24.6%	41	21.2%	38	21.2%	24	16.3%
Gain ≥2 lines but <3 lines	30	14.9%	22	11.3%	27	14.0%	29	16.2%	22	15.0%
Gain ≥1 line but <2 lines	25	12.4%	21	10.8%	15	7.8%	17	9.5%	16	10.9%
Other	20	10.0%	22	11.3%	23	11.9%	21	11.7%	23	15.6%
Gain ≥2 lines	156	77.6%	152	77.9%	155	80.3%	141	78.8%	108	73.5%
One-sided lower 95% CL*	72.2%		72.5%		75.0%		73.1%		66.8%	
Mean (SD) line increase	3.3 (2.1)		3.3 (2.3)		3.4 (2.3)		3.3 (2.2)		3.1 (2.2)	
95% CI for Mean line increase	3.0, 3.6		3.0, 3.6		3.1, 3.8		3.0, 3.7		2.8, 3.5	
N	201		195		193		179		147	
Not reported/IMT removal	1		1		1		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 7.1
IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA) (CUMULATIVE FREQUENCY)

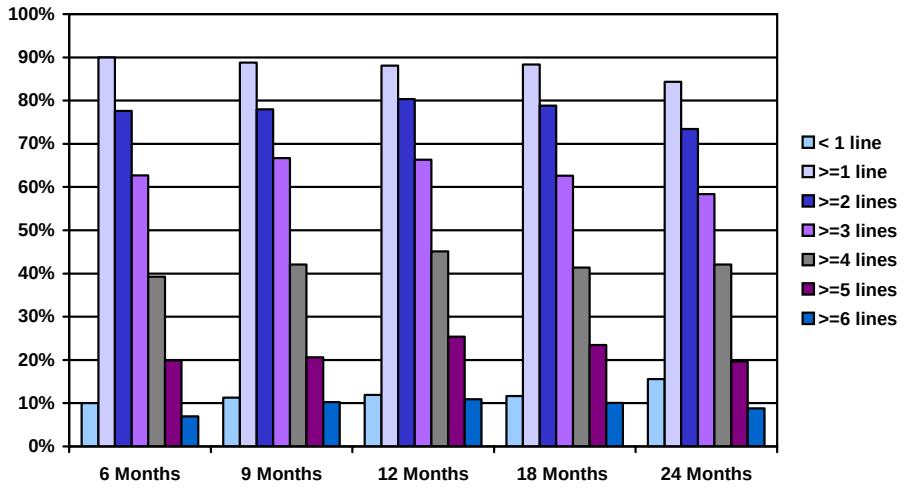
BCDVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	14	7.0%	20	10.3%	21	10.9%	18	10.1%	13	8.8%
Gain ≥5 lines	40	19.9%	40	20.5%	49	25.4%	42	23.5%	29	19.7%
Gain ≥4 lines	79	39.3%	82	42.1%	87	45.1%	74	41.3%	62	42.2%
Gain ≥3 lines	126	62.7%	130	66.7%	128	66.3%	112	62.6%	86	58.5%
Gain ≥2 lines	156	77.6%	152	77.9%	155	80.3%	141	78.8%	108	73.5%
Gain ≥1 line	181	90.0%	173	88.7%	170	88.1%	158	88.3%	124	84.4%
Other	201	100.0%	195	100.0%	193	100.0%	179	100.0%	147	100.0%
Gain ≥2 lines	156	77.6%	152	77.9%	155	80.3%	141	78.8%	108	73.5%
One-sided lower 95% CL*	72.2%		72.5%		75.0%		73.1%		66.8%	
N	201		195		193		179		147	
Not reported/IMT removal	1		1		1		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

Figure 7 shows the improvement in BCDVA for all eyes implanted with IMT.

FIGURE 7 IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY ALL EYES IMPLANTED WITH IMT



Improvement in BCDVA for all study visits, including 1 month and 3 months, may be found in Table A7 in Appendix A.

Improvement in BCDVA stratified by patient's age at implant, IMT model, and gender are provided in Appendix A in Tables A7A.1 through A7C.3. Stratification by age at implant or gender did not affect the improvement in best corrected distance VA. When BCDVA was stratified by the two IMT models, i.e., WA 3.0X and WA 2.2X, a comparison of improvement in lines of BCDVA for these groups suggests somewhat better visual outcomes in subjects implanted with the WA 3.0X at 12 and 18 months. However, the improvements in BCDVA for the WA 2.2X remain well within the efficacy target established in the study protocol.

Improvement in BCDVA stratified by preoperative BCDVA is summarized in Tables 7.2 through 7.4 for 12 months, 18 months and 24 months respectively. Preoperative best corrected distance visual acuity was categorized as moderate impairment (20/80 to 20/160), severe impairment (20/161 to 20/400) and profound impairment (worse than 20/400).

At 12 months, the proportion of patients with moderate impairment that gained three or more lines of BCDVA was 20.0%. The proportion of patients with severe impairment that gained three or more lines of BCDVA was 61.8% and the proportion

of patients with profound impairment that gained two or more lines of BCDVA was 88.9%. This difference was statistically significant ($p < 0.001$).

At 18 months, a gain of at least three lines of BCDVA was observed in 26.3% of patients with moderate impairment, in 60.8% of patients with severe impairment, and in 77.6% in patients with profound impairment ($p< 0.001$). This significant difference ($p=0.0040$) was also observed at 24 months with 23.5% of patients with moderate impairment, 55.4% of eyes with severe impairment, and 76.6% of eyes with profound impairment gaining at least three lines of BCDVA.

Thus, stratification by preoperative BCDVA revealed that patients with profound impairment gained considerably more lines of BCDVA than patients with moderate impairment at 12, 18 and 24 months. These finding establish that the effect of IMT implantation on BCDVA was the greatest for those patients with the greatest need.

TABLE 7.2
IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA) AT 12 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCDVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines	4	20.0%	68	61.8%	56	88.9%
Gain ≥2 lines but <3 lines	7	35.0%	15	13.6%	5	7.9%
Gain ≥1 line but <2 lines	2	10.0%	12	10.9%	1	1.6%
Other	7	35.0%	15	13.6%	1	1.6%
Gain ≥2 lines	11	55.0%	83	75.5%	61	96.8%
One-sided lower 95% CL*	34.7%		67.8%		90.3%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	<.0001					
N	20		110		63	
Not reported/IMT removal	0		0		1	
Total	20		110		64	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 7.3
IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY(BCDVA) AT 18 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCDVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines	5	26.3%	62	60.8%	45	77.6%
Gain ≥2 lines but <3 lines	5	26.3%	14	13.7%	10	17.2%
Gain ≥1 line but <2 lines	2	10.5%	13	12.7%	2	3.4%
Other	7	36.8%	13	12.7%	1	1.7%
Gain ≥2 lines	10	52.6%	76	74.5%	55	94.8%
One-sided lower 95% CL*	32.0%		66.4%		87.2%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	<.0001					
N	19		102		58	
Not reported/IMT removal	0		1		0	
Total	19		103		58	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 7.4
IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA) AT 24 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCDVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines	4	23.5%	46	55.4%	36	76.6%
Gain ≥2 lines but <3 lines	4	23.5%	13	15.7%	5	10.6%
Gain ≥1 line but <2 lines	2	11.8%	10	12.0%	4	8.5%
Other	7	41.2%	14	16.9%	2	4.3%
Gain ≥2 lines	8	47.1%	59	71.1%	41	87.2%
One-sided lower 95% CL*	26.0%		61.8%		76.4%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	0.0040					
N	17		83		47	
Not reported/IMT removal	0		1		0	
Total	17		84		47	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

17.2 IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8 INCHES

Formatted: English (U.S.)

Improvement in BCNVA at 8 inches is summarized in Tables 8 and 8.1. Line change in BCNVA calculation is based on M values, not on the number of letters correctly read. If only 1 or 2 letters could be read correctly at the 8.0M line, which is the worst line on the reading card used in this study, a visual acuity of 10.0M is assumed. If none of the letters could be read correctly, a visual acuity of 12.5M is assumed.

As shown in Table 8, at 8 inches, a gain of at least 2 lines of BCNVA was reported for 137/201 (68.2%) eyes, a gain of $\geq$ 3 lines of BCNVA was reported for 98/201 (48.8%), a gain of $\geq$ 4 lines of BCNVA was reported for 61/201 (30.3%) eyes, a gain of $\geq$ 5 lines of BCNVA was reported for 38/201 (18.9%), and a gain of $\geq$ 6 lines of BCNVA was reported for 18/201 (9.0%) at 6 months.

Very similar outcomes were reported at 12, 18 and 24 months, with a gain of $\geq$ 2 lines of BCNVA reported for approximately 70% of eyes, a gain of $\geq$ 3 lines reported for approximately 50%, a gain of $\geq$ 4 lines of BCNVA in 35% to 40% of eyes, a gain of $\geq$ 5 lines in close to 20% of eyes, and a gain of $\geq$ 6 lines of BCNVA at 8 inches in just under 10% of eyes at each of these visits.

The mean line increase in BCNVA at 8 inches was stable over time with a gain of 2.3 lines (S.D. 2.6) at 6 months, 2.3 lines (S.D. 2.8) at 9 months, 2.4 lines (S.D. 2.9) at 12 months, 2.4 lines (S.D. 2.7) at 18 months, and 2.3 lines (S.D. 3.0) at 24 months.

TABLE 8
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8"

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	18	9.0%	18	9.2%	17	8.9%	15	8.4%	13	8.8%
Gain ≥5 lines but <6 lines	20	10.0%	17	8.7%	18	9.4%	18	10.1%	16	10.9%
Gain ≥4 lines but <5 lines	23	11.4%	25	12.8%	36	18.8%	33	18.4%	22	15.0%
Gain ≥3 lines but <4 lines	37	18.4%	35	17.9%	32	16.7%	26	14.5%	26	17.7%
Gain ≥2 lines but <3 lines	39	19.4%	41	21.0%	30	15.6%	28	15.6%	22	15.0%
Gain ≥1 line but <2 lines	29	14.4%	23	11.8%	22	11.5%	22	12.3%	15	10.2%
Other	35	17.4%	36	18.5%	37	19.3%	37	20.7%	33	22.4%
Gain ≥2 lines	137	68.2%	136	69.7%	133	69.3%	120	67.0%	99	67.3%
One-sided lower 95% CL*	62.3%		63.9%		63.3%		60.8%		60.4%	
Mean (SD) line increase	2.3 (2.6)		2.3 (2.8)		2.4 (2.9)		2.4 (2.7)		2.3 (3.0)	
95% CI for Mean line increase	2.0, 2.7		1.9, 2.7		2.0, 2.8		2.0, 2.8		1.8, 2.8	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.
* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 8.1
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" (CUMULATIVE FREQUENCY)

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	18	9.0%	18	9.2%	17	8.9%	15	8.4%	13	8.8%
Gain ≥5 lines	38	18.9%	35	17.9%	35	18.2%	33	18.4%	29	19.7%
Gain ≥4 lines	61	30.3%	60	30.8%	71	37.0%	66	36.9%	51	34.7%
Gain ≥3 lines	98	48.8%	95	48.7%	103	53.6%	92	51.4%	77	52.4%
Gain ≥2 lines	137	68.2%	136	69.7%	133	69.3%	120	67.0%	99	67.3%
Gain ≥1 line	166	82.6%	159	81.5%	155	80.7%	142	79.3%	114	77.6%
Other	201	100.0%	195	100.0%	192	100.0%	179	100.0%	147	100.0%
Gain ≥2 lines	137	68.2%	136	69.7%	133	69.3%	120	67.0%	99	67.3%
One-sided lower 95% CL*	62.3%		63.9%		63.3%		60.8%		60.4%	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.
* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

Table A8 in Appendix A summarizes the improvement in best corrected near visual acuity at 8” for all implanted eyes at each follow-up interval. Improvement in BCNVA at 8 inches stratified by patient’s age at implant, IMT model, gender, and preoperative BCDVA are displayed in Tables A8A.1 through A8D.3 of Appendix A. None of the stratification factors had a significant impact on best corrected near visual acuity at 8 inches, with the exception of preoperative BCDVA. At 24 months, patients with profound impairment gained considerably more lines of BCNVA at 8” than patients with moderate impairment at study entry.

Formatted: English (U.S.)

17.3 IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 16 INCHES

Improvement in BCNVA at 16 inches is summarized in Tables 9 and 9.1. Again, line change in BCNVA calculation is based on M values, not on the number of letters correctly read. If only 1 or 2 letters could be read correctly at the 8.0M line, which is the worst line on the reading card used in this study, a visual acuity of 10.0M is assumed. If none of the letters could be read correctly, a visual acuity of 12.5M is assumed.

The mean line increase in best corrected near visual acuity at 16 inches was 2.1 lines (S.D. 2.4) at 6 months, 2.4 lines (S.D. 2.4) at 9 months, 2.4 lines (S.D. 2.5) at 12 months, 2.3 lines (S.D. 2.4) at 18 months, and 2.3 lines (S.D. 2.6) at 24 months.

As shown in Table 9.1 , at 6 months, a gain of $\geq$ 2 lines of BCNVA at 16 inches was reported for 136/201 (67.7%) eyes. This included 104 eyes (51.7%) that gained at least three lines, 55 eyes (27.4%) that gained at least four lines, 19 (9.5%) eyes that gained at least five lines, and 8/201 (4.0%) eyes that gained at least six lines of BCNVA at 16 inches. These proportions of eyes gaining 2, 3, 4, 5 and 6 lines of BCNVA at 16 inches remained generally stable at 9 months, 12 month, 18 months and 24 months, supporting the good long-term effect of the IMT on best corrected near acuity.

It is noteworthy that nearly a third of the implanted eyes gained $\geq$ 4 lines of BCNVA, with 27.4% of eyes at 6 months, 33.9% at 9 and 12 months, 31.3% at 18 months, and 31.9% at 24 months gaining 4 or more lines of BCNVA at 16." Even more notably, 10% to 15% of eyes in the study cohort gained 5 or more lines of BCNVA at 16 inches.

The proportion of eyes achieving a gain of 3 or more lines was generally consistent when best corrected near acuity was measured at 8 inches or at 16 inches.

Table A9 in Appendix A summarizes the improvement in best corrected near visual acuity at 16 inches for all implanted eyes at each follow-up visit from one month. Tables A9A.1 through A9D.3 in Appendix A summarize the improvement in BCNVA at 16 inches stratified by patient's age at implant, gender, IMT model and preoperative BCDVA. Impact of stratification factors was observed at 18 months only; specifically eyes implanted with WA 3.0X and eyes with profound impairment at baseline gained significantly more lines of BCNVA at 16 inches than eyes implanted with WA 2.0X or moderate impairment at baseline, respectively.

TABLE 9
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 16"

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	8	4.0%	9	4.6%	14	7.3%	10	5.6%	8	5.4%
Gain ≥5 lines but <6 lines	11	5.5%	20	10.3%	23	12.0%	13	7.3%	15	10.2%
Gain ≥4 lines but <5 lines	36	17.9%	37	19.0%	28	14.6%	33	18.4%	24	16.3%
Gain ≥3 lines but <4 lines	49	24.4%	34	17.4%	38	19.8%	35	19.6%	31	21.1%
Gain ≥2 lines but <3 lines	32	15.9%	42	21.5%	33	17.2%	32	17.9%	27	18.4%
Gain ≥1 line but <2 lines	25	12.4%	21	10.8%	23	12.0%	23	12.8%	12	8.2%
Other	40	19.9%	32	16.4%	33	17.2%	33	18.4%	30	20.4%
Gain ≥2 lines	136	67.7%	142	72.8%	136	70.8%	123	68.7%	105	71.4%
One-sided lower 95% CL*	61.8%		67.1%		65.0%		62.5%		64.7%	
Mean (SD) line increase	2.1 (2.4)		2.4 (2.4)		2.4 (2.5)		2.3 (2.4)		2.3 (2.6)	
95% CI for Mean line increase	1.8, 2.4		2.0, 2.7		2.1, 2.8		2.0, 2.7		1.9, 2.7	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.
* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 9.1
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 16"
(CUMULATIVE FREQUENCY)

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines	8	4.0%	9	4.6%	14	7.3%	10	5.6%	8	5.4%
Gain ≥5 lines	19	9.5%	29	14.9%	37	19.3%	23	12.8%	23	15.6%
Gain ≥4 lines	55	27.4%	66	33.8%	65	33.9%	56	31.3%	47	32.0%
Gain ≥3 lines	104	51.7%	100	51.3%	103	53.6%	91	50.8%	78	53.1%
Gain ≥2 lines	136	67.7%	142	72.8%	136	70.8%	123	68.7%	105	71.4%
Gain ≥1 line	161	80.1%	163	83.6%	159	82.8%	146	81.6%	117	79.6%
Other	201	100.0%	195	100.0%	192	100.0%	179	100.0%	147	100.0%
Gain ≥2 lines	136	67.7%	142	72.8%	136	70.8%	123	68.7%	105	71.4%
One-sided lower 95% CL*	61.8%		67.1%		65.0%		62.5%		64.7%	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.
* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

Formatted: English (U.S.)

17.4 IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8 OR 16 INCHES

Improvement in BCNVA measured at 8 or 16 inches is summarized in Tables 10 and 10.1. A gain of lines indicates that the subject experienced a gain in BCNVA at either 8" or 16."

A gain of ≥ 2 lines of BCNVA at either 8 or 16 inches was observed in 80.1% (161/201) of eyes at 6 months and remained stable at 82.8% (159/192) at 12 months, 79.3% (142/179) at 18 months, and 79.6% (117/147) at 24 months for all IMT implanted eyes. A gain of ≥ 3 lines of BCNVA at 8 or 16 inches was observed in 66.7% (134/201) at 6 months and similarly remained stable at 67.7% (130/192) at 12 months, 65.4% (117/179) at 18 months, and 65.3% (96/147) at 24 months for all IMT implanted eyes.

Close to 50% of eyes gained ≥ 4 lines of BCNVA at either 8" or 16" at 6, 12, 18 and 24 months. On average, 25% of eyes had a gain of ≥ 5 lines of BCNVA at either 8" or 16" inches across all study visits from 6 months, and about 10% of eyes had a gain of ≥ 6 lines of BCNVA at either 8 or 16 inches at 6, 12, 18 and 24 months.

TABLE 10
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" OR 16"

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines[1]	21	10.4%	22	11.3%	24	12.5%	17	9.5%	15	10.2%
Gain ≥5 lines but <6 lines[2]	26	12.9%	26	13.3%	31	16.1%	24	13.4%	25	17.0%
Gain ≥4 line but <5 lines[3]	40	19.9%	47	24.1%	39	20.3%	46	25.7%	31	21.1%
Gain ≥3 lines but <4 lines[4]	47	23.4%	33	16.9%	36	18.8%	30	16.8%	25	17.0%
Gain ≥2 lines but <3 lines[5]	27	13.4%	29	14.9%	29	15.1%	25	14.0%	21	14.3%
Gain ≥1 line but <2 lines[6]	17	8.5%	16	8.2%	11	5.7%	14	7.8%	10	6.8%
Other	23	11.4%	22	11.3%	22	11.5%	23	12.8%	20	13.6%
Gain ≥2 lines	161	80.1%	157	80.5%	159	82.8%	142	79.3%	117	79.6%
One-sided lower 95% CL[7]	74.9%		75.3%		77.7%		73.7%		73.4%	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with at least one non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* BCNVA gain ≥ 3 lines at either 8" or 16"
† BCNVA gain ≥ 2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 10.1
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" OR 16" (CUMULATIVE FREQUENCY)

BCNVA Change from Baseline	6 Months		9 Months		12 Months		18 Months		24 Months	
	n	%	n	%	n	%	n	%	n	%
Gain ≥6 lines[1]	21	10.4%	22	11.3%	24	12.5%	17	9.5%	15	10.2%
Gain ≥5 lines[2]	47	23.4%	48	24.6%	55	28.6%	41	22.9%	40	27.2%
Gain ≥4 lines[3]	87	43.3%	95	48.7%	94	49.0%	87	48.6%	71	48.3%
Gain ≥3 lines[4]	134	66.7%	128	65.6%	130	67.7%	117	65.4%	96	65.3%
Gain ≥2 lines[5]	161	80.1%	157	80.5%	159	82.8%	142	79.3%	117	79.6%
Gain ≥1 line[6]	178	88.6%	173	88.7%	170	88.5%	156	87.2%	127	86.4%
Other	201	100.0%	195	100.0%	192	100.0%	179	100.0%	147	100.0%
Gain ≥2 lines	161	80.1%	157	80.5%	159	82.8%	142	79.3%	117	79.6%
One-sided lower 95% CL[7]	74.9%		75.3%		77.7%		73.7%		73.4%	
N	201		195		192		179		147	
Not reported/IMT removal	1		1		2		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the M-values.

N = number of treated eyes returned for the visit with at least one non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

[1] BCNVA gain ≥ 6 lines at either 8" or 16"
[2] BCNVA gain ≥ 5 lines at either 8" or 16".
[3] BCNVA gain ≥ 4 lines at either 8" or 16".
[4] BCNVA gain ≥ 3 lines at either 8" or 16".
[5] BCNVA gain ≥ 2 lines at either 8" or 16".
[6] BCNVA gain ≥ 1 line at either 8" or 16".
[7] CL = exact confidence limit. It was calculated based on Clopper Pearson method.

Figure 8 shows the improvement in BCNVA at 8" or 16," and displays very graphically the clinical benefit of the IMT in improving near acuity, with approximately 80% of eyes achieving a gain of 2 or more lines of BCNVA at 8 or 16 inches.

FIGURE 8 IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY AT 8" OR 16"

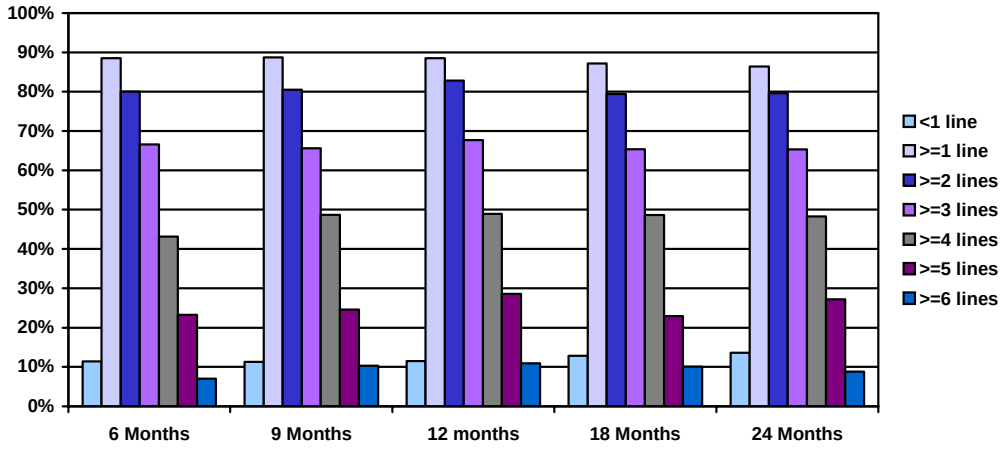


Table A10 in Appendix A summarizes the improvement in best corrected near visual acuity at 8 or 16 inches for all implanted eyes at follow-up visits from 1 month. Tables A10A.1 through A10C.3 in Appendix A summarize the improvement in BCNVA at 8 or 16 inches stratified by patient's age at implant, IMT model, and gender. Stratification by these three factors had no effect on improvement in BCNVA at 8 or 16 inches.

Tables 10.2 through 10.4 summarize the improvement in BCNVA at 8 or 16 inches stratified by preoperative BCDVA. Preoperative best corrected distance visual acuity was categorized as moderate impairment (20/80 to 20/160), severe impairment (20/161 to 20/400) and profound impairment (worse than 20/400).

As shown in Table 10.3, eyes with profound impairment gained significantly more lines of BCNVA at 8 or 16 inches at 18 months than eyes with moderate impairment at study entry.

TABLE 10.2
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" OR 16" AT 12 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCNVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines*	11	55.0%	72	65.5%	47	75.8%
Gain ≥2 lines but <3 lines†	3	15.0%	19	17.3%	7	11.3%
Gain ≥1 line but <2 lines‡	2	10.0%	3	2.7%	6	9.7%
Other	4	20.0%	16	14.5%	2	3.2%
Gain ≥2 lines	14	70.0%	91	82.7%	54	87.1%
One-sided lower 95% CL§	49.2%		75.7%		77.9%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	0.2129					
N	20		110		62	
Not reported/IMT removal	0		0		2	
Total	20		110		64	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with at least one non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* BCNVA gain ≥ 3 lines at either 8" or 16"
† BCNVA gain ≥ 2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 10.3
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" OR 16" AT 18 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCNVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines*	10	52.6%	64	62.7%	43	74.1%
Gain ≥2 lines but <3 lines†	1	5.3%	16	15.7%	8	13.8%
Gain ≥1 line but <2 lines‡	2	10.5%	8	7.8%	4	6.9%
Other	6	31.6%	14	13.7%	3	5.2%
Gain ≥2 lines	11	57.9%	80	78.4%	51	87.9%
One-sided lower 95% CL§	36.8%		70.7%		78.5%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	0.0213					
N	19		102		58	
Not reported/IMT removal	0		1		0	
Total	19		103		58	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with at least one non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* BCNVA gain ≥ 3 lines at either 8" or 16"
† BCNVA gain ≥ 2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ CL = exact confidence limit. It was calculated based on Clopper Pearson method.

