OPHTHALMIC DEVICES PANEL
EXECUTIVE SUMMARY

TRULIGN™ TORIC ACCOMMODATING POSTERIOR CHAMBER INTRAOCULAR LENS (21 CFR 886.3600 INTRAOCULAR LENS)

INDICATION: FOR PRIMARY IMPLANTATION IN THE CAPSULAR BAG OF THE EYE FOR VISUAL CORRECTION OF APHAKIA AND POSTOPERATIVE REFRACTIVE ASTIGMATISM SECONDARY TO REMOVAL OF A CATARACTOUS LENS IN ADULT PATIENTS WITH OR WITHOUT PRESBYOPIA, WHO DESIRE IMPROVED UNCORRECTED DISTANCE VISION AND REDUCTION OF RESIDUAL REFRACTIVE CYLINDER. TRULIGN TORIC PROVIDES APPROXIMATELY ONE DIOPTER OF MONOCULAR ACCOMMODATION WHICH ALLOWS FOR NEAR, INTERMEDIATE, AND DISTANCE VISION WITHOUT SPECTACLES.

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TABLE OF CONTENTS

1.0 Executive Overview 7
2.0 Introduction 15
3.0 Trulign Toric Accommodating Intraocular Lens 18
3.1 Device Description 18
3.2 Proposed Indication for Use 19
4.0 Summary of Nonclinical Studies 20
4.1 Biocompatibility and Toxicologic Testing 20
4.2 Chemical Testing 20
4.3 Optical/Mechanical Testing 20
4.4 Sterilization, Packaging, and Shelf-Life 21
4.4.1 Sterilization 21
4.4.2 Packaging 21
4.4.3 Shelf-Life 21
5.0 Clinical Study 650 22
5.1 Study Design and Plan 22
5.1.1 Rotational Stability 22
5.1.2 Subject Eligibility 23
5.1.2.1 Inclusion Criteria 23
5.1.2.2 Exclusion Criteria 23
5.1.3 Study Materials and Methods 24
5.1.3.1 Test and Control Devices 24
5.1.3.2 Treatment Assignment 24
5.1.3.3 Toric Calculator 24
5.1.3.4 Surgical Procedure 25
5.1.3.5 Clinical Assessments 25
5.1.3.6 Concomitant Therapy 26
5.1.4 Study Endpoints 26
5.1.4.1 Safety Endpoints 26
5.1.4.2 Effectiveness Endpoints 26
5.1.5 Statistical Methods 27
5.1.5.1 Statistical Analysis 27
5.1.5.2 Sample Size Determination 28
5.2 Study Subjects 29
5.2.1 Disposition and Accountability of Subjects 29
5.2.2 Protocol Deviations 30
5.2.3 Analysis Populations 33
5.2.4 Demographics 34
5.3 Safety 35
5.3.1 Safety Outcomes 35
5.3.1.1 Preservation of Best-Corrected Visual Acuity 35
5.3.1.2 Adverse Events 36
5.3.1.3 Serious Adverse Events 39
5.3.1.4 Other Safety Analyses 39

5.3.2 Safety Conclusions....41
5.4 Effectiveness....42
5.4.1 Surgical Parameters....42
5.4.2 Effectiveness Outcomes....42
5.4.2.1 Percent Reduction in Cylinder....42
5.4.2.2 Percentage of Eyes With Reduction in Cylinder Within 0.50 D and 1.00 D of Intended Reduction in Cylinder....43
5.4.2.3 Lens Axis Misalignment as Determined by a Photographic Method....43
5.4.2.4 Absolute Rotation Since Implantation....44
5.4.2.5 Rotational Stability Between Consecutive Visits....45
5.4.2.6 Best-Corrected Distance Visual Acuity Without Glare....45
5.4.2.7 Distance-Corrected Intermediate Visual Acuity at 32 Inches (80 cm)....46
5.4.2.8 Near Visual Acuity With Distance Correction at 16 Inches (40 cm) With and Without the Minimal Reading Add....47
5.4.2.9 Uncorrected Distance, Intermediate, and Near Visual Acuity....48
5.4.2.10 Manifest and Cycloplegic Refraction....52
5.4.2.11 Lens Decentration and Tilt....54
5.4.2.12 Visual Disturbances From Subject Questionnaire....54
5.4.2.13 Comparison Between UCIVA/UCNVA and DCIVA/DCNVA....55
5.4.2.14 Summary of Mean UCDVA, UCIVA, and UCNVA....55
5.4.3 Effectiveness Conclusions....55
6.0 Risk-Benefit Assessment....56
6.1 Risks of Trulign Toric Accommodating IOL....56
6.2 Benefits of Trulign Toric Accommodating IOL....57
6.3 Risk-Benefit Summary....58
7.0 Overall Conclusions....59
8.0 References....60
9.0 Appendix: Global Clinical Experience....63
9.1 Effectiveness....63
9.2 Safety....64