TABLE 10.4
IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY (BCNVA) AT 8" OR 16" AT 24 MONTHS STRATIFIED BY PREOPERATIVE BCDVA

BCNVA Change from Baseline	Moderate Impairment (20/80 to 20/160)		Severe Impairment (20/161 to 20/400)		Profound Impairment (Worse than 20/400)	
	n	%	n	%	n	%
Gain ≥3 lines*	8	47.1%	50	60.2%	38	80.9%
Gain ≥2 lines but <3 lines†	3	17.6%	15	18.1%	3	6.4%
Gain ≥1 line but <2 lines‡	2	11.8%	5	6.0%	3	6.4%
Other	4	23.5%	13	15.7%	3	6.4%
Gain ≥2 lines	11	64.7%	65	78.3%	41	87.2%
One-sided lower 95% CL§	42.0%		69.6%		76.4%	
P-value of Fisher's exact test on comparing %'s of gain ≥2 lines	0.1287					
N	17		83		47	
Not reported/IMT removal	0		1		0	
Total	17		84		47	

Line change was calculated based on the M-values.
N = number of treated eyes returned for the visit with at least one non-missing BCNVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCNVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* BCNVA gain ≥ 3 lines at either 8" or 16"
† BCNVA gain ≥ 2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ CL = exact confidence limit. It was calculated based on Clopper Pearson method.

17.5 IMPROVEMENT IN BEST CORRECTED NEAR VISUAL ACUITY CROSS-CORRELATED WITH IMPROVEMENT IN BEST CORRECTED DISTANCE VISUAL ACUITY

As a means of examining the relationship between improvement in best corrected distance acuity and improvement in best corrected near acuity, the improvement in BCNVA at 8 or 16 inches was cross-correlated with the improvement in BCDVA for all eyes treated at 12 months (Table 11).

A total of 193 eyes had measurements for either BCDVA and BCNVA at 12 months. As shown highlighted in blue, the majority of subjects (161/193 or 83.4%) experienced a gain of lines of both best corrected distance *and* near acuity at 8 inches *or* 16 inches at 12 months. A gain of $\geq$ 2 lines or more in both best corrected distance *and* near visual acuity at 8 *or* 16 inches was achieved by 73.1% (141/193) of eyes and a gain of or $\geq$ 3 lines was reported for 52.8% (102/193) of patients, respectively, at 12 months.

Thus, close to 75% of study subjects experienced a gain of 2 or more lines of best corrected distance and near acuity, and just over 50% gained 3 or more lines of both distance and near visual acuity at 12 months.

TABLE 11
IMPROVEMENT IN BCNVA VERSUS IMPROVEMENT IN BCDVA AT 12 MONTHS
N = 193 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 12 Months	BCDVA at 12 Months						Total n (%)
	Gain ≥3 lines n (%)	Gain ≥2 lines, but < 3 lines n (%)	Gain ≥1 line, but < 2 lines n (%)	Within a gain of <1 line to a loss of 2 lines n (%)	Loss > 2 lines n (%)	Data not available n (%)	
Gain ≥3 lines*	***102 (52.8%)***	***15 (7.8%)***	*7 (3.6%)*	*5 (2.6%)*	*1 (0.5%)*	*0 (0.0%)*	*130 (67.4%)*
Gain ≥2 lines, but < 3 lines†	***18 (9.3%)***	***6 (3.1%)***	*3 (1.6%)*	*2 (1.0%)*	*0 (0.0%)*	*0 (0.0%)*	*29 (15.0%)*
Gain ≥1 line, but < 2 lines‡	*5 (2.6%)*	*3 (1.6%)*	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	11 (5.7%)
Within a gain of <1 line to a loss of 2 lines§	*3 (1.6%)*	*2 (1.0%)*	3 (1.6%)	6 (3.1%)	0 (0.0%)	0 (0.0%)	14 (7.3%)
Loss > 2 lines¶	*0 (0.0%)*	*1 (0.5%)*	0 (0.0%)	5 (2.6%)	2 (1.0%)	0 (0.0%)	8 (4.1%)
Data not available	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)
Total	*128 (66.3%)*	*27 (14.0%)*	15 (7.8%)	19 (9.8%)	4 (2.1%)	0 (0.0%)	193 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent successful outcomes.

* BCNVA gain ≥3 lines at either 8" or 16"
† BCNVA gain ≥2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ BCNVA change within a gain of <1 line to a loss of 2 lines at either 8" or 16", however, BCNVA gain <1 line at both distance.
¶ BCNVA loss >2 lines at both 8" & 16", or one BCNVA loss >2 lines & the other not available.

This level of improvement in both distance and near visual acuity was maintained at 18 months, as shown in Table 12. As shown in bold blue text, a gain of ≥ 2 lines of BCNVA at 8 *or* 16 inches *with* a gain of ≥ 2 lines BCDVA was observed in 127/179 (or 70.9%) at 18 months. Close to 50% of eyes (89/179) gained ≥ 3 lines of BCDVA and ≥ 3 lines of BCNVA at 8 *or* 16 inches.

TABLE 12
IMPROVEMENT IN BCNVA VERSUS IMPROVEMENT IN BCDVA AT 18 MONTHS
N = 179 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 18 Months	BCDVA at 18 Months						Total n (%)
	Gain ≥3 lines n (%)	Gain ≥2 lines, but < 3 lines n (%)	Gain ≥1 line, but < 2 lines n (%)	Within a gain of <1 line to a loss of 2 lines n (%)	Loss > 2 lines n (%)	Data not available n (%)	
Gain ≥3 lines*	***89 (49.7%)***	***16 (8.9%)***	*7 (3.9%)*	*4 (2.2%)*	*1 (0.6%)*	*0 (0.0%)*	*117 (65.4%)*
Gain ≥2 lines, but < 3 lines†	***15 (8.4%)***	***7 (3.9%)***	*2 (1.1%)*	*1 (0.6%)*	*0 (0.0%)*	*0 (0.0%)*	*25 (14.0%)*
Gain ≥1 line, but < 2 lines‡	*5 (2.8%)*	*4 (2.2%)*	3 (1.7%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	14 (7.8%)
Within a gain of <1 line to a loss of 2 lines§	*3 (1.7%)*	*2 (1.1%)*	5 (2.8%)	8 (4.5%)	1 (0.6%)	0 (0.0%)	19 (10.6%)
Loss > 2 lines¶	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	2 (1.1%)	2 (1.1%)	0 (0.0%)	4 (2.2%)
Data not available	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	*112 (62.6%)*	*29 (16.2%)*	17 (9.5%)	17 (9.5%)	4 (2.2%)	0 (0.0%)	179 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent successful outcomes.
* BCNVA gain ≥3 lines at either 8" or 16"
† BCNVA gain ≥2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ BCNVA change within a gain of <1 line to a loss of 2 lines at either 8" or 16", however, BCNVA gain <1 line at both distance.
¶ BCNVA loss >2 lines at both 8" & 16", or one BCNVA loss >2 lines & the other not available.

The continued stability of the gain of lines of best corrected distance and near acuity in the study population is confirmed by the cross-correlation of lines gained in near and distance acuity at 24 month, as shown in Table 13.

A gain of ≥ 2 lines of BCNVA at 8 inches *or* 16 inches *with* a gain of ≥ 2 lines BCDVA was observed in 99/147 (or 67.3%) at 24 months, as shown in bold blue text. At 24 months, 51.0% of eyes (75/147) had a gain of ≥ 3 lines of BCDVA *with* a gain of ≥ 3 lines of BCNVA at 8 inches *or* 16 inches.

TABLE 13
IMPROVEMENT IN BCNVA VERSUS IMPROVEMENT IN BCDVA AT 24 MONTHS
N = 147 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 24 Months	BCDVA at 24 Months						Total
	Gain ≥3 lines n (%)	Gain ≥2 lines, but < 3 lines n (%)	Gain ≥1 line, but < 2 lines n (%)	Within a gain of <1 line to a loss of 2 lines n (%)	Loss > 2 lines n (%)	Data not available n (%)	n (%)
Gain ≥3 lines*	***75 (51.0%)***	***11 (7.5%)***	*5 (3.4%)*	*5 (3.4%)*	*0 (0.0%)*	*0 (0.0%)*	*96 (65.3%)*
Gain ≥2 lines, but < 3 lines†	***6 (4.1%)***	***7 (4.8%)***	*4 (2.7%)*	*4 (2.7%)*	*0 (0.0%)*	*0 (0.0%)*	*21 (14.3%)*
Gain ≥1 line, but < 2 lines‡	*2 (1.4%)*	*1 (0.7%)*	4 (2.7%)	3 (2.0%)	0 (0.0%)	0 (0.0%)	10 (6.8%)
Within a gain of <1 line to a loss of 2 lines§	*3 (2.0%)*	*3 (2.0%)*	3 (2.0%)	7 (4.8%)	0 (0.0%)	0 (0.0%)	16 (10.9%)
Loss > 2 lines¶	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	2 (1.4%)	2 (1.4%)	0 (0.0%)	4 (2.7%)
Data not available	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	*86 (58.5%)*	*22 (15.0%)*	16 (10.9%)	21 (14.3%)	2 (1.4%)	0 (0.0%)	147 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent successful outcomes.

* BCNVA gain ≥3 lines at either 8" or 16"
† BCNVA gain ≥2 lines at either 8" or 16", however, BCNVA gain <3 lines at both distance.
‡ BCNVA gain ≥ 1 line at either 8" or 16", however, BCNVA gain <2 lines at both distance.
§ BCNVA change within a gain of <1 line to a loss of 2 lines at either 8" or 16", however, BCNVA gain <1 line at both distance.
¶ BCNVA loss >2 lines at both 8" & 16", or one BCNVA loss >2 lines & the other not available.

Table AGEE1 in Appendix A summarizes the generalized estimating equation analysis on effectiveness endpoint from 12 to 24 month for all eyes implanted with IMT and Table AGEE2 provides the effectiveness endpoint stratified by patient's age and IMT model.

Based on these analyses, the following baseline parameters were concluded to have an effect on the effectiveness rate of 85% from 12 months to 24 months postoperatively:

- **Preoperative BCDVA** (moderate impairment, severe impairment, and profound impairment): the data presented in Tables 7.2 to 7.4 in this report demonstrate that the group of eyes with profound impairment of BCDVA had the most substantial gain in lines of visual acuity among the three preoperative BCDVA groups. The moderate impairment group had the lowest success rate among the three preoperative BCDVA groups, with more severely impaired eyes achieving the most significant improvement in vision. Thus, the effect was greatest for those eyes with the greatest need, as described earlier in this section of the clinical report.

- **Interaction effect between subject age at implant (<71, 71 to 75, 76 to 80, and >80 years) and IMT model (WA 2.2X and WA 3.0X)**: As shown in Table AGEE2, the improvement in acuity increased from the youngest age group to the oldest age group for subjects with a 2.2X IMT implant, while, for subjects with a 3.0X IMT implant, the improvement in visual acuity among the three younger age groups are similar, but the oldest age group had the lowest success rate among the four age groups. Additionally, it is important to note that the proportion of subjects with a gain of 2 or more lines of BCDVA or BCNVA was well above the protocol target of 50% for all age groups.

- **Interaction effect between the postoperative visit and gender**: Tables A6B.1 to A6B.3 in Appendix A of this report suggest that the improvement in visual acuity at 12 months was slightly higher for female subjects than for males. However, in female subjects, the proportion of eyes with improvement in visual acuity then decreased about 7% at 18 and 24 months while the proportion of eyes achieving an improvement in visual acuity seemed similar from 12 months to 24 months for male subjects. Regardless of the different pattern, the effectiveness outcomes for both female and male subjects were well above the protocol target value of 50%.

17.6 QUALITY OF LIFE

A secondary measure of procedure success under the IMT-002 protocol is quality of life, assessed by the VFQ-25 and the ADL questionnaires.

The VFQ-25 is a 25-item version of the National Eye Institute Vision Function Questionnaire (VFQ). This validated psychometric survey[5] measures vision-targeted health status for persons with chronic eye diseases including macular degeneration.[6] The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question which is an independent component and not part of the composite or individual subscales. This survey comprises the following vision-targeted subscales: general vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitation with peripheral vision, limitations with color vision, and ocular pain. The maximum score is 100 points and 0 is the lowest possible score. A score of 50 represents 50% of the highest possible score.[7] A five (5) point difference in subscale and/or composite scores is generally considered to be clinically significant.[8] Per the IMT-002 study protocol, VFQ-25 questionnaires were administered at baseline, 3, 6, 9, and 12 months.

The Activities of Daily Life questionnaire is a modified version of the Activities of Daily Vision Scale (ADVS),[9] a validated survey that has been broadly used for assessing the impact of visual impairment due to cataract and related vision disorders.[10] The modifications to the ADVS consisted of adjusting questions to more appropriately address challenges facing individuals with end-stage macular degeneration. The scoring system in the ADL is consistent with that of the ADVS and VFQ-25, 100 for a perfect score and 0 for the lowest possible score for subscale and composite analyses. ADL questionnaires were administered at baseline, 3, 6, 9, and 12 months.

Copies of the VFQ-25 and the ADL questionnaires may be found in Appendix F of this report.

17.6.1 VFQ-25

Outcomes for all components of the VFQ-25 are summarized in Table 14. The general vision subscale score of the VFQ-25 was 35.3 (S.D. 15.4) at baseline and increased to 53.9 (S.D. 17.7) at 3 months, 52.7 (S.D. 18.3) at 6 months, 51.0 (S.D. 17.9) at 9 months, and 50.3 (S.D. 19.7) at 12 months. The mean change in the general vision subscale at 12 months, as shown in Table 15, was clinically significant with 14.1 point improvement and a 95% confidence interval (C.I.) of 11.0-17.2.

As shown in Table 14, scores for near activities subcategory also had a substantial increase from 25.5 (S.D. 14.2) at baseline, to 38.6 (S.D. 18.6) at 3 months, 37.9 (S.D. 19.8) at 6 months, 37.8 (S.D. 17.3) at 9 months, and 37.3 (S.D. 18.8) at 12 months. At 12 months, the near activities mean score increased 11.2 points, a clinically significant improvement, with a 95% confidence interval mean of 8.4 to 13.9.

Scores for the subcategory of distance activities increased from 34.3 (S.D. 18.4) at baseline, to 46.3 (S.D. 21.8) at 3 months, 45.4 (S.D. 22.4) at 6 months, 44.2 (S.D. 22.6) at 9 months, and 42.4 (S.D. 23.2) at 12 months. The 12 month mean change in distance activities subscale from baseline was somewhat smaller than for near activities, but at 7.9 point improvement (C.I. 4.4-11.4) was still clinically significant.

Scores for the subcategory activities for vision specific activities related to social functioning, mental health, role difficulties and dependency improved by 8.6, 9.3, 7.3, and 10.0 points, respectively, at 12 months as compared to baseline.

Subscale scores for ocular pain were generally unchanged as were subscale scores for driving. Color vision subscales scores improved somewhat over the 12 month assessment period but not at a clinically significant level. As would be expected with the IMT implanted in one eye and thus restricting peripheral vision in that eye, peripheral vision subscale scores declined by 5.9 points at 12 months (Table 15) this decrease was also considered to be clinically significant.

VFQ-25 overall composite scores represent the average of the subscale scores, excluding the general health rating question. The mean overall VFQ-25 composite score was 44.0 (S.D. 13.3) at baseline, and increased to 52.7 (S.D. 13.6) at 3 months, 51.6 (S.D. 14.2) at 6 months, 51.3 (S.D. 14.2) at 9 months, and 50.3 (S.D. 14.7) at 12 months. The overall composite score change at 12 months increased by 6.0 points (95% C.I. 4.0 to 8.1), representing a clinically significant finding.

At 12 months, the mean score of the general health subscale, which is not a component of the vision specific subscales or the composite score, declined by 5.1 points (Table 15) likely reflecting the impact of other health-related events on the general health of the elderly study population, since it is recognized that general quality of life measures decrease with increasing age.[11]

The VFQ-25 subscales of general vision, near activities, and distance activities have been described as particularly important in demonstrating the difficulty individuals with bilateral severe AMD have in performing daily activities dependent on central vision.[12] At 12 months these respective subscales improved by 14.0 points, 11.2 points, and 7.9 points, respectively, in

patients implanted with the IMT. Additionally, clinically significant improvements across all vision specific subscales (social functioning, mental health, role difficulties, and dependency) were observed. In subscales where no improvement or a decline in performance was expected (color vision, driving and peripheral vision), performance was stable or declined.

TABLE 14
VFQ-25 SCORE

VFQ-25	Baseline	3 Months	6 Months	9 Months	12 Months
General Vision	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	35.34	53.87	52.70	51.02	50.26
Standard Deviation	15.35	17.66	18.29	17.92	19.70
Median	40.00	60.00	60.00	60.00	60.00
Range	0.00, 80.00	20.00, 80.00	20.00, 100.00	20.00, 100.00	20.00, 100.00
Near Activities	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	25.51	38.61	37.87	37.76	37.31
Standard Deviation	14.18	18.61	19.76	17.33	18.76
Median	25.00	33.33	33.33	33.33	33.33
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 91.67	0.00, 100.00
Distance Activities	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	34.26	46.27	45.42	44.22	42.40
Standard Deviation	18.40	21.75	22.39	22.55	23.17
Median	33.33	41.67	41.67	41.67	41.67
Range	0.00, 83.33	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Social Functioning	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	49.33	61.43	60.88	58.61	58.29
Standard Deviation	24.51	21.97	23.65	23.68	22.23
Median	50.00	62.50	62.50	62.50	62.50
Range	0.00, 100.00	12.50, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Mental Health	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	39.81	50.19	49.91	49.11	49.26
Standard Deviation	24.25	26.22	25.52	26.52	26.42
Median	37.50	43.75	43.75	43.75	43.75
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Role Difficulties	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	37.44	46.92	45.31	46.75	44.75
Standard Deviation	23.70	25.36	25.66	27.29	26.62
Median	37.50	50.00	50.00	50.00	37.50
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Dependency	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	37.70	48.91	47.96	47.28	48.32
Standard Deviation	27.18	28.99	27.71	27.75	27.37
Median	33.33	50.00	41.67	41.67	41.67
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00

N = number of treated eyes returned for the visit with VFQ-25 assessment. Records after IMT removal were excluded and reported separately.
Per protocol, VFQ-25 was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.

TABLE 14 (CONTINUED)
VFQ-25 SCORE

VFQ-25	Baseline	3 Months	6 Months	9 Months	12 Months
Driving	**N = 193**	**N = 191**	**N = 191**	**N = 188**	**N = 184**
Mean	2.30	1.52	2.43	1.76	1.90
Standard Deviation	9.32	8.35	10.60	8.58	8.74
Median	0.00	0.00	0.00	0.00	0.00
Range	0.00, 60.00	0.00, 80.00	0.00, 80.00	0.00, 80.00	0.00, 80.00
Peripheral Vision	**N = 206**	**N = 197**	**N = 197**	**N = 194**	**N = 190**
Mean	67.60	66.50	65.48	66.37	62.89
Standard Deviation	27.22	22.03	22.90	22.03	22.38
Median	75.00	75.00	75.00	75.00	50.00
Range	0.00, 100.00	25.00, 100.00	0.00, 100.00	0.00, 100.00	25.00, 100.00
Color Vision	**N = 201**	**N = 192**	**N = 193**	**N = 191**	**N = 188**
Mean	63.93	73.44	71.37	71.34	67.69
Standard Deviation	27.82	25.02	25.38	25.25	26.42
Median	50.00	75.00	75.00	75.00	75.00
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Ocular Pain	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	88.23	90.83	87.63	88.84	88.54
Standard Deviation	15.89	14.46	17.63	16.28	16.89
Median	100.00	100.00	100.00	100.00	100.00
Range	25.00, 100.00	25.00, 100.00	25.00, 100.00	25.00, 100.00	25.00, 100.00
Overall Composite	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	43.97	52.66	51.58	51.33	50.29
Standard Deviation	13.30	13.56	14.21	14.17	14.73
Median	42.44	52.12	50.42	50.30	48.26
Range	14.32, 85.30	16.79, 88.33	17.75, 95.23	20.33, 89.39	16.58, 88.64
General Health	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	63.96	61.31	60.88	59.18	59.72
Standard Deviation	23.09	23.12	23.32	23.17	23.38
Median	75.00	50.00	50.00	50.00	50.00
Range	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00

N = number of treated eyes returned for the visit with VFQ-25 assessment. Records after IMT removal were excluded and reported separately.
Per protocol, VFQ-25 was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.

TABLE 15
CHANGE IN VFQ-25 SCORE FROM BASELINE

Change in VFQ-25	3 Months	6 Months	9 Months	12 Months
General Vision	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	17.99 (20.60)	16.90 (21.23)	15.10 (20.47)	14.09 (21.99)
95% confidence interval for mean*	15.11, 20.87	13.94, 19.86	12.22, 17.99	10.97, 17.22
Median	20.00	20.00	20.00	20.00
Range	-40.00, 60.00	-40.00, 80.00	-20.00, 60.00	-40.00, 60.00
Near Activities	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	12.63 (17.91)	12.10 (19.35)	11.93 (18.68)	11.16 (19.28)
95% confidence interval for mean*	10.12, 15.13	9.41, 14.80	9.30, 14.56	8.42, 13.90
Median	8.34	8.34	8.34	8.34
Range	-33.33, 58.34	-33.34, 58.34	-33.33, 75.00	-25.00, 100.00
Distance Activities	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	11.56 (22.09)	11.04 (22.44)	9.99 (23.58)	7.90 (24.68)
95% confidence interval for mean*	8.47, 14.65	7.91, 14.17	6.67, 13.31	4.40, 11.41
Median	8.34	8.34	8.33	8.33
Range	-41.67, 75.00	-50.00, 75.00	-37.50, 83.34	-50.00, 83.34
Social Functioning	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	11.68 (27.90)	11.13 (25.64)	8.86 (27.42)	8.61 (26.63)
95% confidence interval for mean*	7.78, 15.58	7.55, 14.70	5.00, 12.73	4.83, 12.39
Median	12.50	12.50	12.50	0.00
Range	-75.00, 100.00	-62.50, 87.50	-87.50, 75.00	-75.00, 75.00
Mental Health	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	9.83 (23.24)	9.81 (22.81)	9.15 (22.83)	9.29 (22.54)
95% confidence interval for mean*	6.58, 13.08	6.63, 12.99	5.94, 12.37	6.09, 12.49
Median	6.25	6.25	6.25	6.25
Range	-50.00, 87.50	-50.00, 87.50	-62.50, 81.25	-50.00, 81.25
Role Difficulties	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	9.30 (24.52)	7.88 (26.62)	9.25 (29.41)	7.25 (26.13)
95% confidence interval for mean*	5.87, 12.72	4.16, 11.59	5.10, 13.39	3.54, 10.96
Median	12.50	0.00	0.00	0.00
Range	-75.00, 75.00	-75.00, 87.50	-62.50, 87.50	-62.50, 87.50
Dependency	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	10.64 (27.99)	9.83 (26.81)	9.40 (26.87)	10.02 (27.53)
95% confidence interval for mean*	6.72, 14.55	6.10, 13.57	5.61, 13.18	6.11, 13.93
Median	8.33	8.33	8.33	8.33
Range	-66.67, 83.33	-58.33, 100.00	-41.67, 91.67	-66.67, 100.00

N = number of treated eyes returned for the visit with a non-missing change in VFQ-25 assessment. Records after IMT removal were excluded and reported separately.
Per protocol, VFQ-25 was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.
* Normal distribution approach was used for mean. CI for % was calculated based on Clopper Pearson method.