LISTING OF IN-TEXT TABLES

Table 1 Specifications of Astigmatism-Correcting Toric Intraocular Lenses Available in the United States....17
Table 2 Optical/Mechanical Tests Performed and Passed....21
Table 3 Trulign Toric Accommodating IOL Cylinder Power....24
Table 4 Subject Disposition (All Enrolled Cohort)....29
Table 5 Subject Accountability by Each Scheduled Visit (All Enrolled Cohort)....30
Table 6 Summary of Protocol Deviations....31
Table 7 Statistical Impact of Protocol Deviations and Conservative Imputation on Effectiveness....32
Table 8 Demographics of Study Population (All Enrolled Cohort)....35
Table 9 BCDVA at Each Examination (All Toric IOL; Safety Cohort)....35
Table 10 BCNVA at Each Examination (All Toric IOL; Safety Cohort)....36

Table 11 Frequency of Surgical Adverse Events, Implanted Subjects (Safety Cohort) 36
Table 12 FDA Grid Cumulative Adverse Events Reported at Each Postoperative Visit (Control IOL; Safety Cohort) 38
Table 13 FDA Grid Cumulative Adverse Events Reported at Each Postoperative Visit (All-Toric IOL; Safety Cohort) 38
Table 14 Dilated Assessment of PCO Grade—Forms 3 and 4 (Postoperative Days 30 – 60 and 120 – 180; Safety Cohort) 40
Table 15 Nd:YAG Capsulotomy (Safety Cohort) 40
Table 16 Intraocular Pressure—Preoperative Visit and Form 4 (Postoperative Days 120 – 180; Safety Cohort) 41
Table 17 Surgical Parameters (Effectiveness Cohort) 42
Table 18 Percent Reduction in Absolute Cylinder Expressed as Percentage of Intended Reduction in Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 43
Table 19 Percent of Eyes With Reduction in Cylinder Within 0.50 D and 1.00 D of Intended Reduction in Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 43
Table 20 Absolute Lens Axis Misalignment From Surgical Markings and Target—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 44
Table 21 Absolute Rotation Since Implantation—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 45
Table 22 Rotational Stability Between Consecutive Visits—Form 4 (Postoperative Days 120 – 180; Consistent Cohort) 45
Table 23 BCDVA Without Glare—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 46
Table 24 DCIVA at 32 inches (80 cm)—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 46
Table 25 DCNVA at 16 inches (40 cm)—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 47
Table 26 DCNVA at 16 inches (40 cm) With Add—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 48
Table 27 UCDVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 49
Table 28 UCIVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 49
Table 29 UCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 50
Table 30 UCDVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 50
Table 31 UCIVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 50
Table 32 UCNVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 51
Table 33 Manifest Refraction Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 53
Table 34 Manifest Refraction Spherical Equivalent—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 53
Table 35 Lens Decentration and Tilt—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort) 54

Table 36 Subjects Experiencing ≥ 1 Significant Visual Disturbances—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort).....54
Table 37 Comparison Between UCIVA/UCNVA and DCIVA/DCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort).....55
Table 38 Summary of Mean UCDVA, UCIVA, and UCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort).....55
Table 39 Reduction in Reported Vaulting Incidence 66

LISTING OF IN-TEXT FIGURES

Figure 1 Crystalens Five-O Accommodating Intraocular Lens.....15
Figure 2 Trulign Toric Accommodating Intraocular Lens. 19
Figure 3 Number of Subjects Included in Each Analysis Cohort.....34

ABBREVIATIONS AND DEFINITIONS

Abbreviation/Acronym	Term/Definition
AE	adverse event
ANSI	American National Standards Institute
AT45	Bausch+Lomb model number for parent Crystalens Accommodating IOL (P030002)
AT50SE	Bausch+Lomb model number for Crystalens Accommodating IOL (Control) with diopter powers +17.00 D and above
AT50T	Bausch+Lomb model number for Trulign Toric Accommodating IOL (Test) with diopter powers +17.00 D and above
AT52SE	Bausch+Lomb model number for Crystalens Accommodating IOL (Control) with diopter powers +16.50 D and below
AT52T	Bausch+Lomb model number for Trulign Toric Accommodating IOL (Test) with diopter powers +16.50 D and below
BCVA	best-corrected visual acuity
BCDVA	best-corrected distance visual acuity
BCNVA	best-corrected near visual acuity
CI	confidence interval
Crystalens Toric IOL	name of subject device during development
D	diopter(s)
DCVA	distance-corrected visual acuity
DCIVA	distance-corrected intermediate visual acuity
DCNVA	distance-corrected near visual acuity
DFU	directions for use
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Council on Harmonisation
IDE	Investigational Device Exemption
IOL	intraocular lens
IOP	intraocular pressure
ISO	International Organization for Standardization
LASIK	laser in-situ keratomileusis
LRI	limbal relaxing incision
MRSE	manifest refraction spherical equivalent
Nd:YAG	neodymium:yttrium-aluminum-garnet

Abbreviation/Acronym	Term/Definition
PCO	posterior capsule opacity
PMA	Premarket Approval
PRK	photorefractive keratectomy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SIA	surgically induced astigmatism
SSI	secondary surgical intervention
Trulign	Proposed trade name for subject device
UCDVA	uncorrected distance visual acuity
UCIVA	uncorrected intermediate visual acuity
UCNVA	uncorrected near visual acuity
UCVA	uncorrected visual acuity
US	United States
UVAM	Silicone Elastomer with Benzotrialzole UV absorber [redacted]

1.0 EXECUTIVE OVERVIEW

Background

The Trulign™ Toric Accommodating Posterior Chamber Intraocular Lens (IOL; hereafter Trulign Toric Accommodating IOL) is a modification of the Crystalens Accommodating Posterior Chamber IOL (hereafter Crystalens Accommodating IOL) approved in November 2003 by the United States (US) Food and Drug Administration (FDA) under Premarket Approval (PMA) Application P030002. The Study 650 clinical plan was submitted to Investigational Device Exemption (IDE) [redacted] on March 22, 2010 and approved on April 23, 2010.

Since 2003, more than 315,000 eyes have been implanted worldwide with the Crystalens Accommodating IOL. Designed to reduce spectacle dependence following cataract surgery by correcting defocus and presbyopia, the Crystalens Accommodating IOL has a demonstrated record of safety and effectiveness. However, patients with natural corneal astigmatism who select the Crystalens Accommodating IOL with the counsel of their surgeon have presented a particular challenge.

Corneal astigmatism is very common, both in the general population and among patients presenting for cataract surgery.[1-5] According to one study, corneal astigmatism between 0.25 diopter (D) and 1.25 D occurred in 64.4% of cataract patients, and corneal astigmatism greater than 1.50 D occurred in an additional 22.2% of patients.[6] Another recent study of 23,239 eyes reported corneal astigmatism of more than 1.00 D in 36% of eyes, with a mean magnitude of 0.98 D.[7]

The concern for patients with preexisting corneal astigmatism who select the Crystalens Accommodating IOL is the presence of significant residual corneal astigmatism after cataract surgery and its association with decreased uncorrected visual acuity (UCVA) and patient dissatisfaction. Therefore, in order to minimize residual astigmatism, improve UCVA, and decrease spectacle dependence, these patients generally require a second surgical procedure. These secondary procedures often accompany or follow cataract extraction and IOL implantation, and include refractive surgical procedures such as corneal relaxing incisions, laser in situ keratomileusis (LASIK), and photorefractive keratectomy (PRK).

These secondary surgical procedures pose challenges of their own. A recent publication described some of the limitations of these modalities as follows[8]:

> "Limbal relaxing incisions, wedge resections, and manually created arcuate keratotomy are technically challenging procedures that are often associated with unpredictable results and complications, such as wound gape associated with epithelial ingrowth into the incisions and, occasionally, a full thickness corneal perforation. In addition to these procedures, PRK and LASIK have been studied for the management of corneal astigmatism but are limited in the predictability of outcomes and are fraught with some well-described complications."

Given the prevalence of astigmatism among cataract patients, the Crystalens patient population requiring secondary procedures for astigmatism correction has been sizable. Furthermore, these

secondary procedures have met with mixed results. Therefore, it has become desirable to incorporate a toric design for the correction of astigmatism into the Crystalens Accommodating IOL, thus reducing or eliminating the need for secondary surgical procedures.

Clinical Perspective: *The risks and benefits specifically associated with the addition of a toric optical correction to an approved accommodating lens platform and described in this summary should be weighed in light of the risks and benefits associated with the ancillary procedures currently performed for the correction of astigmatism in conjunction with accommodating lens implantation (e.g., LRI and LASIK).*

Trulign Toric Accommodating Intraocular Lens

The Trulign Toric Accommodating IOL (Models AT50T/AT52T), which was developed as an option for the safe and effective correction of postoperative refractive astigmatism, is a modified version of the currently approved Crystalens Five-O (spherical) Accommodating IOL (Models AT50SE/AT52SE). The only difference between the lens models is the toric posterior optic surface and axis marks on the anterior surface of the Trulign Toric Accommodating IOL. The test lens has an overall diameter of 11.5 mm (Model AT50T) or 12.0 mm (Model AT52T) and an optic body diameter of 5.0 mm, with a spherical dioptric power range of 4.00 D to 33.00 D (in 0.50-D increments). The Trulign Toric Accommodating IOL is available in 3 cylinder powers to address varying degrees of corneal astigmatism: 1.25 D, 2.00 D, and 2.75 D.