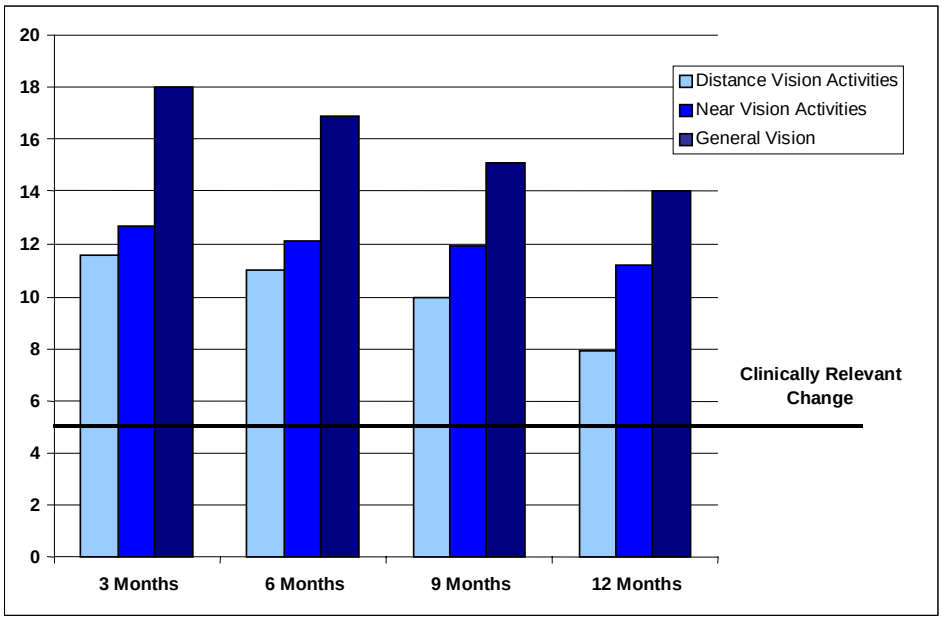
TABLE 15 (CONTINUED)
CHANGE IN VFQ-25 SCORE FROM BASELINE

Change in VFQ-25	3 Months	6 Months	9 Months	12 Months
Driving	**N = 187**	**N = 185**	**N = 184**	**N = 179**
Mean (SD)	-0.82 (7.49)	0.12 (6.69)	-0.29 (6.29)	-0.52 (7.00)
95% confidence interval for mean*	-1.90, 0.26	-0.85, 1.09	-1.21, 0.63	-1.55, 0.51
Median	0.00	0.00	0.00	0.00
Range	-60.00, 35.00	-45.00, 35.00	-45.00, 35.00	-45.00, 40.00
Peripheral Vision	**N = 197**	**N = 197**	**N = 194**	**N = 190**
Mean (SD)	-1.90 (30.82)	-2.66 (33.06)	-1.42 (31.81)	-5.92 (30.99)
95% confidence interval for mean*	-6.23, 2.43	-7.31, 1.98	-5.92, 3.09	-10.36, -1.49
Median	0.00	0.00	0.00	0.00
Range	-75.00, 100.00	-100.0, 100.00	-75.00, 100.00	-75.00, 100.00
Color Vision	**N = 190**	**N = 190**	**N = 189**	**N = 185**
Mean (SD)	8.95 (26.83)	6.71 (27.78)	6.48 (27.43)	3.38 (24.56)
95% confidence interval for mean*	5.11, 12.79	2.74, 10.69	2.55, 10.42	-0.18, 6.94
Median	0.00	0.00	0.00	0.00
Range	-75.00, 100.00	-75.00, 100.00	-75.00, 100.00	-75.00, 75.00
Ocular Pain	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	2.83 (16.78)	-0.44 (18.56)	1.08 (17.39)	0.58 (18.85)
95% confidence interval for mean*	0.48, 5.17	-3.03, 2.15	-1.37, 3.53	-2.09, 3.26
Median	0.00	0.00	0.00	0.00
Range	-50.00, 75.00	-50.00, 62.50	-62.50, 50.00	-75.00, 62.50
Overall Composite	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	8.38 (13.42)	7.43 (13.90)	7.23 (14.16)	6.03 (14.41)
95% confidence interval for mean*	6.50, 10.25	5.49, 9.37	5.24, 9.23	3.98, 8.07
Median	6.56	5.89	4.57	5.34
Range	-20.46, 50.15	-19.73, 50.15	-19.43, 51.85	-31.29, 58.29
n & % of eyes with increase ≥5 points	107 (53.8%)	103 (51.5%)	94 (48.0%)	100 (51.8%)
95% confidence interval for %*	46.6%, 60.8%	44.3%, 58.6%	40.8%, 55.2%	44.5%, 59.0%
General Health	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	-2.89 (20.75)	-3.38 (22.09)	-5.10 (21.32)	-5.05 (21.73)
95% confidence interval for mean*	-5.79, 0.01	-6.46, -0.29	-8.11, -2.10	-8.14, -1.97
Median	0.00	0.00	0.00	0.00
Range	-50.00, 50.00	-100.0, 75.00	-75.00, 50.00	-75.00, 50.00

N = number of treated eyes returned for the visit with a non-missing change in VFQ-25 assessment. Records after IMT removal were excluded and reported separately.
Per protocol, VFQ-25 was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.
* Normal distribution approach was used for mean. CI for % was calculated based on Clopper Pearson method.

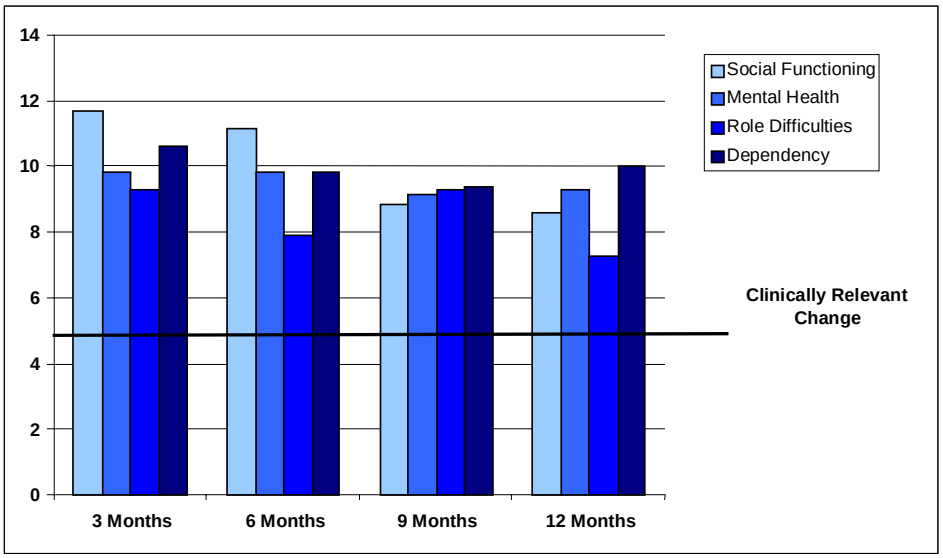
The change in quality of life subscales is illustrated in Figures 9 and 10. As shown in Figure 9, the most significant point change in the quality of vision subscales was reported for general vision, followed by near vision activities and distance vision activities. While there was a small decrease in the point change for general vision over the 12 month follow-up period for this instrument, the point change remained relatively stable for near vision activities.

FIGURE 9 QUALITY OF LIFE VFQ-25
CHANGE IN QUALITY OF VISION SUBSCALES



Improvement in the vision specific activities subscales of the VFQ-25 was most substantial at 3 and 6 months, perhaps reflecting the noticeable change from baseline in best corrected acuity experienced by the majority of study subjects. There was a slight decrease in the point change for social functioning and mental health at 9 months, however, for the most part the values reported remained relatively stable over time for all four subscales.

FIGURE 10 QUALITY OF LIFE VFQ-25
CHANGE IN VISION SPECIFIC ACTIVITIES SUBSCALES



Tables A15A through A15E in Appendix A summarize the change in VFQ-25 composite score from baseline to 12 months for all eyes implanted with IMT stratified by patient's age at implant, gender, IMT model, preoperative BCDVA and 12-month visual acuity improvement respectively. There was no effect of any of these baseline characteristics or of the 12-month visual acuity on the improvement in the VFQ composite score ($p>0.05$). This suggests a broad effect of the IMT on improvement in the VFQ-25 composite score, irrespective of baseline factors, and is consistent with the substantial improvement in visual acuity achieved by approximately 90% of the study population. Table A15F located in Appendix A provides a data listing of subjects (n=7) whose overall VFQ-25 composite score worsened by more than 15 points at the last available visit. Of these 7 subjects, 5 experienced improvement in at least one measure of acuity, and the remaining 2 subjects had no change in acuity.

17.6.2 ACTIVITIES OF DAILY LIVING (ADL)

Activities of Daily Living scores are summarized in Table 16. The ADL questionnaire consists of 36 questions and three constructs, i.e., mobility, distance activities and near activities, and, as described, is a modification of the Activities of Daily Vision Scale (ADVS), a questionnaire developed to provide a reliable and valid means of measuring the patient's perception of visual function impairment in patients with cataract. These modifications were intended to better assess visual activities of patients with moderate to profound visual impairment associated with bilateral end-stage AMD rather than cataract. A copy of the ADL questionnaire utilized in the clinical trial may be found in Appendix F of this report.

As shown in Table 16, the mean total ADL score improved from 41.4 (S.D. 15.6) at baseline to 60.2 (S.D. 17.5) at 3 months, 58.6 (S.D. 18.8) at 6 months, 57.3 (S.D. 19.0) at 9 months, and 55.9 (S.D. 19.6) at 12 months. At 12 months, the mean improvement from baseline was 14.1 points (Table 17). For the subcategory of mobility, the mean ADL score improved from 53.8 (S.D. 19.1) at baseline to 69.7 (S.D. 18.3) at 3 months, 68.0 (S.D. 19.8) at 6 months, 66.8 (S.D. 20.0) at 9 months, and 66.0 (S.D. 20.2) at 12 months. The mobility subscale improved by 12.0 points at 12 months versus baseline (Table 17).

For the subcategory of distance activities, the mean ADL score improved from 43.7 (S.D. 15.5) at baseline to 61.3 (S.D. 18.3) at 3 months, 59.2 (S.D. 19.0) at 6 months, 59.0 (S.D. 19.6) at 9 months, and 57.3 (S.D. 20.2) at 12 months. The distance activities subscale improved by 13.4 points at 12 month versus baseline (Table 17).

As shown in Table 16, the ADL score for the subcategory near activities, the mean ADL score improved from 30.9 (S.D. 18.6) at baseline to 53.2 (S.D. 20.1) at 3 months, 52.2 (S.D. 22.3) at 6 months, 49.6 (S.D. 22.2) at 9 months, and 48.5 (S.D. 22.8) at 12 months. Near activities improved by 17.0 points (Table 17) at 12 months versus baseline.

Tables A17A through A17E in Appendix A summarize the change in ADL total score from baseline at 12 months for all eyes implanted with IMT stratified by patient's age at implant, gender, IMT model, preoperative BCDVA and 12-month visual acuity improvement respectively.

In summary, the total ADL score as well as all three constructs of mobility, distance activities and near activities improved substantially from baseline, with the largest improvement reported for near activities.

TABLE 16
ADL SCORE

ADL	Baseline	3 Months	6 Months	9 Months	12 Months
Mobility	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	53.77	69.71	67.97	66.80	65.99
Standard Deviation	19.08	18.29	19.77	20.03	20.19
Median	56.25	68.75	68.75	68.75	66.75
Range	0.00, 100.00	12.50, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Distance Activities	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	43.71	61.27	59.19	59.03	57.30
Standard Deviation	15.48	18.30	19.04	19.62	20.20
Median	41.75	58.25	58.25	58.25	55.00
Range	0.00, 100.00	12.50, 100.00	8.25, 100.00	4.25, 100.00	4.25, 100.00
Near Activities	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	30.90	53.22	52.23	49.58	48.49
Standard Deviation	18.63	20.09	22.25	22.16	22.77
Median	29.25	54.25	54.25	50.00	45.75
Range	0.00, 100.00	12.50, 100.00	0.00, 100.00	0.00, 100.00	0.00, 100.00
Total	**N = 206**	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean	41.37	60.15	58.63	57.33	55.85
Standard Deviation	15.64	17.47	18.82	19.04	19.62
Median	40.50	60.75	59.50	57.75	54.75
Range	6.25, 100.00	12.50, 100.00	3.50, 98.50	3.50, 97.00	4.25, 100.00

N = number of treated eyes returned for the visit with ADL assessment. Records after IMT removal were excluded and reported separately.
Per protocol, ADL was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.

TABLE 17
CHANGE IN ADL SCORE FROM BASELINE

Change in ADL	3 Months	6 Months	9 Months	12 Months
Mobility	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	15.82 (20.82)	14.00 (22.49)	12.90 (22.46)	11.97 (22.80)
95% confidence interval for mean*	12.91, 18.73	10.87, 17.14	9.73, 16.06	8.74, 15.21
Median	14.50	12.50	12.50	10.50
Range	-35.50, 75.00	-56.25, 81.25	-56.25, 87.50	-56.25, 100.00
Distance Activities	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	17.37 (19.60)	15.29 (20.10)	15.29 (20.68)	13.36 (20.97)
95% confidence interval for mean*	14.63, 20.11	12.48, 18.09	12.38, 18.20	10.38, 16.34
Median	16.50	13.75	12.50	12.50
Range	-21.00, 87.50	-33.50, 66.75	-33.50, 71.00	-33.50, 100.00
Near Activities	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	21.75 (21.55)	20.92 (22.22)	18.30 (23.10)	17.01 (22.27)
95% confidence interval for mean*	18.74, 24.76	17.82, 24.02	15.05, 21.55	13.85, 20.17
Median	20.75	20.75	20.00	16.50
Range	-40.00, 85.75	-35.00, 81.75	-54.25, 80.75	-46.00, 91.50
Total	**N = 199**	**N = 200**	**N = 196**	**N = 193**
Mean (SD)	18.49 (18.40)	16.99 (19.10)	15.82 (19.77)	14.15 (19.63)
95% confidence interval for mean*	15.91, 21.06	14.32, 19.65	13.04, 18.61	11.37, 16.94
Median	18.75	16.88	14.88	12.50
Range	-25.00, 76.75	-35.50, 68.75	-35.50, 69.75	-34.75, 81.25
n & % of eyes with increase ≥10 points	134 (67.3%)	128 (64.0%)	113 (57.7%)	110 (57.0%)
95% confidence interval for %*	60.3%, 73.8%	56.9%, 70.6%	50.4%, 64.7%	49.7%, 64.1%

N = number of treated eyes returned for the visit with a non-missing change in ADL assessment. Records after IMT removal were excluded and reported separately.
Per protocol, ADL was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.
* Normal distribution approach was used for mean. CI for % was calculated based on Clopper Pearson method.

In summary, subscale improvement for near and distance activities as measured by both the ADL and VFQ-25 questionnaires are consistent and appreciable, as are composite scores for both of these instruments.

Table 18 summarizes the correlation between change in VFQ-25 overall composite score and change in total ADL score at 3, 6, 9, and 12 month. The Pearson correlation coefficient, measuring the strength of the linear relationship of the change in VFQ-25 overall composite score and ADL total score, was 0.7221 at 3 month, 0.7020 at 6 month, 0.7195 at 9 month and 0.7357 at 12 month. The statistical significance of the Pearson correlation coefficient was tested with a t-test. Results indicate that there is a statistically significant relationship between change in VFQ-25 composite score and change in ADL total score at each postoperative examination (i.e., $p < 0.0001$ at 3, 6, 9 and 12 months).

TABLE 18
CORRELATION BETWEEN CHANGE IN VFQ-25 OVERALL COMPOSITE SCORE AND CHANGE IN ADL TOTAL SCORE
ALL EYES IMPLANTED WITH IMT AND WITH BOTH VFQ & ADL SCORES

	3 Months	6 Months	9 Months	12 Months
N	199	200	196	193
Pearson Correlation Coefficient (r)	0.7221	0.7020	0.7195	0.7357
P-value for testing H0: r = 0	***<.0001***	***<.0001***	***<.0001***	***<.0001***

N = number of treated eyes with non-missing change from baseline in VFQ-25 overall composite score and ADL score. Records after IMT removal were excluded and reported separately.
Per protocol, VFQ-25 and ADL was performed at baseline, and the 3, 6, 9, and 12 months follow-up visits.

Formatted: English (U.S.)

18.0 SAFETY OUTCOMES

18.1 PRESERVATION OF VISUAL ACUITY

While the majority of study subjects experienced a gain of 2 or more lines of vision, and approximately half of the patients gained 3 or more lines, consideration must be given to the loss of lines in visual acuity reported for this study population with moderate to severe central vision loss. Thus, the safety endpoint for preservation of best corrected visual acuity was defined as follows: no more than 10% of implanted eyes were to experience a loss of >2 lines of either near or distance BCVA without a corresponding improvement (gain of 2 lines or more) in BCVA (a gain of 2 or more lines of near BCVA in eyes with loss of more than 2 lines distance BCVA, and vice versa). Thus, the overall visual acuity safety endpoint consists of the sum of the following three categories:

1) The proportion of eyes with >2 lines loss of BCDVA and no change/loss in BCNVA (8" and 16")
2) The proportion of eyes with >2 lines loss of BCNVA (8" and 16") and no change/loss in BCDVA
3) The proportion of eyes with >2 lines loss of BCDVA and BCNVA.

As shown in Table 19, the proportion of eyes with >2 lines loss of BCDVA and no change/loss of BCNVA, or >2 lines loss of BCNVA and no change/loss of BCDVA, was only 4.5% (9/201) at 6 months, 4.6% (9/195) at 9 months, 5.2% (10/193) at 12 months, 4.5% (8/179) at 18 months, and 6.1% (9/147) at 24 months. The binominal exact p-value for the alternative hypothesis testing safety rate of <10% was <0.05 at the 6, 9, 12, and 18 month follow-up visits, and 0.0696 at the 24 month follow-up visit, indicating that the results were well below the 10% limit established in the study protocol.

Only 1.0% of eyes lost >2 lines of both BCDVA and BCNVA at 6 months; this remained relatively stable over the course of follow-up, with 2.1% of eyes at 9 months, 1.0% at 12 months, 1.1% at 18 months and 1.4% at 24 months. The proportion of eyes with >2 lines loss of BCDVA and no change of BCNVA was 0.5% at 6 months, 1.0% at 9 months, 0.5% at 12 months, 0.6% at 18 months and 0.0% at 24 months. Finally, the proportion of eyes with >2 lines loss in BCNVA and no change in BCDVA was 3.0% at 6 months, 1.5% at 9 months, 3.6% at 12 months, 2.8% at 18 months and 4.8% at 24 months.

In Appendix A, Table A19A summarizes the subjects reported with more than 2 lines loss of BCDVA without at least 2 lines gain in BCNVA at last available visit and Table A19B summarizes the subjects reported with more than 2 lines loss of BCNVA without at least 2 lines gain in BCDVA at last available visit.

TABLE 19
SUMMARY OF VISUAL ACUITY SAFETY ENDPOINTS

BCVA Endpoints	6 Months n (%) % CI	9 Months n (%) % CI	12 Months n (%) % CI	18 Months n (%) % CI	24 Months n (%) % CI
Safety (N=)	201	195	193	179	147
Overall Safety Rate >2 lines loss of BCDVA and no change/loss of BCNVA or >2 lines loss of BCNVA and no change/loss of BCDVA†	***9 (4.5%) 2.4%, 7.7%***	***9 (4.6%) 2.4%, 7.9%***	***10 (5.2%) 2.8%, 8.6%***	***8 (4.5%) 2.2%, 7.9%***	***9 (6.1%) 3.2%, 10.4%***
Binomial exact p-value for Ha: safety rate < 10%	***0.0033***	***0.0048***	***0.0120***	***0.0055***	***0.0696***
>2 lines loss of BCDVA and BCNVA‡	2 (1.0%) 0.2%, 3.1%	4 (2.1%) 0.7%, 4.6%	2 (1.0%) 0.2%, 3.2%	2 (1.1%) 0.2%, 3.5%	2 (1.4%) 0.2%, 4.2%
>2 lines loss of BCDVA and no change/loss in BCNVA§	1 (0.5%) 0.0%, 2.3%	2 (1.0%) 0.2%, 3.2%	1 (0.5%) 0.0%, 2.4%	1 (0.6%) 0.0%, 2.6%	0 (0.0%) 0.0%, 2.0%
>2 lines loss of BCNVA and no change/loss of BCDVA§	6 (3.0%) 1.3%, 5.8%	3 (1.5%) 0.4%, 3.9%	7 (3.6%) 1.7%, 6.7%	5 (2.8%) 1.1%, 5.8%	7 (4.8%) 2.3%, 8.8%
Not reported/IMT removal	1	1	1	1	1
Total	202	196	194	180	148

For safety, N = number of records with non-missing BCDVA and BCNVA changes from preop. The records with BCDVA loss > 2 lines and BCNVA missing and the records with BCNVA loss > 2 lines and BCDVA missing were counted as safety events.
Not reported = number of records with missing BCDVA and/or BCNVA changes from preop.
IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately.
Total = number of treated eyes that returned for the visit.
% = n ÷N ×100. %CI = **90%** confidence interval for %. It was calculated based on Clopper Pearson method.

* BCNVA gain ≥2 lines means that either BCNVA at 8" or BCNVA at 16" gained ≥2 lines.

† No gain in BCNVA means that both BCNVA at 8" and BCNVA at 16" did not gain ≥2 lines. No gain in BCDVA means that BCDVA did not gain ≥2 lines.

‡ >2 lines loss in BCNVA means that one BCNVA (8” or 16” lost > 2 lines without the other BCNVA (8” or 16”) gaining ≥2 lines.

§ No change = within a loss of 2 lines to a gain of <2 lines. For BCNVA, it means that both BCNVA at 8" and BCNVA at 16" are within a loss of 2 lines to a gain of <2 lines.

The proportion of eyes with loss of lines of best corrected distance acuity, irrespective of gain in lines of best corrected near vision, is shown in Table 20. The loss in best corrected distance visual acuity is based on LogMAR values. As previously described, if the difference between postoperative LogMAR and preoperative LogMAR is +0.1, the line change is a loss in one line; and if the difference is +0.2, the line change is a loss in two lines. If the difference is between +0.21 and +0.29, the line change is a loss of ≥ two lines but < three lines.

Only 3 eyes (3/201 or 1.5%) were reported to have a loss of >2 lines of BCDVA at 6 months. The percentage of eyes with this loss of BCDVA remained relatively stable over the course of follow-up, with 3.1% (6/195) at 9 months, 2.1% (4/193) at 12 months, 2.2% (4/179) at 18 months, and 1.4% (2/147) at 24 months. The loss in best corrected distance visual acuity for all implanted eyes at follow-up examinations beginning at 1 month is shown in Table A20 in Appendix A.

TABLE 20
LOSS OF BEST CORRECTED DISTANCE VISUAL ACUITY (BCDVA)

BCDVA	6 Months		9 Months		12 Months		18 Months		24 Months	
Change from Baseline	n	%	n	%	n	%	n	%	n	%
Loss >3 lines	2	1.0%	3	1.5%	3	1.6%	2	1.1%	1	0.7%
Loss >2 lines but ≤3 lines	1	0.5%	3	1.5%	1	0.5%	2	1.1%	1	0.7%
Loss ≥1 line but ≤2 lines	2	1.0%	1	0.5%	3	1.6%	1	0.6%	5	3.4%
Other	196	97.5%	188	96.4%	186	96.4%	174	97.2%	140	95.2%
Loss >2 lines	3	1.5%	6	3.1%	4	2.1%	4	2.2%	2	1.4%
One-sided upper 95% CL*	3.8%		6.0%		4.7%		5.0%		4.2%	
N	201		195		193		179		147	
Not reported/IMT removal	1		1		1		1		1	
Total	202		196		194		180		148	

Line change was calculated based on the LogMAR values. A LogMAR value change of 0.1 is a 1-line change. N = number of treated eyes returned for the visit with non-missing BCDVA preoperatively and postoperatively. Not reported = number of treated eyes returned for the visit with missing BCDVA preoperatively or postoperatively. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit. % = n ÷N ×100.

* CL = exact confidence limit. It was calculated based on Clopper Pearson method.

In Appendix A, Tables A20A andA20B summarize the loss in BCNVA at 8 inches and 16 inches respectively; Table A20C summarizes the loss in best corrected near visual acuity at 8 inches or 16 inches with no gain of ≥2 lines at the other near distance.

Table 21 summarizes the loss of BCNVA at 8 or 16 inches cross-correlated with the loss of BCDVA at 12 months (n=193), to determine the number of eyes with a loss of more than 2 lines of both best corrected distance and best corrected near acuity. As shown in blue print, at 12 months, only two eyes (2/193 or 1.0%) experienced a loss of more than 2 lines of both best corrected distance and near acuity at 8 inches *or* 16 inches. It should be noted that for eyes with missing data, labeled in Table 21 as "data not available," it is assumed that this represents a loss of lines for purposes of this analysis.

TABLE 21
LOSS OF BCNVA VERSUS LOSS IN BCDVA AT 12 MONTHS
N = 193 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 12 Months	BCDVA at 12 Months						Total n (%)
	Loss >3 lines n (%)	Loss >2 lines but ≤3 lines n (%)	Loss ≥1 line but ≤2 lines n (%)	Within a loss of <1 line to a gain of <2 lines n (%)	Gain ≥2 lines n (%)	Data not available n (%)	
Loss >3 lines*	***2 (1.0%)***	***0 (0.0%)***	*1 (0.5%)*	*5 (2.6%)*	1 (0.5%)	*0 (0.0%)*	9 (4.7%)
Loss >2 lines but ≤3 lines†	***0 (0.0%)***	***0 (0.0%)***	*0 (0.0%)*	*1 (0.5%)*	2 (1.0%)	*0 (0.0%)*	3 (1.6%)
Loss ≥1 line but ≤2 lines‡	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	6 (3.1%)	1 (0.5%)	0 (0.0%)	7 (3.6%)
Within a loss of <1 line to a gain of <2 lines§	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	4 (2.1%)	10 (5.2%)	0 (0.0%)	14 (7.3%)
Gain ≥2 lines¶	1 (0.5%)	0 (0.0%)	2 (1.0%)	15 (7.8%)	141 (73.1%)	0 (0.0%)	159 (82.4%)
Data not available	*0 (0.0%)*	*1 (0.5%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Total	3 (1.6%)	1 (0.5%)	3 (1.6%)	31 (16.1%)	155 (80.3%)	0 (0.0%)	193 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent safety outcomes.

* The maximum loss of BCNVA at 8" or 16" > 3 lines, however, neither distance gains ≥ 2 lines.
† The maximum loss of BCNVA at 8" or 16" > 2 lines (but ≤ 3 lines), however, neither distance gains ≥ 2 lines.
‡ The maximum loss of BCNVA at 8" or 16" ≥ 1 line (but ≤ 2 lines), however, neither distance gains ≥ 2 lines.
§ BCNVA change within a loss of <1 line to a gain of <2 lines at either 8" or 16", however, neither distance gains ≥2 lines.
¶ BCNVA gain ≥2 lines at either 8" or 16".

The same analysis showing the number of eyes with loss of best corrected near visual acuity at 8 or 16 inches cross-correlated with the loss of best corrected distance visual acuity for all eyes treated at 18 months is displayed in Table 22. Of the 179 eyes with both BCDVA and BCNVA measurements at 18 months, only two eyes (2/179 or 1.1%) experienced a loss of more than 2 lines of both best corrected distance *and* near acuity at 8 inches *or* 16 inches at 18 months, as highlighted in blue ink. It should be noted that for eyes with missing data, labeled as "data not available," it is assumed that this represents a loss of lines for purposes of this analysis.

TABLE 22
LOSS OF BCNVA VERSUS LOSS IN BCDVA AT 18 MONTHS
N = 179 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 18 Months	BCDVA at 18 Months						Total
	Loss >3 lines n (%)	Loss >2 lines but ≤3 lines n (%)	Loss ≥1 line but ≤2 lines n (%)	Within a loss of <1 line to a gain of <2 lines n (%)	Gain ≥2 lines n (%)	Data not available n (%)	n (%)
Loss >3 lines*	***1 (0.6%)***	***1 (0.6%)***	*1 (0.6%)*	*2 (1.1%)*	0 (0.0%)	*0 (0.0%)*	5 (2.8%)
Loss >2 lines but ≤3 lines†	***0 (0.0%)***	***0 (0.0%)***	*0 (0.0%)*	*2 (1.1%)*	0 (0.0%)	*0 (0.0%)*	2 (1.1%)
Loss ≥1 line but ≤2 lines‡	*1 (0.6%)*	*0 (0.0%)*	0 (0.0%)	8 (4.5%)	5 (2.8%)	0 (0.0%)	14 (7.8%)
Within a loss of <1 line to a gain of <2 lines§	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	7 (3.9%)	9 (5.0%)	0 (0.0%)	16 (8.9%)
Gain ≥2 lines¶	0 (0.0%)	1 (0.6%)	0 (0.0%)	14 (7.8%)	127 (70.9%)	0 (0.0%)	142 (79.3%)
Data not available	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	2 (1.1%)	2 (1.1%)	1 (0.6%)	33 (18.4%)	141 (78.8%)	0 (0.0%)	179 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent safety outcomes.

* The maximum loss of BCNVA at 8" or 16" > 3 lines, however, neither distance gains ≥ 2 lines.
† The maximum loss of BCNVA at 8" or 16" > 2 lines (but ≤ 3 lines), however, neither distance gains ≥ 2 lines.
‡ The maximum loss of BCNVA at 8" or 16" ≥ 1 line (but ≤ 2 lines), however, neither distance gains ≥ 2 lines.
§ BCNVA change within a loss of <1 line to a gain of <2 lines at either 8" or 16", however, neither distance gains ≥2 lines.
¶ BCNVA gain ≥2 lines at either 8" or 16".

At 24 months, of the 147 eyes with BCDVA and BCNVA measurements, only 2 eyes (2/147 or 1.4%) experienced a loss of more than 2 lines of both best corrected distance *and* near acuity at 8 inches *or* 16 inches. It should be noted that for eyes with missing data, labeled as "data not available," it is assumed that this represents a loss of lines for purposes of this analysis (Table 23).

TABLE 23
LOSS OF BCNVA VERSUS LOSS IN BCDVA AT 24 MONTHS
N = 147 EYES IMPLANTED WITH IMT WITH EITHER BCDVA OR BCNVA

BCNVA at 24 Months	BCDVA at 24 Months						Total
	Loss >3 lines n (%)	Loss >2 lines but ≤3 lines n (%)	Loss ≥1 line but ≤2 lines n (%)	Within a loss of <1 line to a gain of <2 lines n (%)	Gain ≥2 lines n (%)	Data not available n (%)	n (%)
Loss >3 lines*	***1 (0.7%)***	***1 (0.7%)***	*2 (1.4%)*	*2 (1.4%)*	0 (0.0%)	*0 (0.0%)*	6 (4.1%)
Loss >2 lines but ≤3 lines†	***0 (0.0%)***	***0 (0.0%)***	*1 (0.7%)*	*2 (1.4%)*	0 (0.0%)	*0 (0.0%)*	3 (2.0%)
Loss ≥1 line but ≤2 lines‡	*0 (0.0%)*	*0 (0.0%)*	1 (0.7%)	5 (3.4%)	4 (2.7%)	0 (0.0%)	10 (6.8%)
Within a loss of <1 line to a gain of <2 lines§	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	6 (4.1%)	5 (3.4%)	0 (0.0%)	11 (7.5%)
Gain ≥2 lines¶	0 (0.0%)	0 (0.0%)	1 (0.7%)	17 (11.6%)	99 (67.3%)	0 (0.0%)	117 (79.6%)
Data not available	*0 (0.0%)*	*0 (0.0%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	1 (0.7%)	1 (0.7%)	5 (3.4%)	32 (21.8%)	108 (73.5%)	0 (0.0%)	147 (100.0%)

BCDVA Line change was calculated based on the LogMAR values. BCNVA line change was calculated based on M-values.
N = number of eyes with either BCDVA or BCNVA available at the visit. Records after IMT removal were excluded and reported separately.
Light-shaded cells represent safety outcomes.
* The maximum loss of BCNVA at 8" or 16" > 3 lines, however, neither distance gains ≥ 2 lines.
† The maximum loss of BCNVA at 8" or 16" > 2 lines (but ≤ 3 lines), however, neither distance gains ≥ 2 lines.
‡ The maximum loss of BCNVA at 8" or 16" ≥ 1 line (but ≤ 2 lines), however, neither distance gains ≥ 2 lines.
§ BCNVA change within a loss of <1 line to a gain of <2 lines at either 8" or 16", however, neither distance gains ≥2 lines.
¶ BCNVA gain ≥2 lines at either 8" or 16".

Thus, the limit defined in the study protocol that no more than 10% of implanted eyes were to experience a loss of more than 2 lines of either near or distance BCVA without a corresponding improvement (gain of 2 lines or more) in the other measure of BCVA was readily met in this study, with between 5% and 6% of eyes reported in this category over the course of the study. Importantly, only 5 study eyes lost more than 2 lines of both best corrected near **and** best corrected distance acuity during the course of the study.

Complete data for the subjects (n=5) with more than 2 lines loss in BCDVA and BCNVA may be found in Appendix B of this report.

18.2 SLIT LAMP FINDINGS

Results of slit lamp examinations performed over the course of the study are summarized in Tables A24A through A24F in Appendix A. However, slit lamp findings that constituted a complication or adverse event have been included in Tables 46 and 48, which display ocular complications and adverse events.

Table A24F in Appendix A summarizes reports of posterior capsular opacification in all eyes implanted with IMT. Posterior capsule opacification was reported in a single eye (1/174 or 0.6%) at 18 months, and in two eyes (2/147 or 1.4%) at 24 months; both cases were graded "moderate." No Nd:YAG capsulotomies were performed during the study, however, in seven eyes a Nd:YAG laser was used to re-open the peripheral iridectomy.

Positioning of the IMT as evaluated during slit lamp examinations is shown in Table 24. Implant position was reported as centered for the large majority of eyes at each examination. In two eyes the IMT was reported to be "malpositioned" at day 7. In one eye (PtID 031-203), improper positioning of the IMT resulted in corneal decompensation and the IMT was explanted during corneal transplantation (see Section 18.7, Ocular Adverse Events).

The IMT identified in Table 24 as "centered & other" had a small amount of condensation inside the optics; on operative day 0, the IMT was explanted and has been reported as a device failure (See Section 18.8, Device Failures).

At the last available visit, 197/206 implants (95.6%) were reported to be centered, in one eye (1/206 or 0.5%) the IMT was tilted, and the IMT had been explanted in 8/206 eyes (3.9%).

TABLE 24
IMT POSITIONING

Status	Operative n (%)	1 Day n (%)	7 Day n (%)	1 Month n (%)	3 Months n (%)
Centered	205 (99.5%)	206 (100.0%)	200 (97.6%)	199 (96.6%)	198 (98.5%)
Tilted	0 (0.0%)	0 (0.0%)	3 (1.5%)	3 (1.5%)	1 (0.5%)
Malpositioned*	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	1 (0.5%)
Centered & Tilted	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Centered & Other†	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMT Removal	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)
N	206	206	205	206	201
Not reported	0	0	0	0	0
Total	206	206	205	206	201

Status	6 Months n (%)	9 Months n (%)	12 Months n (%)	18 Months n (%)	24 Months n (%)	Last Visit n (%)
Centered	199 (98.5%)	194 (99.0%)	193 (99.5%)	178 (99.4%)	148 (100.0%)	197 (95.6%)
Tilted	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.5%)
Malpositioned*	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Centered & Tilted	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Centered & Other†	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IMT Removal	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (3.9%)
N	202	196	194	179	148	206
Not reported	0	0	0	1	0	0
Total	202	196	194	180	148	206

N = number of treated eyes returned for the visit with non-missing IMT positioning data, Not reported = number of treated eyes returned for the visit with missing IMT positioning data, Total = number of treated eyes returned for the visit. % = n / N x 100.

* Malposition — 7 Day: anterior optic is at iris plane; not in front of iris plane, inferiorly decentered. 1 Month: inferiorly decentered in sulcus. 3 Months: inferiorly decentered. 6 Months: inferiorly decentered. 9 Months: IMT inferiorly decentered. 12 Months: inferiorly decentered

† Other — Operative: small amount condensation inside optics

18.3 INTRAOCULAR PRESSURE

Intraocular pressure (IOP) and change in IOP from baseline for all eyes implanted with the IMT is displayed in Table 25. Mean IOP was 15.7 mm Hg (S.D. 3.0) at baseline, increased slightly to 22.1 mm Hg (S.D. 9.7) at Day 1, likely as a result of viscoelastic use, and then was generally stable the remainder of the study. The mean change in IOP from baseline was 6.4 mm Hg (S.D. 9.6) at Day 1, however there was no appreciable change between 1 month and 24 months, indicating that the rise in IOP was transient following IMT implantation. This observation is further underscored by the very small number of eyes that experienced an increase of more than 10 mm Hg in IOP; while 61 eyes experienced an increase in IOP > 10mmHg at day 1, eleven (11) eyes had this pressure increase at day 7, this adverse event was reported for only 2 eyes or no eyes between month 1 through month 24. Thus, IMT implantation does not have any long term effect on IOP.

TABLE 25
INTRAOCULAR PRESSURE (IOP) AND CHANGE IN IOP FROM BASELINE

IOP	Baseline n (%)	1 Day n (%)	7 Day n (%)	1 Month n (%)	3 Months n (%)
N	206	206	205	203	199
Mean	15.70	22.12	16.10	15.65	14.68
Standard Deviation	3.00	9.68	6.39	4.04	3.63
Median	16.0	20.0	16.0	16.0	14.0
Range	8, 22	5, 68	0, 50	3, 34	5, 30
Not reported/IMT removal	0	0	0	3	2
Total	206	206	205	206	201
Change from Baseline					
N		206	205	203	199
Mean		6.41	0.40	-0.08	-1.05
Standard Deviation		9.55	6.34	4.00	3.83
95% confidence interval		5.10, 7.72	-0.48, 1.27	-0.63, 0.47	-1.59, -0.52
Median		4.0	0.0	0.0	-2.0
Range		-11, 47	-13, 32	-11, 13	-10, 14
Decrease > 10 mm Hg		1 (0.5%)	6 (2.9%)	1 (0.5%)	0 (0.0%)
Decrease 6 to 10 mm Hg		11 (5.3%)	22 (10.7%)	15 (7.4%)	23 (11.6%)
Decrease 1 to 5 mm Hg		39 (18.9%)	67 (32.7%)	76 (37.4%)	95 (47.7%)
No Change		12 (5.8%)	19 (9.3%)	25 (12.3%)	14 (7.0%)
Increase 1 to 5 mmHg		49 (23.8%)	56 (27.3%)	73 (36.0%)	58 (29.1%)
Increase 6 to 10 mm Hg		33 (16.0%)	24 (11.7%)	11 (5.4%)	8 (4.0%)
Increase > 10 mm Hg		61 (29.6%)	11 (5.4%)	2 (1.0%)	1 (0.5%)
Not reported/IMT removal		0	0	3	2
Total		206	205	206	201

For absolute IOP, N = number of treated eyes returned for the visit with non-missing IOP. Not reported = number of treated eyes returned for the visit with missing IOP. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit.
For change, N = number of treated eyes returned for the visit with non-missing IOP preoperatively or postoperatively. Not reported = number of treated eyes returned for the visit with missing IOP preoperatively or postoperatively. Total = number of treated eyes returned for the visit.

TABLE 25 (CONTINUED)
INTRAOCULAR PRESSURE (IOP) AND CHANGE IN IOP FROM BASELINE

IOP	6 Months n (%)	9 Months n (%)	12 Months n (%)	18 Months n (%)	24 Months n (%)
N	198	195	194	179	148
Mean	14.26	14.30	14.02	14.93	14.89
Standard Deviation	3.53	3.37	3.19	3.54	3.36
Median	14.0	14.0	14.0	15.0	15.0
Range	2, 25	0, 27	1, 22	0, 26	5, 26
Not reported/IMT removal	4	1	0	1	0
Total	202	196	194	180	148
Change from Baseline					
N	198	195	194	179	148
Mean	-1.43	-1.36	-1.71	-0.78	-0.83
Standard Deviation	3.67	3.50	3.53	3.67	3.43
95% confidence interval	-1.95, -0.92	-1.86, -0.87	-2.21, -1.21	-1.32, -0.24	-1.39, -0.27
Median	-1.0	-2.0	-2.0	-1.0	-1.0
Range	-10, 9	-12, 8	-11, 8	-12, 11	-10, 11
Decrease > 10 mm Hg	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	0 (0.0%)
Decrease 6 to 10 mm Hg	26 (13.1%)	21 (10.8%)	30 (15.5%)	14 (7.8%)	14 (9.5%)
Decrease 1 to 5 mm Hg	96 (48.5%)	100 (51.3%)	86 (44.3%)	78 (43.6%)	65 (43.9%)
No Change	21 (10.6%)	14 (7.2%)	23 (11.9%)	27 (15.1%)	20 (13.5%)
Increase 1 to 5 mmHg	49 (24.7%)	55 (28.2%)	50 (25.8%)	51 (28.5%)	45 (30.4%)
Increase 6 to 10 mm Hg	6 (3.0%)	4 (2.1%)	4 (2.1%)	7 (3.9%)	3 (2.0%)
Increase > 10 mm Hg	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)
Not reported/IMT removal	4	1	0	1	0
Total	202	196	194	180	148

For absolute IOP, N = number of treated eyes returned for the visit with non-missing IOP. Not reported = number of treated eyes returned for the visit with missing IOP. IMT removal = number of treated eyes with IMT removal at the visit. Records after IMT removal were excluded and reported separately. Total = number of treated eyes returned for the visit.
For change, N = number of treated eyes returned for the visit with non-missing IOP preoperatively or postoperatively. Not reported = number of treated eyes returned for the visit with missing IOP preoperatively or postoperatively. Total = number of treated eyes returned for the visit.

18.4 ENDOTHELIAL CELL DENSITY (ECD)

To evaluate change in endothelial cell density over time, specular microscopy was performed preoperatively and at the Month 3, 6, 9, 12, 18 and 24 examinations in both the operated eyes and fellow eyes. Three images were obtained at each visit and were sent to a central reading center (B. McCarey, Ph.D., Emory University) for analysis. The mean endothelial cell density for all 3 images obtained at each visit for each eye was used in all analyses. As is standard practice at the Emory University specular microscopy reading center, the quality of each image was graded as good (3), fair (2), poor (1) or indistinct (0). This was particularly important in the current study since concerns had been expressed by the participating clinical sites of the considerable difficulty in obtaining good specular images as a result of reflection from the IMT.

As described in the statistical methods section of this report (Section 8), the average of ECD measurements taken at the same visit for the same eye was calculated and treated as the ECD value of the eye at the visit. The percentage change in the ECD from baseline was calculated as follows for each eye:

% Change in ECD from baseline
= (Postoperative ECD – Baseline ECD) ÷ Baseline ECD × 100%

In addition to the ECD change from baseline, the change in ECD between two consecutive postoperative visits was calculated for each eye as follows:

% Change in ECD between two consecutive postoperative visits
= (Visit-2 ECD – Visit-1 ECD) ÷ Visit-1 ECD × 100%

Descriptive statistics such as mean, standard deviation, median, and range, and the 90% confidence interval for the mean were calculated for percentage change in the ECD from baseline at each postoperative visit.

On the following pages of this report, data are presented for mean ECD and percentage change in ECD in the IMT implanted eyes alone and as compared to fellow eyes and pseudophakic fellow eyes. Additional analyses were also performed to evaluate the effect of various clinical parameters on postoperative ECD; these parameters included corneal status on postoperative Day 1; axial length; anterior chamber depth; surgical order (i.e., learning curve); incision type (limbal incision vs. scleral tunneling); surgeon's specialty (cornea trained vs. non-cornea trained); subject's age at implant; preoperative ECD; and the operative use of the viscoelastic Healon V.

Finally, analyses were performed to determine whether greater endothelial cell loss at 3 months, which reflects the effect of surgical trauma, was predictive of loss in ECD at later visits.

18.4.1 ACCOUNTABILITY FOR ENDOTHELIAL CELL DENSITY ANALYSES

Table 26 summarizes accountability for all implanted subjects with regard to specular microscopy results at the time of database closure. ECD data from the central reading center for specular images were available for analysis for 192/206 (93.2%) subjects at 3 months, 198/206 (96.1%) subjects at 6 months, 190/206 (92.2%) subjects at 9 months, 186/206 (90.3%) subjects at 12 months, 180/206 (87.4%) subjects at 18 months, 144/206 (69.9%) subjects at 24 months at the time of database lock. Accountability, i.e. the proportion of eyes eligible for the examination window and not discontinued or lost to follow-up, is 94.1% (192/204) at 3 months, 98.0% (198/202) at 6 months, 94.1% (190/202) at 9 months, 93.5% (186/199) at 12 months, 91.4% (180/197) at 18 months and 92.9% (144/155) at 24 months.

TABLE 26
ENDOTHELIAL CELL DENSITY ACCOUNTABILITY
(N = 206 EYES SUCCESSFULLY IMPLANTED WITH IMT)

Total Subjects (N) = 206		3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Available for Analysis	n/N (%)	192/206 (93.2%)	198/206 (96.1%)	190/206 (92.2%)	186/206 (90.3%)	180/206 (87.4%)	144/206 (69.9%)
Discontinued	n/N (%)	2/206 (1.0%)	4/206 (1.9%)	4/206 (1.9%)	7/206 (3.4%)	9/206 (4.4%)	16/206 (7.8%)
Deceased	n/N (%)	1/206 (0.5%)	3/206 (1.5%)	3/206 (1.5%)	5/206 (2.4%)	7/206 (3.4%)	10/206 (4.9%)
IMT Removed*	n/N (%)	1/206 (0.5%)	1/206 (0.5%)	1/206 (0.5%)	2/206 (1.0%)	2/206 (1.0%)	6/206 (2.9%)
Active (Not yet eligible for the interval)	n/N (%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	35/206 (17.0%)
Lost to Follow-up†	n/N (%)	0/206 (0.0%)	0/206 (0.0%)	0/206 (0.0%)	1/206 (0.5%)	3/206 (1.5%)	6/206 (2.9%)
Missed Visit‡	n/N (%)	12/206 (5.8%)	4/206 (1.9%)	12/206 (5.8%)	12/206 (5.8%)	14/206 (6.8%)	5/206 (2.4%)
% Accountability = Available for Analysis ÷ (Enrolled - Discontinued - Not yet eligible)		192/204 (94.1%)	198/202 (98.0%)	190/202 (94.1%)	186/199 (93.5%)	180/197 (91.4%)	144/155 (92.9%)

DB was frozen for data entry on 06/20/2005. However, it was reopened for necessary data revision and was frozen on 07/18/2005 for PMA.
Some exam records did not have a corresponding ECD records and some ECD records did not have a corresponding exam records.
010-202's office chart was lost and no 24-month data could be collected. The subject was included in the "Missed Visit" row.
N = Total number of enrolled eyes with an IMT.
One eye canceled surgery. Five eyes were reported with an aborted implantation. Six eyes were reported with IMT removal at surgery. These eyes were excluded from analyses, however their safety data will be discussed separately.

* Eight eyes were reported with IMT removal postoperatively at the time of DB closure. Six of these eight eyes have been exited from the study. The records after IMT explant are not included in the analyses of the impact of IMT on ECD, but are presented separately.

† Lost to follow-up: Eyes were not examined at the visit interval, and were not considered active or discontinued.

‡ Missed visit: Eyes were not examined for ECD at the scheduled visit, however ECD was assessed or may have been assessed at a subsequent visit. This also includes the subjects who had returned for the examinations but did not have the ECD readings.

18.4.2 ENDOTHELIAL CELL DENSITY AND PERCENT CHANGE IN ECD FROM BASELINE IN IMT-IMPLANTED EYES

Table 27 shows ECD for all IMT implanted eyes. As shown, the most significant decrease in mean ECD occurred between baseline and 3 months, with mean ECD of 2496.1 cells/mm^2 (S.D. 354.3) at baseline and 1996.9 cells/mm^2 (S.D. 585.9) at 3 months. From 6 months through 24 months, mean ECD was 1936.8 cells/mm^2 (S.D. 579.7) at 6 months, 1890.8 cells/mm^2 (S.D. 572.3) at 9 months, 1871.3 cells/mm^2 (S.D. 592.1) at 12 months, 1878.1 cells/mm^2 (S.D. 618.2) at 18 months, and 1786.4 cells/mm^2 (S.D. 602.6) at 24 months.

TABLE 27
ENDOTHELIAL CELL DENSITY (MEAN, SD)
ALL EYES IMPLANTED WITH IMT

ECD	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	206	192	198	190	186	180	144
Mean	2496.13	1996.87	1936.83	1890.82	1871.29	1878.11	1786.36
Standard Deviation	354.33	585.92	579.73	572.29	592.09	618.22	602.61
Median	2510.0	2026.3	2017.8	1938.8	1929.5	1977.5	1860.0
Range	1695.0, 3356.0	432.3, 3125.7	385.3, 2935.7	309.0, 3008.0	310.7, 2959.0	351.0, 2900.0	385.7, 2930.0
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥3000	13 (6.3%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2500 to <3000	92 (44.7%)	44 (22.9%)	35 (17.7%)	27 (14.2%)	29 (15.6%)	31 (17.2%)	17 (11.8%)
2000 to <2500	80 (38.8%)	55 (28.6%)	66 (33.3%)	61 (32.1%)	56 (30.1%)	57 (31.7%)	43 (29.9%)
1500 to <2000	21 (10.2%)	59 (30.7%)	56 (28.3%)	59 (31.1%)	57 (30.6%)	46 (25.6%)	46 (31.9%)
1000 to <1500	0 (0.0%)	17 (8.9%)	24 (12.1%)	26 (13.7%)	23 (12.4%)	25 (13.9%)	20 (13.9%)
<1000	0 (0.0%)	16 (8.3%)	17 (8.6%)	16 (8.4%)	21 (11.3%)	21 (11.7%)	18 (12.5%)
95% CI for % of eyes with ECD<1000	0.0%, 1.8%	4.8%, 13.2%	5.1%, 13.4%	4.9%, 13.3%	7.1%, 16.7%	7.4%, 17.3%	7.6%, 19.0%

N = number of successful IMT implanted eyes returned for the visit with non-missing ECD.
% = n ÷N ×100
95% CI was calculated based on Clopper Pearson method.

The same information on endothelial cell density is shown in Table 28 for a 24-month consistent cohort of eyes implanted with the IMT, representing ECD for 130 eyes with all visits from baseline through 24 months.

A scattergram showing endothelial cell density over time for each IMT-implanted eye is provided in Figure 11.