Clinical Study 650

Bausch + Lomb conducted a prospective, randomized, multicenter, single-masked clinical trial to evaluate the safety and effectiveness of the Trulign Toric Accommodating IOL (Models AT50T/AT52T) in reducing postoperative refractive astigmatism in subjects undergoing cataract extraction and IOL implantation. The parent Crystalens Accommodating IOL is approved in the US under PMA P030002, and the Trulign Toric Accommodating IOL is considered a modification of the parent IOL. As identified in International Organization for Standardization (ISO)/TR 22979 [2006], the safety or performance questions raised by a "Level B" modification to a monofocal IOL can "be adequately addressed with a limited clinical investigation." Since there are no recognized standards that address modifications to accommodating or toric IOLs, the Study 650 clinical plan was developed with input from FDA, in accordance with consensus standard ISO 11979-7 [2006], and considering American National Standards Institute (ANSI) Toric Z80.30 standard [June 7, 2009]. Clinical Study 650 was approved under IDE [redacted] on April 23, 2010.

The study was conducted following international standards for toric IOLs (ISO 11979-7 [2006] and the ANSI standard Toric Z80.30 [June 7, 2009]) and Good Clinical Practice (GCP) guideline. As specified in guidance documents, a control arm was incorporated into the trial using the currently approved spherical parent Crystalens Accommodating IOL. Statistical

comparisons between Crystalens Accommodating IOL (control) and the Trulign Toric Accommodating IOL (test) were made to assess the outcomes.

The safety and effectiveness of the Trulign Toric Accommodating IOL were confirmed in Clinical Study 650. As presented herein, the Trulign Toric Accommodating IOL met or exceeded Study 650 protocol endpoints, including

- All safety and performance endpoints identified in Annex B of ISO 11979-7:2006(E), "FDA Grid"; and
- All primary and secondary effectiveness outcome measures identified in the ISO and ANSI standards.

Study Design

Eligible subjects were evaluated preoperatively to obtain a medical history and to establish a baseline for their ocular condition. One eye of each subject in the lowest astigmatic cylinder range (i.e., predicted postoperative corneal astigmatism ranging from 0.83 D to 1.32 D) was randomly assigned in a 1:1 ratio to be implanted with the toric test lens (Trulign Toric Accommodating IOL, Models AT50T/AT52T[i]) with the lowest cylinder power (1.25 D) or the spherical control lens (Crystalens Accommodating IOL, Models AT50SE/AT52SE). Randomization occurred prior to surgery, after all toric lens calculations were completed and eligibility was established. One eye of each subject within the higher cylinder ranges was implanted with the Trulign Toric Accommodating IOL with cylinder power 2.00 D or 2.75 D. Postoperatively, subjects received a comprehensive ophthalmic examination at regular intervals (up to 330-420 days postoperative or until rotational stability had been achieved) based on the following study visit schedule: Form 1 (postoperative Days 1-2); Form 2 (postoperative Days 7-14); Form 3 (postoperative Days 30-60); Form 4 (postoperative Days 120-180); Form 5 (postoperative Days 245-301); and Form 6 (postoperative Days 330-420).

Clinical Perspective: *Because this was a monocular study, measurement of quality of life benefits such as spectacle independence for various tasks cannot be realistically assessed. In addition, it is well known that binocular visual acuity often exceeds monocular visual acuity, particularly at intermediate and near range, due to summation effects. Therefore, the measurement of monocular acuities alone, such as performed in this study, represents an important limitation.*

[i] Bausch + Lomb believed that the AT52SE (control lens) and AT52T (test lens) IOLs had been approved for inclusion in Clinical Study 650. After submission of the PMA Supplement, FDA informed Bausch + Lomb that the AT52SE and AT52T IOLs were not approved for use in the study. Further discussions are presented in "Population and Study Cohorts" in Section 1.0 (Executive Overview) and in Section 5.2.2 (Protocol Deviations).

Eligibility

Subjects 18 years of age or older with a diagnosis of age-related cataract were eligible for participation. Key inclusion criteria were the following: required lens power of 16.00 D to 27.00 D; predicted postoperative corneal astigmatism between 0.83 D and 2.50 D (as determined by a toric calculator); potential for best-corrected visual acuity (BCVA) of 20/32 or better in the study eye; and BCVA of 20/40 or worse. Key exclusion criteria were the following: conditions associated with increased risk of zonular rupture; inability to achieve pupil dilation of 5.0 mm; and difference in corneal astigmatism measured with the IOL Master and the topographer greater than 0.50 D using vector analysis.

Study Endpoints

Safety

- Preservation of BCVA at distance and near
- Incidences of complications and adverse events (AEs)

Effectiveness—Primary

- Percent reduction in cylinder
- Percent of eyes with reduction of cylinder within 0.50 D and 1.00 D of intended
- Lens axis misalignment by photographic method

Effectiveness—Secondary

- Lens misalignment by postoperative manifest refraction and vector analysis
- Intermediate visual acuity with distance correction at 32 inches (80 cm)
- Distance-corrected near visual acuity (DCNVA) at 16 inches (40 cm), with and without minimal reading add for DCNVA
- Best-corrected distance visual acuity (BCDVA)
- Uncorrected distance (UCDVA), intermediate (UCIVA), and near (UCNVA) visual acuity

Population and Study Cohorts

A total of 229 subjects were enrolled (All Enrolled Cohort): 220 subjects at 8 sites in the US and 9 subjects at a single site in Canada. Of the 229 subjects, 227 who underwent surgery and were implanted with study lens (test or control) in one eye were included in the Safety Cohort. Two subjects were not implanted with the study lens at the time of surgery due to either mild capsulorhexis tear or posterior capsular rupture. The Effectiveness Cohort (N = 215) excluded 14 subjects: 2 not implanted with the study lens, and 12 who had major protocol deviations. The Consistent Cohort (N = 121) included the All Toric IOL-implanted subjects from the Effectiveness Cohort who did not miss any follow-up visits; this cohort was used for the rotational stability analysis.

Bausch + Lomb believed that the AT52SE (control lens) and AT52T (test lens) IOLs had been approved for inclusion in Clinical Study 650 under [redacted]/S053. The Sponsor instructed the Investigators to implant IOLs with spherical equivalent power of <17.00 D as part of the protocol amendments to expand the spherical lens power ranges for the study. There were a total of 10 Model AT52 lenses implanted in this study with a spherical equivalent power of <17.00 D and a 12.0 mm overall diameter: 5 Toric 1.25 D lenses (Model AT52T), 1 Toric 2.75 D lens (Model AT52T), and 4 Control lenses (Model AT52SE). After submission of the PMA Supplement, FDA informed the Sponsor that they did not believe that the AT52SE and AT52T IOLs were approved for use in the study. Implantation of these IOLs has not been counted as protocol deviations by the Sponsor for the study analyses as the Investigators did not deviate from the protocol.

In response to the FDA request in deficiency letter dated 31 August 2012, primary, secondary, and other key analyses were analyzed without inclusion of the AT52 implanted eyes. These analyses were submitted to FDA as response to deficiency 5 in Amendment 04 to P030002/S027. The results of these analyses demonstrated that there were no significant changes in the outcomes when AT52 implanted eyes were excluded. Based on this, the Sponsor believes that the clinical results achieved with this lens design are poolable with those achieved with the AT50 lenses due to the similarity of outcomes in terms of rotational stability. The difference in IOL design between the AT50 and AT52 is limited to a difference of 0.5 mm in overall diameter. Therefore, the results from both lens models were pooled for analysis and are reported in this document and all subsequent analyses for this study.

Safety

All safety outcomes (BCVA at distance and near, and the incidences of complications and AEs) met or exceeded the requirements outlined in the FDA Grid.

BCVA at Distance and Near (Safety Cohort)

Best-corrected distance visual acuity was 20/40 or better in the majority (> 97%) of the All Toric IOL (i.e., sum of Toric 1.25 D, Toric 2.00 D, and Toric 2.75 D) eyes at the postoperative visits (i.e., Forms 3 and 4, including unscheduled visits). All postoperative results exceeded the 92.5% value provided in the FDA Grid for BCDVA of 20/40 or better.

Consistent with the BCDVA findings, best-corrected near visual acuity (BCNVA) of 20/40 or better was reported in > 98% of All Toric IOL eyes at the postoperative visits.

Incidences of Complications and AEs Compared With FDA Grid (Safety Cohort)

A total of 4 cumulative AEs (i.e., AEs that occurred at any time throughout the study) were reported. Of these AEs, 2 occurred in Toric IOL eyes (1 macular edema [0.7%] and 1 secondary surgical intervention (SSI) [0.7%]) and 2 AEs occurred in Control IOL eyes (1 macular edema [1.3%] and 1 SSI [1.3%]). The 2 cases of SSI involved lens repositioning that was not related to lens axis misalignment or rotation. One eye in the Control IOL cohort experienced lens malposition at postoperative Day 1. One eye in the Toric 2.00 IOL cohort experienced lens vaulting at Form 4. Both lenses were repositioned without sequelae.