TABLE 28
ENDOTHELIAL CELL DENSITY (MEAN, SD)
24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

ECD	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	130	130	130	130	130	130	130
Mean	2499.73	1998.44	1929.71	1878.74	1832.09	1845.62	1789.71
Standard Deviation	354.39	562.04	571.77	568.47	579.83	604.28	601.95
Median	2506.8	2026.3	2024.2	1953.3	1917.2	1943.2	1873.3
Range	1695.0, 3356.0	492.3, 2907.3	431.0, 2935.7	309.0, 2931.3	310.7, 2786.7	434.0, 2825.7	385.7, 2930.0
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
≥3000	7 (5.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2500 to <3000	59 (45.4%)	29 (22.3%)	22 (16.9%)	17 (13.1%)	18 (13.8%)	18 (13.8%)	15 (11.5%)
2000 to <2500	52 (40.0%)	38 (29.2%)	45 (34.6%)	45 (34.6%)	39 (30.0%)	44 (33.8%)	39 (30.0%)
1500 to <2000	12 (9.2%)	41 (31.5%)	36 (27.7%)	40 (30.8%)	43 (33.1%)	32 (24.6%)	42 (32.3%)
1000 to <1500	0 (0.0%)	12 (9.2%)	15 (11.5%)	16 (12.3%)	12 (9.2%)	21 (16.2%)	18 (13.8%)
<1000	0 (0.0%)	10 (7.7%)	12 (9.2%)	12 (9.2%)	18 (13.8%)	15 (11.5%)	16 (12.3%)
95% CI for % of eyes with ECD<1000	0.0%, 2.8%	3.8%, 13.7%	4.9%, 15.6%	4.9%, 15.6%	8.4%, 21.0%	6.6%, 18.3%	7.2%, 19.2%

N = number of successful IMT implanted eyes with ECD at all visits.
% = n ÷N ×100
95% CI was calculated based on Clopper Pearson method.

FIGURE 11
ENDOTHELIAL CELL DENSITY IN IMT-IMPLANTED EYES

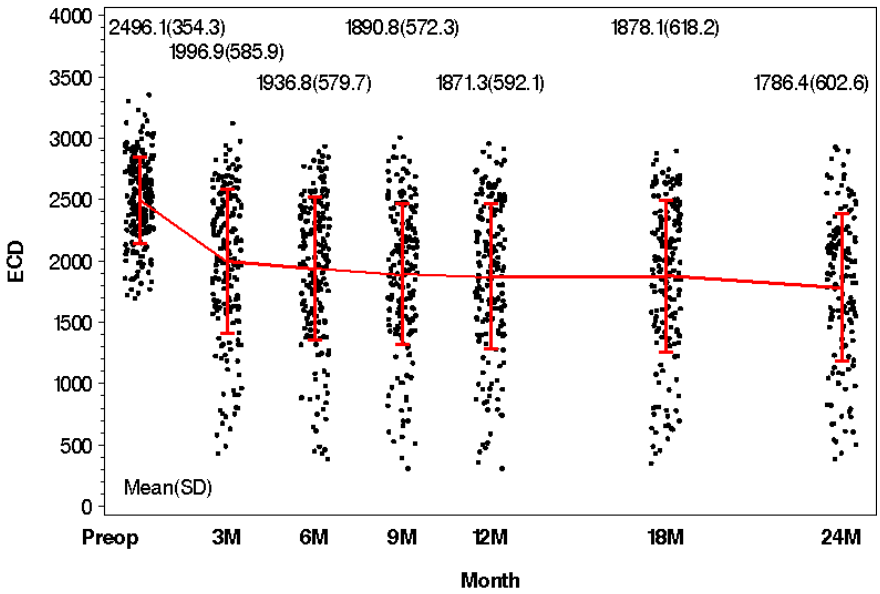


Table 29 shows the percentage change in ECD from baseline for all implanted eyes, and the same analysis is presented in Table 30 for a consistent cohort of eyes with all visits through 24 months. Mean change from baseline to 3 months was 20.0% (S.D. 21.1%), increasing slightly to 22.4% (S.D. 20.9%) at 6 months and to 24.4% (S.D. 20.5%) at 9 months. The percent change in ECD from baseline to 12 months was 25.3% (S.D. 21.3%) and from baseline to 18 months was 25.2% (S.D. 22.2%). A slightly larger percent loss in ECD was observed from baseline to 24 months (28.2%, S.D. 22.5%). Thus, the mean decrease in endothelial cell density for the total population of study eyes was somewhat higher than the target identified in the study protocol, i.e., a loss of less than or equal to 17% at one year post IMT implantation. However, it is clear from this analysis that the reduction in ECD is most pronounced at 3 months following IMT implantation, and seems to level off at subsequent postoperative examinations.

TABLE 29
PERCENTAGE CHANGE IN ECD FROM BASELINE (MEAN, SD)
ALL EYES IMPLANTED WITH IMT

ECD % Change from Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	192	198	190	186	180	144
Mean	-20.0%	-22.4%	-24.4%	-25.3%	-25.2%	-28.2%
Standard Deviation	21.1%	20.9%	20.5%	21.3%	22.2%	22.5%
90% confidence interval for mean	-22.5%, -17.5%	-24.8%, -19.9%	-26.9%, -22.0%	-27.9%, -22.7%	-28.0%, -22.5%	-31.3%, -25.1%
Median	-13.0%	-17.0%	-19.2%	-20.9%	-21.3%	-24.2%
Range	-85.1%, 18.0%	-84.4%, 30.9%	-87.5%, 13.5%	-87.6%, 12.7%	-87.9%, 25.1%	-80.9%, 28.1%
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Decrease >40%	34 (17.7%)	36 (18.2%)	37 (19.5%)	40 (21.5%)	36 (20.0%)	37 (25.7%)
Decrease 30.01% to 40%	17 (8.9%)	21 (10.6%)	24 (12.6%)	26 (14.0%)	27 (15.0%)	19 (13.2%)
Decrease 20.01% to 30%	25 (13.0%)	28 (14.1%)	31 (16.3%)	30 (16.1%)	30 (16.7%)	28 (19.4%)
Decrease 10.01% to 20%	36 (18.8%)	48 (24.2%)	45 (23.7%)	41 (22.0%)	32 (17.8%)	26 (18.1%)
Decrease 0.01% to 10%	55 (28.6%)	53 (26.8%)	42 (22.1%)	38 (20.4%)	44 (24.4%)	27 (18.8%)
Increase 0.0% to 10%	20 (10.4%)	8 (4.0%)	8 (4.2%)	10 (5.4%)	8 (4.4%)	5 (3.5%)
Increase 10.01% to 20%	5 (2.6%)	3 (1.5%)	3 (1.6%)	1 (0.5%)	2 (1.1%)	1 (0.7%)
Increase 20.01% to 30%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)
Increase 30.01% to 40%	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase >40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of successful IMT implanted eyes returned for the visit with non-missing ECD change from baseline.
Percentage change in ECD from baseline = (postop - baseline) ÷baseline ×100.
% = n ÷N ×100

TABLE 30
PERCENTAGE CHANGE IN ECD FROM BASELINE (MEAN, SD)
24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

ECD % Change from Baseline	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
N	130	130	130	130	130	130
Mean	-19.6%	-22.4%	-24.5%	-26.4%	-25.9%	-28.2%
Standard Deviation	21.5%	21.8%	21.6%	22.2%	23.0%	22.7%
90% confidence interval for mean	-22.7%, -16.5%	-25.6%, -19.2%	-27.6%, -21.3%	-29.6%, -23.1%	-29.2%, -22.5%	-31.5%, -24.9%
Median	-12.4%	-15.8%	-18.9%	-22.2%	-22.0%	-24.2%
Range	-74.9%, 12.8%	-82.5%, 30.9%	-87.5%, 11.6%	-87.4%, 12.7%	-80.5%, 25.1%	-80.9%, 28.1%
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Decrease >40%	26 (20.0%)	26 (20.0%)	29 (22.3%)	32 (24.6%)	28 (21.5%)	33 (25.4%)
Decrease 30.01% to 40%	9 (6.9%)	13 (10.0%)	11 (8.5%)	16 (12.3%)	21 (16.2%)	17 (13.1%)
Decrease 20.01% to 30%	13 (10.0%)	17 (13.1%)	20 (15.4%)	24 (18.5%)	21 (16.2%)	26 (20.0%)
Decrease 10.01% to 20%	25 (19.2%)	30 (23.1%)	30 (23.1%)	23 (17.7%)	19 (14.6%)	24 (18.5%)
Decrease 0.01% to 10%	37 (28.5%)	34 (26.2%)	32 (24.6%)	26 (20.0%)	30 (23.1%)	23 (17.7%)
Increase 0.0% to 10%	16 (12.3%)	6 (4.6%)	6 (4.6%)	8 (6.2%)	8 (6.2%)	5 (3.8%)
Increase 10.01% to 20%	4 (3.1%)	3 (2.3%)	2 (1.5%)	1 (0.8%)	2 (1.5%)	1 (0.8%)
Increase 20.01% to 30%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.8%)	1 (0.8%)
Increase 30.01% to 40%	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Increase >40%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of successful IMT implanted eyes with ECD change from baseline at all visits.
Percentage change in ECD from baseline = (postop - baseline) ÷baseline ×100.
% = n ÷N ×100

18.4.3 PERCENT CHANGE IN ECD BETWEEN VISITS FOR IMT-IMPLANTED EYES AND PSEUDOPHAKIC FELLOW EYES

Since the most significant decrease in endothelial cell density was observed at 3 months, as would be anticipated given the large incision required for implantation of the IMT, change across visits from 3 months through 24 months was then analyzed to determine whether the initial cell loss continued over the course of follow-up. Additionally, in order to compare the change in ECD after 3 months in the IMT cohort to a clinically relevant control group, the percentage change in ECD in pseudophakic fellow eyes (n=36) was calculated.

The percentage change in ECD between consecutive postoperative visits for all eyes implanted with IMT vs. pseudophakic fellow eyes is summarized in Table 31, and displayed in Figure 12 as well.

Mean percentage change in ECD for IMT-implanted eyes was –2.7% (SD 14.6%) between 3 to 6 months, -2.4% (SD 14.7%) between 6 to 9 months, -1.5% (SD 15.0%) between 9 to 12 months, +2.0% (SD 20.9%) between 12 to 18 months, and–2.6% (SD 13.5%) between 18 to 24 months. For pseudophakic fellow eyes, mean change in ECD was -1.1% (S.D. 10.7%) between 3 to 6 months, -1.7% (S.D. 11.1%) between 6 to 9 months,

+0.5% (S.D. 18.6%) between 9 to 12 months, +2.8% (S.D. 14.5%) between 12 to 18 months, and -1.5% (S.D. 7.6%) between 18 to 24 months.

No statistically significant differences in change in ECD between visits were observed between IMT implanted and pseudophakic fellow eyes. Given the similarities of the implantation procedure for an IMT and for a standard intraocular lens, the absence of differences between IMT implanted and pseudophakic fellow eyes is not unexpected. It is interesting to note that in the cohort of pseudophakic fellow eyes, a similar increase in ECD was observed between 12 to 18 months, supporting the variability of ECD outcomes.

An analysis of a 24-month consistent cohort of eyes was not performed since the consistent cohort of all pseudophakic fellow eyes consists of only 21 eyes.

TABLE 31
PERCENTAGE CHANGE IN ECD BETWEEN CONSECUTIVE POSTOPERATIVE VISITS
ALL EYES IMPLANTED WITH IMT VERSUS ALL PSEUDOPHAKIC FELLOW EYES

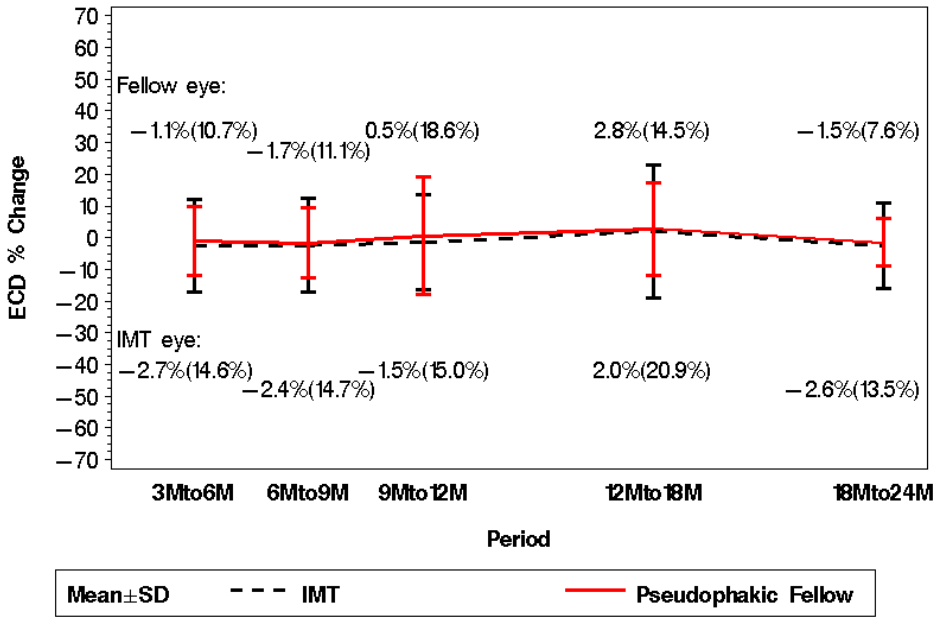
Difference in ECD (%) Change*	3 Months to 6 Months	6 Months to 9 Months	9 Months to 12 Months	12 Months to 18 Months	18 Months to 24 Months
IMT Eyes					
N	187	188	179	176	142
Mean (SD)	-2.7% (14.6%)	-2.4% (14.7%)	-1.5% (15.0%)	2.0% (20.9%)	-2.6% (13.5%)
Median	-2.4%	-1.2%	-1.6%	0.8%	-2.4%
90% confidence interval for mean	-4.4%, -0.9%	-4.2%, -0.6%	-3.3%, 0.4%	-0.6%, 4.6%	-4.5%, -0.7%
Fellow Eyes					
N	31	31	31	32	24
Mean (SD)	-1.1% (10.7%)	-1.7% (11.1%)	0.5% (18.6%)	2.8% (14.5%)	-1.5% (7.6%)
Median	-1.7%	-1.2%	-4.2%	1.7%	-2.5%
90% confidence interval for mean	-4.4%, 2.2%	-5.1%, 1.6%	-5.1%, 6.2%	-1.6%, 7.1%	-4.1%, 1.2%
Wald's Test (GEE Model†) for Comparing Mean % Change Between IMT and Fellow Eyes					
P-value	0.4564	0.6292	0.3278	0.7540	0.5403

N = Total number of subjects with a non-missing cell count at both visits for IMT and fellow eyes. The cell count change is missing if ECD is missing at either visit.

* % change in ECD = (later postop visit - previous postop visit) ÷previous postop visit ×100. A negative value means a reduction and a positive value means an increase.

† GEE model on the percentage change in ECD from baseline at the corresponding visit with IMT/Fellow eye as the factor and an unstructured correlation matrix.

FIGURE 12
MEAN AND STANDARD DEVIATION OF ECD PERCENTAGE CHANGE BETWEEN CONSECUTIVE POSTOPERATIVE VISITS EYES IMPLANTED WITH IMT VERSUS PSEUDOPHAKIC FELLOW EYES



18.4.4 ANALYSIS OF IMAGES GRADED AS "GOOD"

Since all images were used in calculating the mean ECD for each eye, irrespective of the quality of the image, the analyses presented in the previous sections on change in ECD represent a conservative approach to this analysis. For purposes of comparison, a subset of these analyses are presented for outcomes of specular microscopy readings only for images graded as "good" by the specular microscopy reading center. First, accountability of images for IMT and fellow eyes graded as "good" is summarized in Table 32. As shown, preoperatively, the proportion of images graded as "good" was similar for IMT-implanted eyes and pseudophakic eyes. However, postoperatively, there were approximately 10% fewer "good" images in the IMT group than in the pseudophakic fellow eye cohort.

TABLE 32
PROPORTION OF EYES WITH SPECULAR IMAGES GRADED AS "GOOD"
SUBJECTS IMPLANTED WITH IMT

Eye	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
IMT Eyes	168/206 (81.6%)	121/192 (63.0%)	144/198 (72.7%)	142/190 (74.7%)	142/186 (76.3%)	151/180 (83.9%)	119/144 (82.6%)
Fellow Eyes	169/204 (82.8%)	162/190 (85.3%)	160/196 (81.6%)	167/191 (87.4%)	163/188 (86.7%)	166/181 (91.7%)	135/146 (92.5%)
Phakic Fellow Eyes	136/168 (81.0%)	135/157 (86.0%)	135/163 (82.8%)	141/159 (88.7%)	134/154 (87.0%)	137/148 (92.6%)	112/121 (92.6%)
Pseudophakic Fellow Eyes	33/36 (91.7%)	27/33 (81.8%)	25/33 (75.8%)	26/32 (81.3%)	29/34 (85.3%)	29/33 (87.9%)	23/25 (92.0%)

Since the quality of the specular image has significant impact on the calculation of endothelial cell density, the percent change in ECD between consecutive visits was analyzed using only those specular images graded as "good" by the reading center. As shown in Table 33, the overall course of percent change in ECD is very similar for the "good" images as were reported for the total cohort of IMT-implanted eyes. However, the change in ECD over the course of follow-up from 6 months appears to more clearly decrease at each interval, as would be expected following large-incision intraocular surgery.

TABLE 33
PERCENTAGE CHANGE IN ECD BETWEEN CONSECUTIVE POSTOPERATIVE VISITS BASED ON SPECULAR IMAGES GRADED AS "GOOD"
ALL EYES IMPLANTED WITH IMT

Percentage Change	3 Months to 6 Months	6 Months to 9 Months	9 Months to 12 Months	12 Months to 18 Months	18 Months to 24 Months
N	97	117	114	121	105
Mean (SD)	-3.8% (16.0%)	-1.7% (14.3%)	-1.2% (16.2%)	1.9% (24.0%)	-0.0% (15.4%)
90% confidence interval for mean	-6.5%, -1.1%	-3.9%, 0.5%	-3.7%, 1.4%	-1.7%, 5.6%	-2.5%, 2.5%
Median	-3.0%	-0.6%	-2.2%	-0.6%	-1.0%
Range	-48.2%, 55.4%	-42.4%, 41.9%	-54.2%, 73.3%	-45.8%, 161.5%	-41.4%, 79.7%

N = Total number of eyes with a non-missing cell count at both visits. The cell count change is missing if ECD is missing at either visit.
Percentage change in ECD between two visits = (later postop visit - previous postop visit) ÷previous postop visit ×100. A negative value means a reduction and a positive value means an increase. % = n ÷N ×100

To ensure that no selection bias was introduced into the analysis of ECD for only "good" specular images, endothelial cell density was stratified by image quality, as shown in Table 34. ECD was compared for "good" images versus "other" images, representing the images graded as fair, poor or indistinct. As shown, there were no statistically significant differences in ECD between "good" images and "other" images, i.e., those images graded as fair, poor or indistinct. Thus, the analysis of "good" images shown in Table 34 does not appear to be biased with regard to the distribution of ECDs, and may represent a more accurate analysis of the available specular microscopy data for the study population.

It should be noted that the "N" shown in these tables does not correlate directly with the number of IMT-implanted eyes, since this "N" represents the number of eyes with certain grade for quality of each image.

TABLE 34
ENDOTHELIAL CELL DENSITY STRATIFIED BY SPECULAR IMAGE QUALITY
ALL EYES IMPLANTED WITH IMT

ECD	Preop	3 Months	6 Months	9 Months	12 Months	18 Months	24 Months
Good ECD Image Quality							
N*	168	121	144	142	142	151	119
Mean	2487.9	1954.4	1913.7	1901.8	1850.0	1871.5	1819.1
Standard Deviation	361.3	619.1	599.5	583.2	602.8	607.5	571.4
Median	2522.5	2028.0	1998.3	1961.8	1913.9	1934.0	1891.0
Minimum	1715.0	417.0	431.0	385.5	310.7	434.0	456.5
Maximum	3384.0	3106.0	2959.0	3008.0	2959.0	2900.0	3067.0
Other ECD Image Quality							
N*	99	139	128	119	110	105	79
Mean	2476.3	2038.0	1975.6	1896.5	1937.7	1923.8	1809.9
Standard Deviation	364.0	579.8	584.2	576.6	547.1	608.9	649.5
Median	2500.0	2058.0	2060.3	1933.5	1973.5	2007.3	1887.0
Minimum	1608.0	463.0	382.0	309.0	317.0	351.0	385.7
Maximum	3300.0	3448.0	3058.0	2931.3	2959.0	2894.5	2895.7
GEE Model with ECD Image Quality as the Factor†							
Estimated Mean Difference (GEE)	-27.7	-10.8	-6.4	23.1	-67.0	-38.6	28.5
95% CI of Mean Difference	-60.3, 5.0	-56.0, 34.4	-45.3, 32.5	-23.8, 70.1	-113.3, -20.6	-79.4, 2.1	-16.4, 73.4
P-value of Wald test	0.0964	0.6399	0.7469	0.3341	0.0046	0.0632	0.2135

The average of ECD reading was calculated for each subject in each of the two ECD image groups at each visit. A subject could have ECD images with both good and other quality at a visit. Therefore, a subject could be included in both quality groups.

* For "Good ECD Image Quality" group, N = number of IMT eyes with good ECD images at the corresponding visit. For "Other ECD Image Quality" group, N = number of IMT eyes with ECD images quality worse than "Good" at the corresponding visit.

† The ECD averages of a subject at a visit were treated as repeated measurements. The unstructured working correlation matrix was assumed.

18.4.5 STABILITY OF ENDOTHELIAL CELL DENSITY

Since the postoperative percent changes in ECD between visits are correlated, GEE analysis was performed to compare the differences in this outcome among different visit intervals. The percent change in ECD at the interval of 12 to 18 months was used as the basis for comparison of the results from other intervals. As shown in Table 35, the percent change in ECD from 12 to 18 months is not statistically significantly different from the percent change in ECD from 9 to 12 months (p = 0.2077) and from 18 to 24 months (p = 0.0657). The Wald test for comparing the period effects suggests that the differences among the different time intervals are not statistically significant (p = 0.1962).

TABLE 35
GENERALIZED ESTIMATING EQUATION ANALYSIS ON PERCENTAGE CHANGE IN ENDOTHELIAL CELL DENSITY BETWEEN VISITS ALL EYES IMPLANTED WITH IMT

Parameter	Time Period	Estimate	Standard Error	90% CI	P-value
Intercept		1.55%	1.59%	(-1.06%, 4.17%)	0.3288
Period	3 Months to 6 Months	-4.30%	2.06%	(-7.68%, -0.92%)	0.0364
	6 Months to 9 Months	-3.76%	1.79%	(-6.71%, -0.81%)	0.0360
	9 Months to 12 Months	-2.80%	2.22%	(-6.45%, 0.85%)	0.2077
	12 Months to 18 Months (Reference Visit)	0.00%			
	18 Months to 24 Months	-4.33%	2.35%	(-8.19%, -0.46%)	0.0657
	Wald Statistics for Time Period				0.1962

To confirm these results, GEE analysis was performed to compare the differences in this outcome among different visit intervals for the 24-month consistent cohort of eyes implanted with IMT. Although Table 36 shows that the percent change in ECD from 12 to 18 months is not statistically significantly different from the percent change in ECD from 9 to 12 months (p = 0.0847), it is significantly different from 18 to 24 months (p=0.0492) for the 24-month consistent cohort. However, the Wald test for comparing the period effects suggests that the differences among the different time intervals are not statistically significant (p = 0.3008) for the 24-month consistent cohort of eyes implanted with IMT.

TABLE 36
GENERALIZED ESTIMATING EQUATION ANALYSIS ON PERCENTAGE CHANGE IN ECD BETWEEN VISITS 24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

Parameter	Time Period	Estimate	Standard Error	90% CI	P-value
Intercept		1.73%	1.57%	(-0.85%, 4.31%)	0.2691
Period	3 Months to 6 Months	-4.44%	2.27%	(-8.17%, -0.71%)	0.0504
	6 Months to 9 Months	-3.64%	1.95%	(-6.85%, -0.42%)	0.0630
	9 Months to 12 Months	-3.94%	2.29%	(-7.70%, -0.18%)	0.0847
	12 Months to 18 Months (Reference Visit)	0.00%			
	18 Months to 24 Months	-4.33%	2.20%	(-7.94%, -0.71%)	0.0492
	Wald Statistics for Time Period				0.3008

18.4.6 ANNUALIZED PERCENT CHANGE IN IMT IMPLANTED EYES AND PSEUDOPHAKIC FELLOW EYES

For each eye, the percent change in ECD between each pair of visits from 9 months to 24 months was calculated. An estimated annual percentage change based on a between-visit percentage change was then calculated as the between-visit percentage change divided by the interval in months and multiplied by 12. For example, the estimated annual percentage change based on the 12-to-18-month change is the 12-to-18-month percentage change divided by 6 and multiplied by 12. If an IMT-implanted eye had ECD data at 9, 12, 18 and 24 months, then the eye had six estimated annual ECD percentage changes. The final estimation of the annual ECD percentage change for this eye consists of the average of these six available estimated annual percent changes. This calculation averages out the possible up-and-down ECD evaluations due to inter-interval variation. The overall annual ECD percentage change was calculated based on these estimated annual percentage changes.

The mean, standard deviation, and 90% confidence interval of this calculation of annual percent change in ECD is summarized in Table 37 for IMT implanted eyes. As shown, for the 188 IMT implanted eyes with at least one postoperative ECD percentage change at 9 months or later, the mean annual percent change in ECD from 9 months to 24 months is -0.5% (S.D. 28.6%). The 90% confidence interval of the mean annual percentage change is –4.0% to 2.9%. This finding suggests that ECD is generally stable from 9 months on. The annual ECD percentage change was also calculated for the 24-month consistent cohort of 130 IMT implanted eyes, as shown in Table 38. For this cohort of eyes, the mean annual percent change in ECD is -3.0% (S.D. 15.0%; 90% confidence interval –5.2% to -0.8%).