When comparing FDA Grid AEs occurring through Form 4 in the Toric IOL eyes, the cumulative rate of reported macular edema (1/151 [0.7%]) is below the FDA Grid rate (3.0%). The cumulative rate of reported SSI (1/151 [0.7%]) is also below the rate established in the FDA Grid (0.8%).

Clinical Perspective: *All the reported safety events represent known complications of cataract surgery in general and of the approved parent platform accommodating IOL in particular. No events were related to the addition of the toric optic to the parent platform, and no SSIs were necessary to correct lens axis misalignment or rotation.*

Effectiveness

The Trulign Toric Accommodating IOL demonstrated superior effectiveness for correcting residual refractive astigmatism in Study 650. This is exemplified by the percent reduction in cylinder and the achievement of UCDVA when compared with the Control IOL. Additionally, the Trulign Toric Accommodating IOL demonstrated excellent rotational stability and absence of significant visual disturbances.

Percent Reduction in Cylinder (Effectiveness Cohort)

The primary statistical analysis consists of a comparison of reduction in cylinder between the low-cylinder Toric IOL (1.25 D) eyes and Control IOL eyes at the time point at which rotational stability was achieved (i.e., Form 4, Days 120-180). The mean percent reduction in absolute cylinder was significantly greater in the Toric 1.25 IOL eyes compared with the Control IOL eyes (81.1% vs 46.3%, respectively; $p<0.001$).

Manifest and Cycloplegic Refraction (Effectiveness Cohort)

A comparison of the mean refractive cylinders of the Toric 1.25 IOL eyes and the Control IOL eyes revealed that the Toric 1.25 IOL eyes had a statistically significant lower mean (standard deviation [SD]) absolute residual cylinder (–0.47 D [0.420 D]) compared with the Control IOL eyes (–0.90 D [0.617 D]). The mean difference (0.43) between the 2 cohorts was statistically significant ($p<0.001$).

The Toric IOLs also demonstrated refractive predictability. The accuracy to target for manifest refraction spherical equivalent (MRSE) was 73.7% within 0.50 D of target and 93.2% within 1.00 D of target.

Rotational Stability (Effectiveness Cohort and Consistent Cohort)

In the Effectiveness Cohort, the mean (SD) absolute rotation since implantation was 1.78° (1.971°) for the Toric 1.25 IOL eyes, 1.35° (1.083°) for the Toric 2.00 IOL eyes, and 1.68° (1.628°) for the Toric 2.75 IOL eyes. The majority (>96%) of eyes demonstrated ≤ 5.0° of absolute rotation since implantation, with no eyes demonstrating ≥ 10.0° of absolute rotation since implantation. Moreover, according to the ANSI Toric Z80.30 standard, stability of the Toric IOL axis is achieved when 90% of the implanted lenses rotate ≤ 5.0° between

2 consecutive visits at least 3 months apart. In the Consistent Cohort, 99.2% of the Toric IOLs demonstrated ≤ 5.0° of rotation between visits.

DCIVA and DCNVA (Effectiveness Cohort)

When comparing the All Toric IOLs versus Control IOLs, no compromise in mean DCIVA (0.06 vs 0.07 logMAR; p=0.760), DCNVA (0.30 vs 0.30 logMAR; p=0.912), or Add (1.43 D vs 1.60 D p=0.046) was demonstrated.

UCDVA, UCIVA, and UCNVA (Effectiveness Cohort)

The mean logMAR (corresponding Snellen) monocular uncorrected visual acuity was 0.10 (20/25) at distance (20 feet), 0.04 (20/20) at intermediate (32 inches), and 0.29 (20/40) at near (16 inches).

At FDA's request, additional unplanned analyses were performed assessing UCDVA, UCIVA, and UCNVA with adjustment for Form 4 MRSE. These analyses demonstrate a statistically significant superiority in MRSE-adjusted UCDVA of the Toric 1.25 IOL over the Control IOL (p=0.007). For MRSE-adjusted UCIVA, a trend was evident for the superiority of the Toric 1.25 IOL over the Control IOL (p=0.062). However, adjustment for MRSE had no effect on UCNVA (p= 0.579). When controlling for MRSE, the Toric IOL was superior to the Control IOL for UCDVA and, to a lesser extent, for UCIVA, as would be expected.

In contrast, UCNVA is primarily affected by the magnitude of accommodation of the Crystalens Accommodating IOL at 1.00 D and the resulting effect of pseudophakic presbyopia. The magnitude of the spherical blur at near (1.50 D on average in both cohorts) is the primary source of compromise in UCNVA (approximately 20/40). The magnitude of this blur effectively prevents discrimination between the magnitude of residual astigmatism in UCNVA in the Toric 1.25 IOL and Control IOL cohorts.