TABLE 37
ANNUAL ECD PERCENTAGE CHANGE
ESTIMATED BASED ON RECORDS BETWEEN 9 TO 24 MONTHS
ALL EYES IMPLANTED WITH IMT

Visit Period	N	Mean (SD)	90% Confidence Interval	Median	Range	Estimated Annual Mean % Change Mean (SD)	90% Confidence Interval for Annual Mean % Change
9 Months to 12 Months	179	-1.5% (15.0%)	-3.3%, 0.4%	-1.6%	-54.2%, 76.1%	-5.8% (60.1%)	-13.3%, 1.6%
9 Months to 18 Months	175	-1.4% (16.4%)	-3.4%, 0.6%	-2.2%	-47.2%, 115.0%	-1.9% (21.8%)	-4.6%, 0.9%
9 Months to 24 Months	139	-5.0% (16.4%)	-7.3%, -2.7%	-3.9%	-56.5%, 62.9%	-4.0% (13.1%)	-5.8%, -2.1%
12 Months to 18 Months	176	2.0% (20.9%)	-0.6%, 4.6%	0.8%	-44.1%, 161.5%	4.0% (41.8%)	-1.2%, 9.3%
12 Months to 24 Months	142	-2.3% (15.9%)	-4.5%, -0.1%	-1.1%	-45.5%, 62.0%	-2.3% (15.9%)	-4.5%, -0.1%
18 Months to 24 Months	142	-2.6% (13.5%)	-4.5%, -0.7%	-2.4%	-47.6%, 60.8%	-5.2% (27.0%)	-9.0%, -1.5%
Average	188					-0.5% (28.6%)	-4.0%, 2.9%

N = number of treated eyes returned for the visit period with a non-missing change in ECD.
For each IMT eye, the annual percentage change in ECD based on a visit period was calculated as (later postop ECD - previous postop ECD) ÷ previous postop ECD × 100 ÷ number of months × 12. Then the mean, SD, and 90% confidence interval of the annual percentage change in ECD was calculated.

TABLE 38
ANNUAL ECD PERCENTAGE CHANGE
ESTIMATED BASED ON RECORDS BETWEEN 9 TO 24 MONTHS
24-MONTH CONSISTENT COHORT OF EYES IMPLANTED WITH IMT

Visit Period	N	Mean (SD)	90% Confidence Interval	Median	Range	Estimated Annual Mean % Change Mean (SD)	90% Confidence Interval for Annual Mean % Change
9 Months to 12 Months	130	-2.2% (13.5%)	-4.2%, -0.2%	-2.2%	-37.0%, 58.9%	-8.8% (54.0%)	-16.7%, -1.0%
9 Months to 18 Months	130	-1.4% (17.4%)	-3.9%, 1.1%	-1.8%	-47.2%, 115.0%	-1.9% (23.3%)	-5.3%, 1.5%
9 Months to 24 Months	130	-4.7% (15.5%)	-6.9%, -2.4%	-3.8%	-53.5%, 62.9%	-3.7% (12.4%)	-5.5%, -1.9%
12 Months to 18 Months	130	1.7% (17.9%)	-0.9%, 4.3%	0.8%	-42.1%, 113.8%	3.5% (35.9%)	-1.7%, 8.7%
12 Months to 24 Months	130	-1.8% (15.3%)	-4.0%, 0.4%	-1.0%	-45.5%, 62.0%	-1.8% (15.3%)	-4.0%, 0.4%
18 Months to 24 Months	130	-2.6% (11.6%)	-4.3%, -0.9%	-2.2%	-32.3%, 43.2%	-5.2% (23.3%)	-8.6%, -1.8%
Average	130					-3.0% (15.0%)	-5.2%, -0.8%

N = number of treated eyes returned for the visit period with a non-missing change in ECD.
For each IMT eye, the annual percentage change in ECD based on a visit period was calculated as (later postop ECD - previous postop ECD) ÷ previous postop ECD × 100 ÷ number of months × 12. Then the mean, SD, and 90% confidence interval of the annual percentage change in ECD was calculated.

18.4.7 FACTORS CONTRIBUTING TO ENDOTHELIAL CELL LOSS AT 3 MONTHS

Since the most significant loss in ECD occurred at 3 months, factors that may have contributed to early cell loss have been evaluated. These factors included preoperative ECD, anterior chamber depth, axial length, surgical order, incision type and size, surgeon specialty, age at time of implant, surgeon, axial length, use of Healon V during IMT implantation and corneal status on postoperative day 1.

As described in Section 8.0, Statistical Methods, the statistical analyses on the effects of these clinical parameters on the mean 3-month ECD percentage change from baseline involved a number of steps intended to identify those parameters with a significant effect on 3-month ECD. These steps are repeated here, as follows.

- Univariate one-way ANOVA was performed first to identify the potentially significant factors for multivariate analyses. Any parameter with a p-value $\leq$ 0.15 was considered a potential factor in the multivariate analyses. The significance level of 0.15 was chosen to include any potential effects.

- Once the potential factors were identified, the two-factor ANOVA (Type III) was performed on every pair of potential factors to examine the potential two-factor interaction effects on the 3-month ECD percentage change from baseline. Any interaction effect with a p-value of 0.15 or less was considered a potential factor in the next multivariate analyses step.

- Once the potential main effects and interaction effects were identified, the backward procedure in the multivariate analyses was used to select the final model for the 3-month ECD percentage change from baseline. A significance level of 0.10 was used to remove a main factor (effect) from the model and a significance level of 0.15 was used to remove an interaction effect from the backward procedure.

- Interaction terms were examined first. The interaction effect with the largest p-value of > 0.15 was removed and a reduced model (i.e., the model without the interaction effect) was fitted. This procedure was repeated until all interaction effects in the model were $\leq$ 0.15.

- The main effects with the significant interaction effects in the model would not be removed. However, main effects that were not associated with interaction effects in the model were examined. The main effect that had the largest p-value of > 0.10 was removed and a reduced model was

fitted. This procedure was repeated until all main effects that were examined were ≤ 0.10.

- After several iterations, the final model for the 3-month ECD percentage change from baseline on the significant factors was then identified.

Table 39 below summarizes the p-values used for each step of the model fitting procedure. The final model identified that Day 1 corneal edema, and surgeon specialty are the two factors that appear to affect the mean change in ECD from baseline to 3 months.

TABLE 39
ECD PERCENTAGE CHANGE AT 3 MONTHS FROM BASELINE
MODELING ANALYSES
ALL EYES IMPLANTED WITH IMT & ECD CHANGE AT 3 MONTHS

Model No.	Factor	P-value*	Action
Univariate Analysis (One Factor at a Time)†			
1	Day 1 Corneal Edema	***<.0001***	Selected as one of the potential factors for the Backward Procedure since p-value ≤0.15.
2	ACD	0.1918	
3	Surgical Order	0.4654	
4	Incision Type	0.8604	
5	Incision Size	***0.0199***	Selected as one of the potential factors for the Backward Procedure since p-value ≤0.15.
6	Surgeon's Specialty	***0.0032***	Selected as one of the potential factors for the Backward Procedure since p-value ≤0.15.
7	Subject's Age at Implant	0.3556	
8	Preoperative ECD	0.1842	
9	Surgeon	0.2455	
10	Axial Length	0.8648	
11	Use of Healon V	0.4602	
Multivariate Analysis (Two Factors at a Time)†			
12	Day 1 Corneal Edema	<.0001	
	Incision Size	0.2756	
	Day 1 Corneal Edema & Incision Size Interaction	0.7800	
13	Day 1 Corneal Edema	<.0001	
	Surgeon's Specialty	0.0490	
	Day 1 Corneal Edema & Surgeon's Specialty Interaction	0.5550	
14	Incision Size	0.1776	
	Surgeon's Specialty	0.0489	
	Incision Size & Surgeon's Specialty Interaction	0.4680	
Final Model Selection (Backward Procedure)†			
15	Day 1 Corneal Edema	<.0001	
	Incision Size	0.2763	Removed from the model since p-value > 0.1.
	Surgeon's Specialty	0.1328	
16	Day 1 Corneal Edema	<.0001	Final Model.
	Surgeon's Specialty	0.0336	

* Based on type III analysis of ANOVA.

† Univariate approach was used to identify potential factors used in the Backward Procedure for selecting the final model. A factor with a p-value of ≤0.15 was considered for the Backward Procedure. Two-factor full models were used to identify the potential interactions of the factors identified by the univariate approach. An interaction effect with a p-value of ≤0.15 was considered for the Backward Procedure. For the Backward Procedure, a main factor with the largest p-value > 0.10 or an interaction with the largest p-value > 0.15 was removed and a reduced model was fitted. A final model was determined when all the main-effect p-values in the model were ≤0.10 and all the interaction-effect p-values in the model were ≤0.15.

As shown in Table 40, based on the least square estimation, IMT implanted eyes reported with normal cornea or 1+ corneal edema at postoperative Day 1 had a smaller mean percentage loss in ECD at 3 months than those with ≥ 2+ corneal edema on postoperative Day 1 (12.7% versus 35.2%; p<0.0001). Furthermore, study subjects implanted by cornea specialists had less endothelial cell loss at 3 months than non-cornea specialists (20.7% versus 27.2%; p=0.0336).

TABLE 40
ECD PERCENTAGE CHANGE AT 3 MONTHS FROM BASELINE
MODELING ANALYSES — FINAL MODEL
ALL EYES IMPLANTED WITH IMT & ECD CHANGE AT 3 MONTHS

Factor Level	Least Square Means 95% CI	Comparison	P-value*
Day-1 Corneal Edema			
Normal/1+Edema	-12.74% (-15.97%, -9.51)	Normal/1+Edema vs. ≥2+Edema	<.0001
≥2+Edema	-35.18% (-40.76%, -29.61)		
Surgeon's Specialty			
Corneal	-20.72% (-26.23%, -15.21)	Corneal vs. Non-corneal	0.0336
Non-corneal	-27.20% (-30.48%, -23.93)		

* Type III analysis of ANOVA for Day 1 Corneal Edema and Surgeon's Specialty.

This analysis was repeated to further examine which baseline and operative factors might have had an effect on endothelial cell loss from baseline to 3 months specifically in those eyes that lost more than 20% in ECD. The same steps as were used for the Logistic Regression Model were applied for this analysis, and results of the model fitting are shown in Appendix Table A40A. As before, the final model identified Day 1 corneal edema and surgeon specialty as the two factors associated with a higher percentage of subjects reported with a loss in ECD of ≥ 20% at 3 months.

18.4.8 EFFECT OF 3-MONTH ECD LOSS ON OVERALL LOSS OF ECD

Having identified factors contributing to endothelial cell loss at 3 months, the time point at which the most significant loss in ECD from baseline was reported, an additional analysis was performed to determine whether patients with greater endothelial cell loss at 3 months were at risk for greater ongoing loss of ECD. To this end, change in ECD between consecutive postoperative visits was stratified by 3-month ECD $\leq$ 20% and > 20%, and by 3-month ECD $\geq$1000 cells/mm^2 and ECD <1000 cells/mm.^{2}

As shown in Table 41, significant differences in endothelial cell loss were observed between eyes with 3 month ECD of $\leq$ 20% as compared to eyes with 3 month ECD > 20% through 12 months. However, no difference was observed between the two groups of eyes from 18 months to 24 months postoperatively, suggesting that greater endothelial cell loss at 3 months is not predictive of continued greater loss at 2 years.

Similarly, stratification of change in ECD over the course of the study by 3-month loss in ECD of $\leq$1000 cells/mm^2 versus >1000 cells/mm^2 showed no difference in endothelial cell loss between 9 to 12 months, 12 to 18 months, or 18 to 24 months (Table 42). Thus, higher levels of endothelial cell loss at 3 months are not predictive of greater endothelial cell loss at later visits.

TABLE 41
PERCENTAGE CHANGE IN ECD BETWEEN CONSECUTIVE POSTOPERATIVE VISITS STRATIFIED BY ECD PERCENT LOSS FROM BASELINE AT 3 MONTHS OF ≤ 20% VS > 20%
ALL EYES IMPLANTED WITH IMT

Percentage Change	3 Months to 6 Months	6 Months to 9 Months	9 Months to 12 Months	12 Months to 18 Months	18 Months to 24 Months
Eyes with ECD % Loss from Baseline ≤ 20% at 3 Months					
N	114	109	108	107	87
Mean (SD)	-4.9% (10.1%)	-1.8% (12.1%)	0.0% (16.0%)	-0.2% (13.9%)	-2.7% (11.8%)
90% confidence interval for mean	-6.5%, -3.4%	-3.7%, 0.1%	-2.5%, 2.6%	-2.4%, 2.0%	-4.9%, -0.6%
Median	-4.0%	-0.1%	-1.5%	-0.7%	-2.0%
Range	-51.4%, 29.7%	-43.2%, 41.9%	-33.9%, 76.1%	-44.1%, 54.1%	-34.4%, 32.8%
Eyes with ECD % Loss from Baseline > 20% at 3 Months					
N	73	71	65	62	51
Mean (SD)	0.9% (19.1%)	-3.6% (18.5%)	-2.7% (11.9%)	3.5% (21.9%)	-1.7% (14.7%)
90% confidence interval for mean	-2.9%, 4.6%	-7.2%, 0.1%	-5.1%, -0.2%	-1.1%, 8.2%	-5.1%, 1.7%
Median	0.9%	-3.3%	-2.3%	1.8%	-2.7%
Range	-48.2%, 54.6%	-37.5%, 61.0%	-37.0%, 21.7%	-30.1%, 113.8%	-24.2%, 60.8%
Wilcoxon Test for Comparing ECD % Change Between Two Subgroups					
P-value	***0.0010***	0.1127	0.7815	0.4214	0.7609

Enrolled eyes without an IMT implant were excluded. Eyes without data on ECD at 3 months were also excluded.
N = number of successful IMT implanted eyes with non-missing ECD change in the corresponding visit period.
Percentage change in ECD between two visits = (later postop visit - previous postop visit) ÷previous postop visit ×100. A negative value means a reduction and a positive value means an increase.
% = n ÷N ×100

TABLE 42
PERCENTAGE CHANGE IN ECD BETWEEN CONSECUTIVE POSTOPERATIVE VISITS STRATIFIED BY ECD AT 3 MONTHS OF ≤ 1000 CELLS/MM^2 VS > 1000 CELLS/MM^2 ALL EYES IMPLANTED WITH IMT

Percentage Change	3 Months to 6 Months	6 Months to 9 Months	9 Months to 12 Months	12 Months to 18 Months	18 Months to 24 Months
Eyes with ECD ≥1000 at 3 Months					
N	173	167	161	156	127
Mean (SD)	-2.8% (14.0%)	-1.9% (14.5%)	-1.0% (14.9%)	1.1% (15.0%)	-2.7% (12.4%)
90% confidence interval for mean	-4.5%, -1.0%	-3.8%, -0.1%	-2.9%, 0.9%	-0.9%, 3.1%	-4.5%, -0.9%
Median	-2.6%	-0.9%	-1.6%	0.9%	-2.7%
Range	-51.4%, 54.6%	-43.2%, 61.0%	-37.0%, 76.1%	-44.1%, 55.0%	-34.4%, 60.8%
Eyes with ECD <1000 at 3 Months					
N	14	13	12	13	11
Mean (SD)	-1.2% (21.1%)	-10.0% (18.4%)	-0.9% (10.8%)	2.2% (35.7%)	1.4% (18.0%)
90% confidence interval for mean	-11.2%, 8.8%	-19.1%, -0.9%	-6.5%, 4.7%	-15.4%, 19.9%	-8.4%, 11.3%
Median	-1.1%	-17.8%	-0.9%	-2.6%	1.5%
Range	-44.9%, 34.1%	-28.3%, 41.7%	-17.1%, 15.5%	-30.1%, 113.8%	-24.2%, 43.2%
Wilcoxon Test for Comparing ECD % Change Between Two Subgroups					
P-value	0.4247	***0.0103***	0.8883	0.1442	0.3455

Enrolled eyes without an IMT implant were excluded. Eyes without data on ECD at 3 months were also excluded.
N = number of successful IMT implanted eyes with non-missing ECD change in the corresponding visit period.
Percentage change in ECD between two visits = (later postop visit - previous postop visit) ÷previous postop visit ×100. A negative value means a reduction and a positive value means an increase.
% = n ÷N ×100

18.4.9 ECD <1,000 CELLS/MM^2

A total of 29 IMT-implanted eyes had ECD of less than 1,000 cells/mm^2 reported at any postoperative visit. As shown in Table 43, the majority of eyes with ECD < 1000 cells/mm^2 (65.5% or 19/29) had Day 1 edema with a grade of 2+ or more, as compared to only 18.6% (33/177) of the IMT-implanted eyes with ECD greater than 1000 cells/mm.^{2} The difference in distribution of corneal edema graded as normal/1+ edema and $\geq$2 + edema for the two groups of eyes with ECD <1000 cells/mm^2 and eyes with ECD $\geq$ 1000 cells/mm^2 was statistically significant (p<0.0001).

TABLE 43
DAY 1 CORNEAL STATUS OF NORMEAL/1+ EDEMA AND ≥ 2+ EDEMA VERSUS IMT IMPLANTED EYES WITH ECD < 1000 CELLS/MM^2 AND IMT IMPLANTED EYES WITHOUT ECD < 1000 CELLS/MM^2

Day 1 Corneal Status	IMT Eyes with ECD < 1000† N= 29	IMT Eyes without ECD < 1000 N=177
Normal/1+ Edema	10/29 (34.5%)	144/177 (81.4%)
≥ 2+ Edema	19/29 (65.5%)	33/177 (18.6%)
Fisher's Exact p-value	<.0001	

† IMT eyes reported with ECD < 1000 at <u>any</u> postoperative visits.

A review of the patient profiles for the subgroup of eyes with ECD of less than 1,000 cells/mm^2 indicated that a relatively large number of these eyes had reports of iris-related adverse events/complications such as iris damage, iris prolapse, iris atrophy, iritis, iris incarceration, and/or flat anterior chamber or anterior chamber shallowing. A comparison of the incidence of flat or shallow anterior chamber or iris-related events in eyes with and without ECD of < 1,000 cells/mm^2 is shown in Table 44. This comparison confirmed that these complications occurred at a higher frequency in eyes with ECD < 1,000 cells/mm^2 than in eyes with ECD $\geq$ 1,000 cells/mm^2, i.e., 9/29 (31.0%) vs. 21/177 (15.3%). Although this difference is of only borderline statistical significance (p = 0.06), it suggests that these complications, largely reported in the early postoperative period and all related to surgery, constitute a contributing factor in the significant cell loss in this subgroup of eyes. This finding also supports the important role of training in the implantation procedure for the IMT, as a means of minimizing the occurrence of these events.

TABLE 44
FLAT ANTERIOR CHAMBER OR IRIS RELATED SAFETY EVENTS VERSUS IMT IMPLANTED EYES WITH ECD < 1000 CELLS/MM^2 AND IMT IMPLANTED EYES WITHOUT ECD < 1000 CELLS/MM^2

Safety Event Status	IMT Eyes with ECD < 1000† N= 29	IMT Eyes without Reporting ECD < 1000 N=177
With Flat Anterior Chamber or Iris Related Safety Events*	9/29 (31.0%)	27/177 (15.3%)
Without Flat Anterior Chamber or Iris Related Safety Events	20/29 (69.0%)	150/177 (84.7%)
Fisher's Exact p-value	0.0606	

* Includes iris atrophy, iris damage, iris incarceration, iris prolapse, and iritis.
† IMT eyes reported with ECD < 1000 at <u>any</u> postoperative visits.

Information for the 29 eyes with postoperative ECD < 1000 cells/mm^2 at any visit is summarized in Table A42A, which provides a line listing for these eyes.

18.4.10 ADDITIONAL ANALYSES OF ECD

Additional analyses of endothelial cell density were performed and are found in Appendix A, as follows.

Mean ECD and percentage change in ECD stratified by Day 1 corneal edema, ACD, surgical order, incision type, incision size, surgeon's specialty, patient's age at implant, preoperative ECD, surgeon, axial length, and use of the viscoelastic Healon V during IMT implantation are provided in Tables A27A thought A27K (mean ECD) and in A29A through A29K (percentage change).

In order to evaluate the decrease in ECD after 3 months, the generalized estimating equation (GEE) modeling technique was performed. GEE considered ECD percentage changes at different visits for an eye as repeated measurements of the eye and treated the repeated measurements as correlated responses in the analyses. The results of the GEE analysis on ECD from 3 to 24 months for all eyes implanted with IMT are summarized in Table A36A and for the 24-month consistent cohort in Table A36B.

At 3 and 6 months, ECD was significantly different from the 18-month results, but the 9 and 12-month ECD data were not significantly different from the results at 18-month data. These modeling results show that following the significant reduction in ECD at 3 months due to implantation of the IMT, the reduction in ECD stabilizes between 9 and 12 months. However, the 24-month mean ECD is statistically significantly different from the 18-month mean ECD. It should be noted that based on the GEE analyses, the mean ECD at 18 months is larger than that at 12 months. This unexplainable increase might influence the change from 18 months to 24 months.

Percentage change in ECD between consecutive postoperative visits are summarized in Appendix Tables A31A through A31D for all eyes implanted with IMT, for the 24-month consistent cohort of eyes implanted with IMT, for fellow eyes of subjects implanted with IMT, and for pseudophakic fellow eyes of subjects implanted with the IMT respectively.

Tables A37A and A37B summarize the annual ECD percentage change estimated based on records between 9 to 24 months for fellow eyes and for pseudophakic fellow eyes of subjects implanted with the IMT respectively. Table A38A provides the annual ECD percentage change estimated based on records between 9 to 24 months stratified by clinically important factors.

18.5 OCULAR COMPLICATIONS

Any event directly related to the surgical procedure required for implantation of the IMT, and occurring in the operative and immediate postoperative period was defined as an ocular complication for eyes with successful or unsuccessful IMT implantation, i.e., those eyes in which the IMT could not be implanted. Ocular complications are shown in Table 45 for eyes not successfully implanted with the IMT and in Table 46 for IMT-implanted eyes. Table 46 shows complications for all regularly scheduled visits, as well as for all unscheduled interim visits, and include events reported at visits following postoperative IMT removal. The cumulative incidence of each complication is also displayed in Table 46.

As shown in Table 46, the most prevalent complication reported for the study population consisted of increased IOP requiring treatment within the first week after surgery, with 50 cases (24.3%) reported at Day 1 and 14 cases (6.8%) reported at Day 7. Reports of increased IOP requiring treatment occurring beyond 7 days were classified as adverse events and are shown in Table 48. Increased IOP requiring treatment was transient and occurred largely within the first week following IMT implantation, with only a few eyes presenting with IOP requiring treatment at 1 month or beyond. This acute increase in IOP was likely associated with the use of high molecular weight viscoelastic material (Healon V) both in the eye and to coat the IMT.

Other commonly reported complications following IMT implantation were corneal edema, iris prolapse, corneal abrasions, hyphema, and iris damage. A total of 14 (6.8%) cases of corneal edema occurring within 30 days of surgery were reported; all cases of corneal edema were first reported on postoperative Day 1 and only three cases of corneal edema were noted at the 1 month visit. Six cases of corneal edema were reported beyond 1 month and were considered as adverse events (Table 48).

Iris prolapse was observed in 12 eyes, with the majority reported within 7 days of IMT implantation. Eleven (5.3%) cases of corneal abrasion were reported, however, this finding resolved early and without sequelae. Ten (4.9%) cases of hyphema were reported, eight at Day 1 and three at Day 7. Seven eyes (3.4%) had iris damage. Seven eyes (3.4%) were also reported with iris transillumination defects. The majority of complications were transient in nature, as supported by the reduction in frequency of these events over time.

TABLE 45
REPORTED OCULAR COMPLICATIONS
EYES WITH IMT NOT SUCCESSFULLY IMPLANTED

Complications	Operative N = 11	Day 1 N = 11	Day 7 N = 10	1 Month N = 11	3 Months N = 6	6 Months N = 2	9 Months N = 0	12 Months N = 2	18 Months N = 0	24 Months N = 0	Interim N = 4	Cumulative N = 11
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Aborted surgery	5 (45.5%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	5 (45.5%)
Choroidal detachment	2 (18.2%)	1 (9.1%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	2 (18.2%)
Choroidal hemorrhage	1 (9.1%)	1 (9.1%)	1 (10.0%)	1 (9.1%)	1 (16.7%)	0 (0.0%)		0 (0.0%)			1 (25.0%)	1 (9.1%)
Cortical remnants	1 (9.1%)	1 (9.1%)	1 (10.0%)	1 (9.1%)	1 (16.7%)	0 (0.0%)		0 (0.0%)			1 (25.0%)	1 (9.1%)
Increased IOP requiring treatment ≤ 7 days	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			1 (25.0%)	2 (18.2%)
Iris damage	1 (9.1%)	1 (9.1%)	1 (10.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			1 (25.0%)	1 (9.1%)
Iritis ≤ 30 days	0 (0.0%)	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
Posterior capsular rupture	7 (63.6%)	2 (18.2%)	2 (20.0%)	1 (9.1%)	1 (16.7%)	1 (50.0%)		0 (0.0%)			1 (25.0%)	7 (63.6%)
Vitreous hemorrhage ≤ 7 days	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
Vitreous loss	2 (18.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	2 (18.2%)
Vitreous loss - vitrectomy required	6 (54.5%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	6 (54.5%)
Wound leak	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
Zonular dehiscence ≤ 7 days	1 (9.1%)	1 (9.1%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			1 (25.0%)	1 (9.1%)

% = n/N ×100.
The same complication could have been reported for a subject at multiple visits.