UCIVA/UCNVA Versus DCIVA/DCNVA (Effectiveness Cohort)

Concerns related to the achievement of UCIVA and UCNVA due to residual refractive error (i.e., myopia or astigmatism) can be addressed by the outcomes reported for DCIVA and DCNVA. These outcomes represent intermediate and near vision with full correction of any residual ametropia in place. In Study 650, no significant differences were found when comparing the mean uncorrected and distance-corrected visual acuities at intermediate and near.

Clinical Perspective: *The expected amplitude of accommodation for the parent platform IOL is 1.00 D. Therefore, at a range closer than 1 meter, the dual effect of pseudophakic presbyopic blur (in both treatment and control groups) and residual astigmatic pseudoaccommodation (in the control group) tends to reduce the distinction in visual performance at near and intermediate that is clearly seen at distance.*

Visual Disturbances (Effectiveness Cohort)

As reported by subject questionnaire, 127 of the 128 (99.2%) All Toric IOL subjects did not experience any significant increase in visual disturbances. It was determined the single eye in the Toric 2.00 IOL group that reportedly had a significant increase in visual disturbance at the Form 4 visit (4-6 months postoperative) developed moderate posterior capsule opacity (PCO). The subject subsequently underwent neodymium:yttrium-aluminum-garnet (Nd:YAG) capsulotomy, after which resolution of visual disturbances was reported. No subjects in the highest cylinder correction cohort (Toric 2.75 IOL) reported significant visual disturbances.

Conclusions

Results from Study 650 demonstrate that the Trulign Toric Accommodating IOL is safe and effective for its intended use. The parent lens design and material have a proven safety and effectiveness profile with more than 315,000 implants since the first clinical experience more than a decade ago. Under controlled clinical investigation (Study 650), the Trulign Toric Accommodating IOL met or exceeded both the safety and the effectiveness endpoints established for the trial. The Trulign Toric Accommodating IOL demonstrated excellent rotational stability with favorable effectiveness and safety compared with the Control IOL, and it met or exceeded the historical control ("FDA Grid") standards. With respect to presbyopic management, the Trulign Toric Accommodating IOL provides good distance, intermediate, and functional near vision. Additionally, unlike multifocal IOLs, its accommodative design minimizes the loss of contrast sensitivity and photic phenomena (glare and halos), further supporting a favorable risk-benefit ratio for visual correction of aphakia, presbyopia, and astigmatism. These results support the safe and effective use of the Trulign Toric Accommodating IOL in the proposed patient population.

Overall, the Trulign Toric Accommodating IOL demonstrated a safety profile consistent with that of the Control (Crystalens Accommodating) IOL and other currently approved IOLs, and it demonstrated the ability to correct residual refractive astigmatism and improve UCDVA without compromising intermediate and near vision performance.

Given the results from Study 650, the following revisions (**bold** and *italics*) to the currently approved FDA labeling for the Crystalens Accommodating IOL are proposed:

- The ***Trulign Toric*** Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia and ***postoperative refractive astigmatism*** secondary to removal of a cataractous lens in adult patients with or without presbyopia ***who desire improved uncorrected distance vision and reduction of residual refractive cylinder***. The ***Trulign Toric*** Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter (D) of monocular accommodation, which allows near, intermediate, and distance vision without spectacles.

2.0 INTRODUCTION

Overview of Parent Crystalens Accommodating Intraocular Lens

The parent Crystalens Accommodating IOL (Model AT45) was the subject of PMA Application P030002. This application included preclinical and clinical data and information supporting the safety and effectiveness of the Crystalens Accommodating IOL. The PMA data were reviewed and recommended for approval by the Ophthalmic Devices Panel on May 23, 2003, and FDA subsequently approved PMA Application P030002 for the Crystalens Accommodating IOL on November 14, 2003.

As presented in the original PMA application, the Crystalens IOL is an accommodating IOL with a monofocal optic and hinged haptics. Because it has a monofocal optic, there is always a single point of focus. It provides good distance, intermediate, and functional near vision. The Crystalens Accommodating IOL has been clinically shown to provide approximately 1.00 D of accommodation.

Since the original FDA approval, various models of the Crystalens Accommodating IOL have been approved and are currently marketed in more than 65 countries worldwide (Five-O [spherical; Models AT50SE/AT52SE, **Figure 1**], AO [aspheric; Models AT50AO/AT52AO], and UVAM [aspheric; Models AO1UV/AO2UV]. The Crystalens Accommodating IOL has a proven safety and effectiveness profile with more than 315,000 eyes implanted globally since its introduction in 2003. Additional discussion of this global clinical experience is provided in **Section 9.0**.