TABLE 46
REPORTED OCULAR COMPLICATIONS
ALL EYES IMPLANTED WITH IMT

Complications	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anterior chamber hemorrhage	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Anterior segment neovascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Anterior synechiae	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	3 (1.5%)
Bleb	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Blepharitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	2 (1.1%)	3 (2.0%)	2 (1.8%)	7 (3.4%)
Blurred vision	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Cataract	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Cataract removal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.0%)
Chalazion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	2 (1.0%)
Conjunctival injection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (1.9%)
Corneal abrasion	0 (0.0%)	3 (1.5%)	4 (2.0%)	4 (1.9%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	11 (5.3%)
Corneal edema ≤ 30 days	0 (0.0%)	14 (6.8%)	7 (3.4%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	14 (6.8%)
Corneal endothelial touch	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Cortical remnants	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Cyclitic membrane ≤ 7 days	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Cyclodialysis cleft	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	1 (0.5%)
Descemet's membrane separation	3 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Disc hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Dry eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	2 (1.4%)	0 (0.0%)	3 (1.5%)
Ectropion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Endothelial folds	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.9%)	2 (1.0%)
Flat anterior chamber ≤ 21 days	2 (1.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Folds in corneal graft	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Glaucoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	1 (0.5%)
Haze	0 (0.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	2 (1.8%)	2 (1.0%)

% = n/N ×100.
The same complication could have been reported for a subject at multiple visits.

TABLE 46 *(CONTINUED)*
REPORTED OCULAR COMPLICATIONS
ALL EYES IMPLANTED WITH IMT

Complications	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hypertony	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Hyphema	0 (0.0%)	8 (3.9%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	10 (4.9%)
Hypotony	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	2 (1.8%)	2 (1.0%)
Increased IOP requiring treatment ≤ 7 days	0 (0.0%)	50 (24.3%)	14 (6.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	57 (27.7%)
Increased IOP ≤ 15 days	0 (0.0%)	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Iridotomy ≤ 7 days	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Iris atrophy ≤ 7 days	0 (0.0%)	3 (1.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)
Iris damage	7 (3.4%)	5 (2.4%)	5 (2.4%)	5 (2.4%)	5 (2.5%)	5 (2.5%)	5 (2.6%)	4 (2.1%)	4 (2.2%)	3 (2.0%)	1 (0.9%)	7 (3.4%)
Iris incarceration	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Iris prolapse	6 (2.9%)	3 (1.5%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	12 (5.8%)
Iris transillumination defects ≤ 21 days	0 (0.0%)	4 (1.9%)	6 (2.9%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.4%)
Iritis ≤ 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Keratitic precipitates on IMT	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Ophthalmic migraine	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Other*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
Peribulbar hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Peripapillary hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Phthisis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (0.5%)
Posterior capsular rupture	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Posterior capsule opacification	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (0.5%)
Retinal detachment	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Significant anterior chamber bleeding	3 (1.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Strabismus surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Superficial punctate keratitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Surgical mydriasis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)

% = n/N ×100.
The same complication could have been reported for a subject at multiple visits.
* hematuria/hospitalization

TABLE 46 *(CONTINUED)*
REPORTED OCULAR COMPLICATIONS
ALL EYES IMPLANTED WITH IMT

Complications	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Suture rupture	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	4 (1.9%)
Uveitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Vitreous bulge	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vitreous in anterior chamber ≤ 7 days	0 (0.0%)	0 (0.0%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)
Vitreous loss	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vitreous loss - vitrectomy required	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Watery eyes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (1.1%)	3 (2.0%)	1 (0.9%)	3 (1.5%)
Worsening cataract (fellow eye)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Worsening of subretinal scarring	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Wound leak	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)

% = n/N ×100.
The same complication could have been reported for a subject at multiple visits.

18.6 OCULAR ADVERSE EVENTS

Ocular adverse events for eyes not successfully implanted with the IMT are summarized in Table 47. Ocular adverse events reported for all eyes implanted with an IMT are summarized by visit in Table 48, which displays adverse events for all regularly scheduled visits, unscheduled interim visits, and all visits for study subjects following postoperative IMT removal. The cumulative incidence of each adverse event is also provided.

As shown, only 2 (1.0%) operative adverse events were reported in eyes implanted with an IMT. These adverse events consisted of an IMT with condensation on the device and an IMT with a broken haptic, both of which required replacement. These are further described in section 18.7, Device Failures.

The most commonly reported adverse event in this clinical trial consisted of inflammatory deposits on the IMT. Over the course of the study, this was reported for a total of 51 (24.8%) eyes. Pigment deposits on the IMT were reported in 23 (11.2%) of the study eyes. Neither the inflammatory deposits nor the pigment deposits on the IMT affected visual acuity. Guttae were reported in 16 eyes (7.8%). In decreasing order of incidence, posterior synechiae were reported for 15 eyes (7.3%) and iritis at 30 days or later was reported for 12 eyes (5.8%). Iris transillumination defects observed after postoperative day 21 have been reported for 11 eyes (5.3%) in total, dry eye was reported for 10 eyes (4.9%), and subconjunctival hemorrhage and foreign body sensation were reported for 9 eyes each (4.4%). Iris atrophy, distorted pupil, and increased IOP requiring treatment were reported for 7 eyes (3.4%) each. Anterior chamber inflammation and corneal edema reported 30 days or more after surgery were observed in six eyes each (2.9%).

The IMT was removed from 8 eyes during the postoperative period. Four subjects (008-207, 008-208, 010-206, 012-210) requested removal of the IMT since they were dissatisfied with the device; in 2 of these 4 eyes, visual acuity was improved from baseline and in the other 2 eyes, visual acuity had decreased from baseline. The IMT was removed from two eyes (013-202, 023-217) due to condensation of the telescope portion of the IMT (see Section 18.7: Device Failure). Removal of the IMT was also performed in the eyes (013-209, 031-203) that underwent corneal transplantation as a result of corneal decompensation. Preoperative and last available BCDVA for eyes that underwent IMT removal are shown on the following page.

PREOPERATIVE AND LAST AVAILABLE BCDVA
EYES THAT UNDERWENT POSTOPERATIVE IMT REMOVAL (N = 8)

PtID	Preop BCDVA (LogMAR)	Last Available BCDVA (LogMAR)	Comments
008-207	20/320 (1.20)	20/289 (1.16)	Patient was dissatisfied with IMT
008-208	20/219 (1.04)	20/240 (1.08)	Patient was dissatisfied with IMT
010-206	20/381 (1.28)	CF	Patient was dissatisfied with IMT Last available BCDVA was reported on the day of IMT removal
012-210	20/276 (1.14)	20/145 (0.86)	Patient was dissatisfied with IMT
013-202	20/348 (1.24)	-	Postoperative IMT removal due to device failure (condensation). No BCDVA reported post IMT removal.
013-209	20/303 (1.18)	20/219 (1.04)	Postoperative IMT removal due to corneal decompensation.
023-217	20/348 (1.24)	20/458 (1.36)	Postoperative IMT removal due to device failure (condensation).
031-203	20/551 (1.44)	20/1000 (1.70)	Postoperative IMT removal due to corneal decompensation. Last available BCDVA was reported 8 days post IMT removal

The two eyes that underwent corneal transplantation are further described as follows:

In Patient 013-209, during implantation of the IMT of WA 3.0X in the left eye there was spontaneous prolapse of the superior iris, which prevented visualization of the capsular bag. The IMT was placed in the ciliary sulcus, and at the end of the procedure, the IMT was in place with moderate depth of the anterior chamber. The superior iris was atrophic due to the prolapse and did not constrict with a miotic agent. At the 1 month visit, endothelial cell density had decreased to 633.3 cells/mm^2 and there were no other ophthalmic findings. Over the course of additional follow-up, visual acuity improved, however, endothelial cell density further decreased to 463.3 cells/mm^2 at 9 months. At the 9 month visit, corneal decompensation was diagnosed, and corneal transplantation was performed. Surgery and postoperative recovery were uneventful, and at 6 months following transplantation, slit lamp examination revealed normal cornea, normal endothelium, no cells and no flare in the anterior chamber. Intraocular pressure was 15 mmHg. Distance visual acuity was approximately 20/220 (LogMAR 1.04).

In Patient 31-203, intraoperatively, positive vitreous pressure resulted in iris prolapse. On the first postoperative day, intraocular pressure was increased, and the inferior aspect of the IMT was covered by the inferior iris. Over the course of follow-up, the IMT was observed to be decentered inferiorly, with one of the haptics in the sulcus

rather than in the capsular bag. Over the next several months, the patient's visual acuity gradually deteriorated and cornea edema worsened. At 6 months, endothelial cell density had decreased to 385.3 cells/mm^2 and corneal edema was present. A decision was made to perform a corneal transplantation. During the corneal transplant procedure, the surgeon attempted to reposition the IMT and noticed that one of the haptics was in the sulcus and the other in the bag. When attempting removal of the haptic from the sulcus, the posterior capsule ruptured. Subsequently an anterior chamber IOL was inserted. Postoperatively, no complications were reported and the eye was quiet, with normal IOP and appearance of the cornea during slit lamp examination.

All remaining adverse events were reported at a frequency of 2.0% or less. With the exception of inflammatory deposits and pigment deposits on the IMT, guttae, and iris findings (posterior synechiae, iris atrophy, transillumination defects), the incidence of adverse events at 12, 18, and 24 months was low, indicating that most adverse events resolved over time.

The Patient ID for eyes in which the IMT was not successfully implanted are provided in Table A47A in Appendix A; subject IDs are provided for all implanted eyes in Table A48A. Detailed data line listings are provided in Tables A47B and A48B for all adverse events reported in these study cohorts.

Case summaries for each of the serious or significant adverse events may be found in Appendix B of this clinical report. A patient profile presenting complete data for each of these study subjects is provided in Appendix C.

TABLE 47
REPORTED OCULAR ADVERSE EVENTS
EYES WITH IMT NOT SUCCESSFULLY IMPLANTED

Adverse Events	Operative N = 11	Day 1 N = 11	Day 7 N = 10	1 Month N = 11	3 Months N = 6	6 Months N = 2	9 Months N = 0	12 Months N = 2	18 Months N = 0	24 Months N = 0	Interim N = 4	Cumulative N = 11
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Distorted pupil	0 (0.0%)	2 (18.2%)	1 (10.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	2 (18.2%)
Floaters	0 (0.0%)	1 (9.1%)	1 (10.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
IMT dislocation	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
IMT removal	6 (54.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	6 (54.5%)
Iris atrophy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)			0 (0.0%)	1 (9.1%)
Iris transillumination defects	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		1 (50.0%)			0 (0.0%)	2 (18.2%)
Subretinal hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	1 (16.7%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)
Zonular dehiscence > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)	0 (0.0%)	0 (0.0%)		0 (0.0%)			0 (0.0%)	1 (9.1%)

% = n/N ×100.
The same adverse event could have been reported for a subject at multiple visits.

TABLE 48
REPORTED OCULAR ADVERSE EVENTS
ALL EYES IMPLANTED WITH IMT

Adverse Events	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Anterior chamber inflammation > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	3 (1.7%)	0 (0.0%)	3 (2.8%)	6 (2.9%)
Anterior ischemic optic neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Choroidal neovascularization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)	2 (1.1%)	2 (1.4%)	0 (0.0%)	5 (2.4%)
Conjunctivitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	4 (1.9%)
Corneal decompensation > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Corneal edema > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	3 (2.0%)	2 (1.8%)	6 (2.9%)
Cyclitic membrane > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Cystoid macular edema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Decrease in visual acuity	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.1%)	3 (2.0%)	2 (1.8%)	4 (1.9%)
Device failure	1 (0.5%)	2 (1.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Diplopia	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	2 (1.8%)	3 (1.5%)
Distorted pupil	0 (0.0%)	1 (0.5%)	3 (1.5%)	3 (1.5%)	3 (1.5%)	5 (2.5%)	4 (2.0%)	4 (2.1%)	4 (2.2%)	2 (1.4%)	3 (2.8%)	7 (3.4%)
Dry eye	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	6 (3.1%)	4 (2.1%)	3 (1.7%)	1 (0.7%)	4 (3.7%)	10 (4.9%)
Entropion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Exposed suture	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (2.8%)	3 (1.5%)
Eye pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	1 (0.6%)	1 (0.7%)	3 (2.8%)	3 (1.5%)
Flat anterior chamber > 21 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	0 (0.0%)	1 (0.5%)
Floaters	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	2 (1.0%)
Focal striae	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Foreign body sensation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (1.0%)	4 (2.0%)	4 (2.0%)	4 (2.1%)	4 (2.2%)	1 (0.7%)	7 (6.4%)	9 (4.4%)
Guttae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	7 (3.5%)	8 (4.1%)	13 (6.7%)	11 (6.1%)	9 (6.1%)	3 (2.8%)	16 (7.8%)
IMT dislocation	0 (0.0%)	0 (0.0%)	2 (1.0%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
IMT removal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (7.3%)	8 (3.9%)
IMT replacement	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Increased IOP requiring treatment > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	2 (1.4%)	3 (2.8%)	7 (3.4%)

% = n/N ×100.

The same adverse event could have been reported for a subject at multiple visits.

TABLE 48 (CONTINUED)
REPORTED OCULAR ADVERSE EVENTS
ALL EYES IMPLANTED WITH IMT

Adverse Events	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Inflammatory deposits on IMT	0 (0.0%)	2 (1.0%)	9 (4.4%)	2 (1.0%)	5 (2.5%)	18 (8.9%)	21 (10.7%)	25 (12.9%)	24 (13.3%)	10 (6.8%)	6 (5.5%)	51 (24.8%)
Inflammatory membrane	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	1 (0.5%)
Iridotomy > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Iris atrophy > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1.9%)	4 (2.0%)	4 (2.0%)	3 (1.5%)	6 (3.1%)	7 (3.9%)	7 (4.7%)	2 (1.8%)	7 (3.4%)
Iris transillumination defects > 21 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	9 (4.5%)	9 (4.5%)	9 (4.6%)	8 (4.1%)	8 (4.4%)	6 (4.1%)	2 (1.8%)	11 (5.3%)
Iritis > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	4 (2.2%)	1 (0.7%)	7 (6.4%)	12 (5.8%)
Keratic precipitates on IMT > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.9%)	2 (1.0%)
Obstructed iridectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Ocular allergy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Pigment deposits on IMT	0 (0.0%)	1 (0.5%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	4 (2.0%)	12 (6.1%)	12 (6.2%)	13 (7.2%)	7 (4.7%)	4 (3.7%)	23 (11.2%)
Pigment epithelium around the peripheral iridectomy > 30 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Posterior synechiae	0 (0.0%)	0 (0.0%)	4 (2.0%)	4 (1.9%)	7 (3.5%)	9 (4.5%)	8 (4.1%)	8 (4.1%)	7 (3.9%)	4 (2.7%)	4 (3.7%)	15 (7.3%)
Ptosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Secondary glaucoma	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Subconjunctival hemorrhage	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (5.5%)	9 (4.4%)
Subretinal hemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.7%)	1 (0.9%)	3 (1.5%)
Synechiae	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Tearing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Visual disturbance	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Vitreous flare	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Vitreous hemorrhage > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (1.5%)
Vitreous in anterior chamber > 7 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	4 (1.9%)

% = n/N ×100.
The same adverse event could have been reported for a subject at multiple visits.

18.7 DEVICE FAILURES

A total of four device failures have been reported in this 24-month study. Two failures involved a broken haptic. One case occurred prior to implantation and one occurred during implantation, requiring intraoperative IMT replacement. The two other device failures consisted of condensation in the telescope portion of the IMT, and resulted in postoperative IMT removal. Case summaries for each of these eyes if provided in Appendix B, in Appendix B.8 (intraoperative IMT removal) and in Appendix B.9 (postoperative IMT removal).

18.8 NON-OCULAR ADVERSE EVENTS

All non-ocular adverse events for the study subjects are summarized in Table 49. A total of 12 subjects (5.8%) were diagnosed with cancer, and four of these subjects died of cancer. Six additional subjects died during the course of the study; the causes of death included pneumonia, cardiac arrest, natural causes and congestive heart failure. Infection and pneumonia were reported for 6 subjects each, arrhythmia and CVA/TIA were reported for 5 subjects each, and bronchitis, ulcer and hypertension were reported for 4 subjects each.

TABLE 49
REPORTED NON-OCULAR ADVERSE EVENTS

Events	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Abdominal problems	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Angiography-3 stents	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Arrhythmia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	1 (0.9%)	5 (2.4%)
Blood in stool	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Bradycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Bronchitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	2 (1.4%)	0 (0.0%)	4 (1.9%)
CVA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
CVA-TIA	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (1.8%)	4 (1.9%)
Cancer	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	2 (1.1%)	1 (0.7%)	5 (4.6%)	12 (5.8%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Carotid surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Chest pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Cholecystectomy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Confusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Congestive heart failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Contusion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (9.2%)	10 (4.9%)
Decreased mobility	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Depression	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.0%)
Diabetes	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)
Facial nerve paralysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Fractured femur	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Fractured heel bone	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Fractured toe	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Fractured wrist	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)

% = n/N ×100.
The same event could have been reported for a subject at multiple visits.

TABLE 49 (CONTINUED)
REPORTED NON-OCULAR EVENTS

Events	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Headache	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	2 (1.0%)
Hearing loss	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Hip replacement	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Hospitalization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Hypercholesterolemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	2 (1.8%)	4 (1.9%)
Hypotension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Incontinence	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.6%)	1 (0.7%)	2 (1.8%)	6 (2.9%)
Inguinal hernia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Kidney stones	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Knee replacement	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (1.5%)
Leg pain	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Myocardial infarction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	3 (1.5%)
Other*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (1.5%)	3 (1.5%)	2 (1.1%)	5 (3.4%)	10 (9.2%)	21 (10.2%)
Oxycontin overdose	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Pansinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Parkinson's disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Periorbital bruising	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Pneumonia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (4.6%)	6 (2.9%)
Renal failure	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)
Ruptured pseudoaneurysm	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Scalp hematoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Sepsis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Shingles	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	2 (1.0%)

% = n/N ×100.

The same event could have been reported for a subject at multiple visits.

* Including abdominal aorta stent placed, acute diverticulitis, bad reaction to Advil, benign prostate hypertrophy, bone transplant lower gum, carpal tunnel surgery in right hand, combined prostate & bladder surgical procedure & hospitalization, enlarged prostate, gallstones - pain, hernia surgery, hospitalization: unknown etiology fever, hospitalized for chest pain, hospitalized for chest pain; ischemic heart disease w/ angina, irritable bowel syndrome, open heart surgery, osteoporosis, peripheral vascular disease, pinched nerve in back, pulled back muscle, rupture of varicose vein upper lip, screw removal from elbow post fracture, septal deviation, sexually assault, and hematuria.

TABLE 49 (CONTINUED)
REPORTED NON-OCULAR EVENTS

Events	Operative N = 206	Day 1 N = 206	Day 7 N = 205	1 Month N = 206	3 Months N = 201	6 Months N = 202	9 Months N = 196	12 Months N = 194	18 Months N = 180	24 Months N = 148	Interim N = 109	Cumulative N = 206
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Shortness of breath	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0 (0.0%)	1 (0.5%)
Sinusitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	1 (0.9%)	1 (0.5%)
Spinal stenosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Syncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Trauma due to fall	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	3 (1.5%)
UTI	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)	1 (0.5%)
Ulcer	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)	4 (1.9%)

% = n/N ×100.
The same event could have been reported for a subject at multiple visits.

19.0 SUMMARY & CONCLUSIONS

This study report describes the results of the first prospective, multicenter clinical trial of an implantable miniature telescope, VisionCare's Wide Angle Implantable Miniature Telescope (IMT™ by Dr. Isaac Lipshitz), a visual prosthetic device for use in patients with moderate to profound central vision loss resulting from late-stage dry, atrophic (geographic atrophy) or end stage CNV (disciform scar).

At the time of database lock for this report, in July 2005, follow-up was available for 194 eyes at 12 months, 180 eyes at 18 months, and 148 eyes at 24 months. Accountability, i.e., the proportion of eyes eligible for the examination window and not discontinued or lost to follow-up, was excellent, ranging from 100% at 6 months to 95.5% at 24 months. Only 16 subjects have been discontinued from the study, 10 due to death and the remaining 6 following IMT removal. Given the mean age of 75.4 years (SD 7.2, range 55-93 years), this level of accountability is particularly significant, and aids in establishing the reliability of the study results and conclusions.

19.1 EFFECTIVENESS OUTCOMES

The study protocol prospectively defined both effectiveness and safety endpoints. The primary effectiveness endpoint was defined as an improvement of ≥ 2 lines in either near or distance best corrected acuity in at least 50% of the implanted eyes at 12 months post-implantation. This endpoint was based on the anticipation that the IMT would provide patients with improvement in either near or distance vision, not both. However, the clinical benefit of the IMT in the study population significantly exceeded these expectations, with 90% of eyes at 12 months and 86% of eyes at 24 months achieving a gain of ≥ 2 lines in either near or distance best corrected acuity ($p<0.0001$). Even less expected was the very large proportion of eyes that achieved a gain of ≥ 2 lines and ≥ 3 lines of both best corrected distance and near acuity (BCDVA and BDNVA). A gain of ≥ 2 lines BCDVA and BCNVA was reported for 73% of eyes at 12 months, and 67% of eyes at 24 months. Approximately 50% of eyes experienced a gain of ≥ 3 lines of BCDVA and BCNVA from 12 through
24 months of follow-up.

The gain in lines of best corrected distance acuity and best corrected near acuity was also substantial for each measure considered separately. A gain of 2 or more lines of BDCVA was reported for 80% of eyes at 12 months, 79% of eyes at 18 months and 74% of eyes at 24 months. Approximately 60% of eyes gained ≥ 3 lines of BCDVA, 40% of eyes gained ≥ 4 lines of BCDVA, 20% of eyes gained ≥ 5 lines of BCDVA and 10% of eyes gained ≥ 6 lines of BCDVA at the 12, 18 and 24 month visits.

Similar gains in best corrected acuity were observed for measurements made at near. A gain of ≥ 2 lines of BCNVA at either 8 or 16 inches was observed for 83% of eyes at 12 months, and in 80% of eyes at 18 and 24 months. A gain of ≥ 3 lines of

BCNVA at 8 or 16 inches was observed in approximately 65% of eyes at 12, 18 and 24 months. Close to 50% of eyes gained ≥ 4 lines of BCNVA, approximately 25% of eyes had a gain of ≥ 5 lines of BCNVA and about 10% of eyes had a gain of ≥ 6 lines of BCNVA at 12, 18 and 24 months.

Improvement in visual acuity for the study population is summarized in Table 50.

TABLE 50
SUMMARY OF IMPROVEMENT IN VISUAL ACUITY
ALL EYES IMPLANTED WITH IMT

IMPROVEMENT IN VISUAL ACUITY	12 MONTHS (n,%)	18 MONTHS (n,%)	24 MONTHS (n,%)
≥ 2 LINES GAIN OF BCDVA *OR* BCNVA	173 (90.1%)	156 (87.2%)	147 (85.7%)
≥ 2 LINES GAIN OF BCDVA *AND* BCNVA	141 (73.4%)	127 (70.9%)	99 (67.3%)
≥ 3 LINES GAIN OF BCDVA *AND* BCNVA	102 (52.8%)	89 (49.7%)	75 (51.0%)
BCDVA LINES GAINED			
≥ 2 LINES GAIN OF BCDVA	155 (80.3%)	141 (78.8%)	108 (73.5%)
≥ 3 LINES GAIN OF BCDVA	128 (66.3%)	112 (62.6%)	86 (58.5%)
≥ 4 LINES GAIN OF BCDVA	87 (45.1%)	74 (41.3%)	62 (42.2%)
≥ 5 LINES GAIN OF BCDVA	49 (25.4%)	42 (23.5%)	29 (19.7%)
≥ 6 LINES GAIN OF BCDVA	21 (10.9%)	18 (10.1%)	13 (8.8%)
BCNVA LINES GAINED			
≥ 2 LINES GAIN OF BCNVA	159 (82.8%)	142 (79.3%)	117 (79.6%)
≥ 3 LINES GAIN OF BCNVA	130 (67.7%)	117 (65.4%)	96 (65.3%)
≥ 4 LINES GAIN OF BCNVA	94 (49.0%)	87 (48.6%)	71 (48.3%)
≥ 5 LINES GAIN OF BCNVA	55 (28.6%)	41 (22.9%)	40 (27.2%)
≥ 6 LINES GAIN OF BCNVA	24 (12.5%)	17 (9.5%)	15 (10.2%)

This improvement in lines of distance and near acuity was achieved in all age groups across all visits, and for both of the IMT models, WA 2.2X and WA 3.0X. Of even greater importance was the finding that patients with the most severe visual impairment at the time of entry into the study had the most significant benefit from IMT implantation. This was demonstrated by examining visual acuity outcomes for eyes with moderate impairment (20/80 to 20/160), severe impairment (20/161 to 20/400) and profound impairment (worse than 20/400). While all three categories of preoperative visual acuity easily surpassed the overall protocol specified overall effectiveness endpoint, or success rate, of 50% at 12, 18 and 24 months, eyes with profound visual impairment preoperatively showed a higher success rate at 12, 18, and 24 months than eyes with moderate impairment at baseline.

Not surprisingly, these substantial improvements in best corrected distance acuity and best corrected near visual acuity were reflected in quality of life measurements, a secondary effectiveness outcome evaluated in the study population through 12 months. The VFQ-25, a validated 25-item version of the NEI Vision Function Questionnaire (VFQ),[5] measures vision-targeted health status for persons with chronic eye diseases including macular degeneration.[6] The VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question which is an independent component and not part of the composite or individual subscales. A score of 50 represents 50% of the highest possible score.[7] A five (5) point difference in subscale and/or composite scores is generally considered to be clinically significant.[8] The Activities of Daily Life questionnaire is a modified version of the Activities of Daily Vision Scale (ADVS),[9] a validated survey that has been broadly used for assessing the impact of visual impairment due to cataract and related vision disorders.[10]

At 12 months, a clinically significant improvement (>5 points) in the VFQ-25 subscales of general vision, near activities, and distance activities was observed in the study population; these subscales have been described as particularly important in demonstrating the impact of bilateral severe AMD on performance of daily activities dependent on central vision.[12] Additionally, clinically significant improvements across all vision specific subscales (social functioning, mental health, role difficulties, and dependency) were reported. In subscales where no improvement or a decline in performance was expected (color vision, driving and peripheral vision), performance was stable or declined. Also at 12 months, the VFQ-25 overall composite scores, which represent the average of the subscale scores, excluding the general health rating question, increased by 6.0 points (95% C.I. 4.0 to 8.1); this improvement is considered a clinically significant finding.

The most significant point change in the quality of vision subscales was reported for general vision, which increased by 14.1 points, followed by near vision activities (increase 11.1 points) and distance vision activities (increase 7.9 points). While there was a small decrease in the point change for general vision over the 12 month follow-up period, the point change remained relatively stable for near vision activities.

Improvement in the vision specific activities subscales of the VFQ-25 was most substantial at 3 and 6 months, perhaps reflecting the noticeable change from baseline in best corrected acuity experienced by the majority of study subjects. There was a slight decrease in the point change for social functioning and mental health at 9 months, however, for the most part the values reported remained relatively stable over time for all subscales.

To examine the effect of baseline characteristics on the improvement in quality of life, the VFQ-25 composite score from baseline to 12 months was stratified by gender, patient's age at time of entry into the study, IMT model (WA 2.2X and WA 3.0X), preoperative BCDVA and improvement in visual acuity at 12 months. There was no effect of baseline characteristics or of the 12-month visual acuity on the VFQ composite score ($p>0.05$). This suggests a very broad effect of the IMT on improvement in the VFQ-25 composite score, irrespective of baseline factors, and is consistent with the substantial improvement in distance or near visual acuity, or both measures of acuity achieved by the study population.

The mean score for general health subscale, which is not a component of the vision specific subscales or the composite score, declined by 5.1 points. This likely reflects the impact of other health-related events on the general health of the elderly study population, since it is recognized that general quality of life measures decrease with increasing age.[11]

Consistent with the improvement in VFQ-25 scores, mean ADL scores also improved from baseline through 12 months. Subscale improvement for near and distance activities as measured by both the ADL and VFQ-25 questionnaires were consistent and appreciable, as were composite scores for both of these instruments. There was a statistically significant relationship between change in VFQ-25 composite score and change in ADL total score at each postoperative examination (i.e., $p < 0.0001$ at 3, 6, 9 and 12 months).

19.2 SAFETY OUTCOMES

The safety endpoints defined for the clinical trial of the IMT consisted of preservation of best corrected visual acuity, endothelial cell loss and the incidence of complications and adverse events.

Preservation of Best Corrected Acuity

The safety parameter of preservation of best corrected visual acuity established in the study protocol consisted of a limit of $\leq$10% of implanted eyes with a loss of >2 lines of either distance or near (8"and 16") BCVA without a corresponding improvement in the other measure of acuity. Thus, the overall visual acuity safety endpoint consists of the sum of the following three categories:

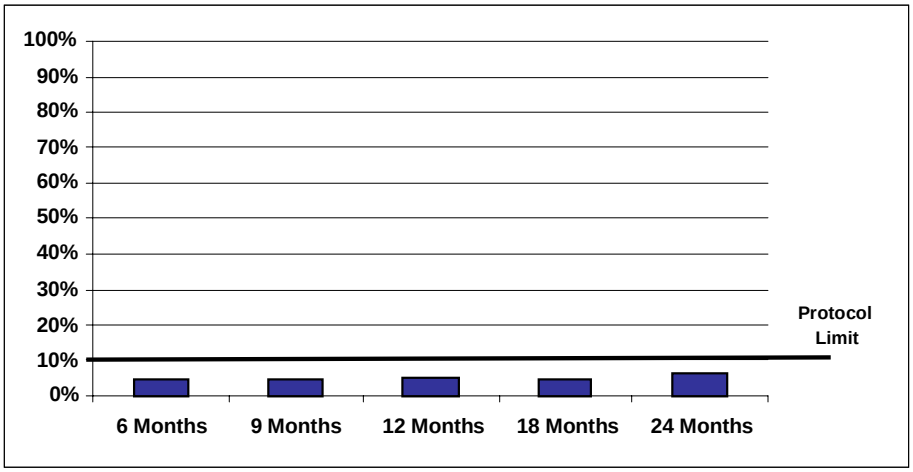
1) The proportion of eyes with >2 lines loss of BCDVA and no change in BCNVA

2) The proportion of eyes with >2 lines loss of BCNVA and no change in BCDVA
3) The proportion of eyes with >2 lines loss of BCDVA and BCNVA.

The proportion of eyes with >2 lines loss of BCDVA and no change/loss of BCNVA, or >2 lines loss of BCNVA and no change/loss of BCDVA, was 5% at 12 and 18 months, and 6% at 24 months. The binominal exact p-value for the alternative hypothesis testing safety rate of <10% was <0.05 at the 6, 9, 12, and 18 month follow-up visits, and 0.0696 at the 24 month follow-up visit, indicating that the results were well below the 10% limit established in the study protocol.

As shown in Figure 6, the number of subjects that experienced a loss of >2 lines of either near or distance BCVA without a corresponding improvement (gain of 2 lines or more) in the other measure of BCVA was well below the safety limit of 10%, establishing excellent preservation of visual acuity in the study population.

FIGURE 6 SAFETY – PRESERVATION OF VISUAL ACUITY
PROPORTION OF EYES WITH
> 2 LINES LOSS OF BCDVA AND NO CHANGE/LOSS OF BCNVA
OR
> 2 LINES LOSS OF BCNVA AND NO CHANGE/LOSS OF BCDVA



Only a very small number of subjects lost >2 lines of both BCDVA and BCNVA, i.e., 1.0% at 12 months, 1.1% at 18 months and 1.4% at 24 months; this represents only 4 eyes of the total study population.

Importantly, associated with the greater benefit to eyes with the most profound visual impairment, a smaller number of these eyes experienced a loss of >2 lines of distance or near acuity without a commensurate gain at 24 months. Thus, at 24 months, more eyes with moderate impairment at baseline than eyes with profound impairment had a

loss of >2 lines of near or distance vision without a commensurate gain. This is an important consideration in patient selection for the IMT, and serves to mitigate concerns on the part of both patients and physicians regarding the risk of additional loss of acuity in patients with the greatest loss of vision from AMD. In fact, the data presented in this report suggest that patients with the most severe visual loss from AMD experience the greatest benefit, with a lower risk of loss of lines of acuity.

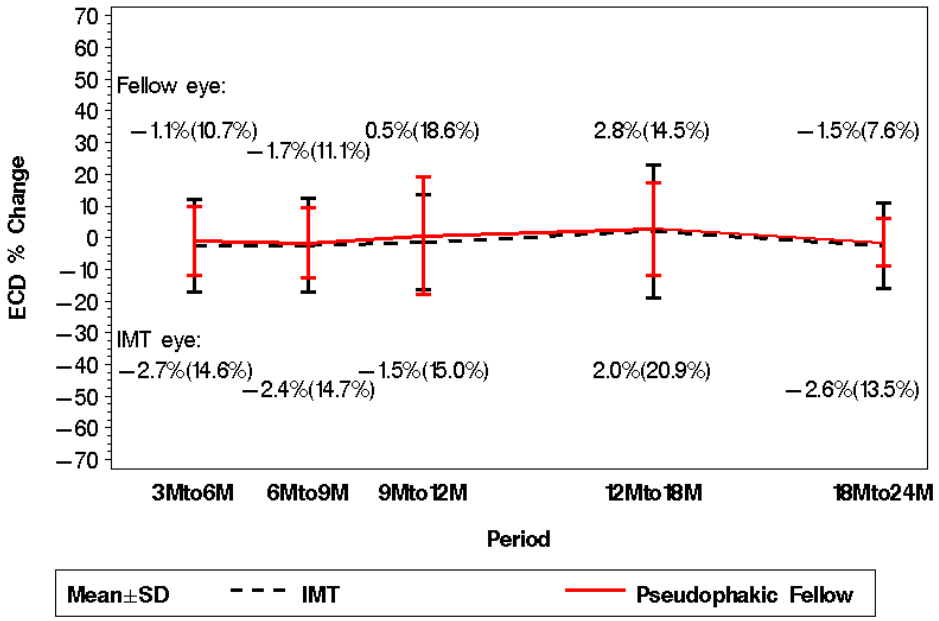
Endothelial Cell Density

As described in this report, to evaluate change in endothelial cell density (ECD) over time, specular microscopy was performed preoperatively and at the Month 3, 6, 9, 12, 18 and 24 examinations in both the operated eyes and fellow eyes. Mean ECD, distribution of mean ECD, and percentage change in ECD in the IMT implanted eyes alone and as compared to fellow eyes and pseudophakic fellow eyes were presented.

The most significant decrease in ECD occurred between baseline and 3 months, with a mean change from baseline to 3 months of 20.0%, increasing slightly to 22.4% at 6 months and to 24.4% at 9 months, then changing only minimally to 25.3% from baseline to 12 months and 25.2% baseline to 18 months. A slightly larger percent loss in ECD was observed from baseline to 24 months, i.e., 28.2%. Thus, the mean decrease in endothelial cell density for the total population of study eyes was somewhat higher than the target of identified in the study protocol, i.e., a loss of less than or equal to 17% at one year post IMT implantation. However, mean percentage change in ECD between consecutive postoperative visits was -2.7% between 3 and 6 months, -2.4% between 6 to 9 months, -1.5% between 9 to 12 months, +2.0% between 12 to 18 months, and -2.6% between 18 to 24 months. Thus, the reduction in ECD was most pronounced at 3 months following IMT implantation, and remained generally stable at later postoperative examinations.

As shown in Figure 12, the change in ECD for the cohort of pseudophakic fellow eyes was similar to that observed in the IMT implanted eyes, and no statistically significant differences in change in ECD between visits were observed between IMT implanted and pseudophakic fellow eyes. Given that the implantation procedure for an IMT is more demanding than for a standard intraocular lens, the absence of differences in change in ECD over time between IMT-implanted and pseudophakic fellow eyes is encouraging.

FIGURE 12
MEAN AND STANDARD DEVIATION OF ECD PERCENTAGE CHANGE BETWEEN CONSECUTIVE POSTOPERATIVE VISITS
EYES IMPLANTED WITH IMT VS PSEUDOPHAKIC FELLOW EYES



VisionCare originally estimated an endothelial cell loss of 17% at 3 months postoperative, stabilizing over the remainder of the patient follow-up. Since IMT implantation requires a 10-12 mm incision, or 5-8 mm larger than is needed for standard cataract surgery, even with a non-foldable lens, a greater percentage loss of endothelial cells was anticipated, compared with standard cataract surgery. The estimate of 17% endothelial cell loss was based on a review of published studies on endothelial cell loss following large incision cataract surgery, in which this range of cell loss was identified.[13-18] A wide range of loss in ECD has been reported, with older reports describing higher levels of endothelial cell loss; this may have been related to the use of larger incisions and larger IOLs than currently employed. However, these findings are likely more representative of the surgical technique used for implantation of the IMT, since a large incision is required and the IMT is appreciably larger than either early or currently available intraocular lenses. For example, in a study of PMMA and silicone plate lenses, endothelial cell loss ranged from 16% to 25% following surgery through a 5.0 mm incision, an incision considerably smaller than that required for insertion of an IMT.[16] Similar findings were described by Liesegang et al, who reported endothelial cell loss ranging from 11.2% to 16.4% at 8 weeks, increasing to as high as 20% at 1 year.[17] In a small study of corneal endothelial morphology after anterior chamber lens implantation,

endothelial cell loss averaged 25%, and changes in endothelial morphology persisted more than one year after intracapsular cataract extraction.[19]

It is noteworthy that two more recent publications[20,21] on endothelial cell loss following cataract surgery, in relatively large series of patients, suggest relatively higher levels of endothelial cell loss than have been previously reported for modern cataract surgery with phacoemulsification.[22,23] In a study of modern phacoemulsification compared with extracapsular cataract surgery, the most significant loss of ECD was observed at 3 months, however ECD continued to decline over the one-year study follow-up. Mean endothelial cell loss at 1 year was approximately 10%, however, after adjusting for age and preoperative ECD using statistical modeling, adjusted mean percent loss in ECD was 14% for ECCE (extracapsular cataract extraction) and 16% for phacoemulsification. Age was associated with higher percent loss in endothelial cell density at one year.[20]

In a comparison of cataract surgery performed using clear corneal incision (CCI) versus scleral tunnel, Beltrame et al reported percent loss in ECD at 3 months of 17% for 3.5 mm clear corneal incisions, 22% for 5.5 mm CCI, and 17% for scleral tunnel incisions.[21] At 12 months, the percent change in ECD had increased to 20%, 24% and 19% for 3.5 mm CCI, 5.5 mm CCI and scleral tunnel incisions, respectively. Endothelial cell loss was similar in 13 study subjects who underwent cataract surgery in the fellow eye during the course of the current study, with a mean loss in ECD of 15.2% (range +2.1% to –55.5%), based on change from the most recent visit prior to surgery to the first available visit after surgery.

Analyses performed to evaluate the effect of various clinical parameters on postoperative ECD identified Day 1 corneal edema and surgeon's specialty as the two factors associated with a higher percentage of subjects reported with a loss in ECD of $\geq$ 20% at 3 months. Further analyses demonstrated that higher levels of endothelial cell loss at 3 months were not predictive of greater endothelial cell loss at later visits. This is an encouraging safety consideration, since endothelial cell loss over time was not affected by 3 month loss in ECD. This is also supported by published literature indicating that initial endothelial cell loss is not predictive of later loss.[24] The impact of surgeon's specialty on endothelial cell loss is another key safety consideration, and underscores the need for surgeon training. This will be addressed with a mandatory surgeon training program to be implemented by VisionCare.

Complications and Adverse Events

The most commonly reported adverse event in this clinical trial consisted of inflammatory deposits and pigment deposits on the anterior surface of the IMT. Neither the inflammatory deposits nor the pigment deposits on the IMT affected visual acuity. Discussion with the study medical monitor and several of the clinical investigators confirmed that these findings were not visually significant, and it was suggested that dilation of the pupil to prevent contact between the anterior surface of the IMT and the iris would be effective in preventing this event.

Other events were reported at an incidence of < 10%. With the exception of inflammatory deposits and pigment deposits on the IMT, guttae, and iris findings (posterior synechiae, iris atrophy, transillumination defects), the incidence of adverse events at 12, 18, and 24 months was low, indicating that most adverse events resolved over time.

The most serious adverse events consisted of an intraoperative choroidal hemorrhage and two cases of corneal decompensation requiring penetrating keratoplasty. The occurrence of a choroidal hemorrhage was not unanticipated, given the size of the incision required to implant the IMT, and the relatively long surgery time. Study surgeons were advised to minimize surgical time, or specifically the time during which the incision was open. In both cases of corneal decompensation, the corneal transplantation was uneventful and the clinical outcomes were good. The company notified all participating clinical sites and institutional review boards, as well as FDA, of the risk of corneal decompensation and choroidal hemorrhage with IMT implantation. To date, no additional cases of corneal decompensation or choroidal hemorrhage have been reported.

The IMT was removed from 8 eyes during the postoperative period, with half of these explants (4 of 8) requested by the study subjects based on dissatisfaction with the device; in 2 of these 4 eyes, visual acuity was improved from baseline and in the other 2 eyes, visual acuity had decreased from baseline. Two implants were removed due to condensation of the telescope portion of the IMT, and from the two eyes that underwent corneal transplantation as a result of corneal decompensation. Implant removal was uneventful in all cases.

As would be expected in this elderly population, a number of non-ocular adverse events have been reported, including 12 subjects who were diagnosed with cancer, four of which resulted in death. Six additional subjects died during the study, with cause of death identified as pneumonia, stroke, cardiac arrest, congestive heart failure, and natural causes.

19.3 CONCLUSIONS

In this prospective multicenter clinical trial of the VisionCare IMT for patients with moderate to profound visual loss resulting from end-stage AMD, effectiveness outcomes significantly exceeded the predefined targets identified in the study protocol. The majority of subjects (approximately 75%) achieved an improvement in best corrected distance acuity of at least 2 lines, with over 60% of eyes gaining 3 or more lines of acuity, 40% gaining 4 or more lines, 20% experiencing a gain of 5 or more lines of distance vision and 10% of eyes achieving a 6-line gain in BCDVA. Similar gains in lines of acuity were achieved for near vision at both 8 and 16 inches. Importantly, loss of acuity was limited to only a very small number of eyes that lost both best corrected distance and near acuity.

With respect to safety, the incidence of complications and adverse events was relatively low, with only a small number of serious adverse events reported over the course of the study. While endothelial cell loss in the IMT-implanted eyes was greater than anticipated, the extensive analyses of change in ECD over the course of the study established the surgical procedure for implantation of the IMT as the single most significant contributor to loss in ECD. The most significant decrease in ECD was observed at 3 months, after which ECD remained relatively stable. Most importantly, there were no statistically significant differences in percent change in ECD between consecutive visits through 24 months when comparing endothelial cell loss of the IMT-implanted eyes to pseudophakic fellow eyes.

The magnitude of endothelial cell loss and the improvement in visual acuity and quality of life/activities of daily living should be considered and contrasted with the safety profile for other, therapeutic intraocular procedures intended to provide patients with visual rehabilitation. Full-thickness penetrating keratoplasty (PKP) is one such procedure. Notwithstanding the significant loss of endothelial cell density,[25,26] full-thickness penetrating keratoplasty is considered the standard of care for visual rehabilitation in a number of indications, including keratoconus, corneal scars or dystrophy, and pseudophakic bullous keratopathy. In a recent report[25] comparing autografts vs. allografts, endothelial cell loss following traditional PKP was 40% (SD 21.34%) after 1 year in a population of 293 patients. Mean improvement in visual acuity was substantial at 3.5 lines. In a longitudinal study of 10-year findings after PKP, endothelial cell loss was 67% (SD 18%) over the 10-year follow-up period, and the rate of endothelial cell loss from 5 years to 10 years was identified as approximately 4.2% per year.[26]

The outcomes of this clinical trial were intended to support a Premarket Application for the IMT, and this study report presents a body of data that describes the benefits as well as the risks of this device. The significant gain in lines of best corrected visual acuity both at distance as well as at near, and the clear translation of this improvement in vision to a clinically important improvement in quality of life, when

taken together with the safety profile for the device establish a very favorable overall risk/benefit ratio. Based on these study outcomes, safety and effectiveness of the IMT have been clearly established in this population of elderly patients suffering from moderate to profound central vision loss associated with end-stage AMD.

20.0 REFERENCES

1. O'Neill C, Jamison J, McCulloch D, Smith D. Age-related macular degeneration: cost-of-illness issues. Drugs & Aging 2001;18:233-41.
2. Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, Peiffer A, Zabriskie NA, Li Y, Hutchinson A, Dean M, Lupski JR, Leppert M. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science 1997;277:1805-7.
3. Brody BL, Gainst AC, Wiliams RA, Smith AR, Lau PW, Dolnak D, Rapaport MH, Kaplan RM, Brown SI. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. Ophthalmology 2001;108:1893-1900.
4. Stelmack J. Quality of life of low-vision patients and outcomes of low-vision rehabilitation. Optom Vis Sci 2001;78:335-42.
5. Mangione CM, Lee PP, Gutierrez P, Spritzer K, Berry S, Hays RD. Development of the 25-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol. 2001;119:1050-8.
6. Clemons TE, Chew EY, Bressler SB, McBee W. National Eye Institute Visual Function Questionnaire in age-related eye disease study (AREDS). Arch Ophthalmol 2003;21:211-7.
7. Mangione CM, Lee PP, Pitts J, Gutierrez P, Berry S, Hays RD. Psychometric properties of the National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 1998;116:1496-1504.
8. Globe DR, Wu J, Azen SP, Varma R. The impact of visual impairment on self-reported visual functioning in Latinos. Ophthalmology 2004;111:1141-9.
9. Mangione CM, Phillips RS, Seddon JM, Lawrence MG, Cook EF, Dailey R, Goldman. Development of the Activities of Daily Vision Scale. A measure of visual functional status. Med Care 1992;30:1111-26.
10. Mangione CM, Orav EJ, Lawrence MG, Phillips RS, Seddon JM, Goldman L. Prediction of visual function after cataract surgery. A prospectively validated model. Arch Ophthalmol 1995;113:1305-11.
11. Martin DC. A randomized controlled open trial of population-based disease and case management in a Medicare plus choice health maintenance organization. Prev Chronic Dis 2004;1:A05.
12. Cahill MT, Banks AD, Stinnett SS, Banks AD, Freedman SF, Toth CA. Vision-Related Quality of Life in Patients with Bilateral Severe Age-Related Macular Degeneration. Ophthalmology, 2005:112:152-8.

13. Bourne WM, Waller RR, Liesegang TJ, Brubaker RF. Corneal trauma in intracapsular and extracapsular cataract extraction with lens implantation. Arch Ophthalmol 1981;99:1375-1376.

14. Heuermann T, Hartmann C, Anders N. Journal of Cataract and Refractive Surgery 2002;28:639-643.

15. Kraff MC, Sanders DR, Lieberman HL. Monitoring for continuing endothelial cell loss with cataract extraction and intraocular lens implantation. Ophthalmology 1982;89:30-34.

16. Levy JH, Pisacano AM. Clinical endothelial cell loss following phacoemulsification and silicone or polymethylmethacrylate lens implantation. J Cataract Refract Surg 1988;14:299-302.

17. Liesegang TJ, Bourne WM, Ilstrup DM. Short- and long-term endothelial cell loss associated with cataract extraction and intraocular lens implantation. Am J Ophthalmol 1984;97:32-39.

18. Oxford Cataract Treatment and evaluation Team (OCTET). Long-term corneal endothelial cell loss after cataract surgery. Results of a randomized controlled trial. Arch of Ophthalmol 1986;104:1170-1175.

19. Glasser DB, Matsuda M, Gager WE, Edelhauser HF. Corneal endothelial morphology after anterior chamber lens implantation. Arch Ophthalmol 1985;103:1347-1349.

20. Bourne RA, Minassian DC, Dart KG, Rosen P, Kaushal S, Wingate N. Effect of cataract surgery on the corneal endothelium: Modern phacoemulsification compared with extracapsular cataract surgery. Ophthalmology 2004;111:679-685.

21. Beltrame G, Salvetat M, Druissi G, Chizzolini M. Effect of incision size and site on corneal endothelial changes in cataract surgery. J Cataract Refract Surg 2002;22:118-125.

22. Diaz-Valle D, Benilez del Castillo Sanchez JM, Castillo A et al. Endothelial damage with cataract surgery techniques. J Cataract Refract Surg 1998;24:951-955.

23. Dick HB, Kohnen T, Jacobi FK, Jacobi KW. Long-term endothelial cell loss following phacoemulsification through a temporal clear corneal incision. J Cataract Refract Surg 1996;22:63-71.

24. Bourne WM, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology 1994;101:1014-1022; discussion by A Sugar, 1022-1023.

Formatted: Italian (Italy)

Formatted: German (Germany)

25. Bertelmann E, Hartmann C, Scherer M, Rieck P. Outcome of rotational keratoplasty. Comparison of endothelial cell loss in autografts vs. allografts. Arch Ophthalmol 2004;122:1437-1440.

26. Ing JJ, Ing HH, Nelson LR, Hodge DO, Bourne WM. Ten-year postoperative results of penetrating keratoplasty. Ophthalmology 1998;105:1855-1865.

Formatted: German (Germany)