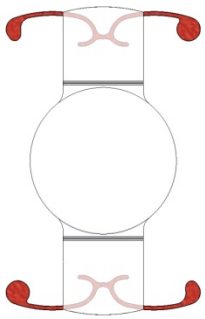


Figure 1 Crystalens Five-O Accommodating Intraocular Lens.

Astigmatism-Correcting Toric Intraocular Lenses

Technological advances, such as phacoemulsification and IOLs, have changed the paradigm of cataract surgery. The goal is no longer only replacement of the cataractous lens, but also achievement of adequate postoperative UCVA independent of spectacles or contact lenses. Management of postoperative residual refractive error is an important step toward that goal.

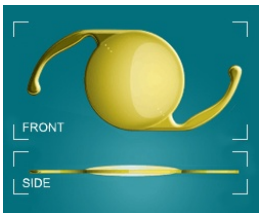
In patients with astigmatism, as little as 0.50 D can influence visual acuity and produce disturbing blur.[9] It has been estimated that 36% of patients undergoing cataract surgery have at

least 1.00 D of preexisting corneal astigmatism.[7] Therefore, these patients must use spectacles or contact lenses or must undergo additional surgical procedures to reduce the astigmatism. Besides spectacles and contact lenses, traditional methods for correction of astigmatism have included incisional relaxing techniques,[10,11] astigmatic keratotomy,[12] and astigmatic correction with the excimer laser.[13] Toric IOLs were conceived with the intent of providing greater predictability and reversibility over keratorefractive procedures. The use of toric IOLs also mitigated some of the disadvantages and side effects of incisional astigmatic correction, such as varied wound healing, corneal denervation, corneal perforation, infection, and wound gape, and it decreased best spectacle-corrected vision due to irregular astigmatism.[14-17] Similarly, it obviated some limitations and side effects of excimer laser correction of astigmatism via surface treatment or LASIK, such as corneal haze, dry eyes, regression, and diffuse lamellar keratitis.[18]

Since initial reports of the use of toric IOLs in cataract surgery in the early 1990s,[19] 2 toric IOLs (STAAR and AcrySof®) have been approved in the US for visual correction in patients with cataract and preexisting corneal astigmatism (**Table 1**[20,21]). The STAAR Toric IOL, approved in November 1998, is a 1-piece plate haptic silicone lens available in a range of spherical powers, but available only in 2 cylinder power options at the IOL plane: 2.00 D and 3.50 D.[20] In a study of patients with cataract and preexisting astigmatism who were implanted with a STAAR Toric IOL (N = 124) or a Control (spherical) IOL (N = 126), UCVA of 20/30 or better was achieved by 45% of 2.00 D Toric IOL subjects versus 26% of Control IOL subjects, and by 52% of 3.50 D Toric IOL subjects versus 16% of Control IOL subjects.[22] The reported concern with this IOL has been poor rotational stability. In one study of 100 eyes implanted with the STAAR Toric IOL, 27 eyes were off axis by 6° to 15° and 14 eyes rotated off axis by more than 15°.[23]

Clinical trial results reported with the more recently approved (September 2005) AcrySof Toric IOL (**Table 1**[20,21]) have shown markedly improved rotational stability with corresponding improvement in refractive cylinder reduction and UCVA. In 494 patients, 244 implanted with the AcrySof Toric IOL (SA60TT) and 250 implanted with the Control IOL (SA60AT), the majority of lenses (81.1%) rotated ≤ 5°.[24] Eyes implanted with the AcrySof Toric IOL were 3 times more likely to achieve ≤ 0.50 D of residual refractive cylinder than Control eyes. Moreover, at Form 5 (120-180 days postoperative), the mean absolute residual refractive cylinder was 0.55 D in the AcrySof toric eyes compared with 1.22 D in the control eyes. The majority (94%) of patients implanted with the AcrySof Toric IOL achieved UCDVA of 20/40 or better.[24] A recent randomized, subject-masked, parallel-group, 1-year multicenter study evaluating the AcrySof Toric IOL showed that 1 year after surgery, 78.0% of the IOLs rotated < 5° and 93.4% rotated < 10°. However, > 10° rotation was observed in 6.7% of the AcrySof Toric IOLs (N = 16), of which 3 rotated 15° to 20°.[25]

Table 1 Specifications of Astigmatism-Correcting Toric Intraocular Lenses Available in the United States

Specifications	Astigmatism-Correcting Toric Intraocular Lenses	
	STAAR Elastic Toric[20]	**AcrySof® Toric[21]**
		
Model number(s)	AA4203TF/AA4203TL	SN6AT3, SN6AT4, SN6AT5, SN6AT6, SN6AT7, SN6AT8, SN6AT9
Optic type	Biconvex, toric	Biconvex, toric, aspheric
Cylinders	2.0 and 3.5	1.50 D, 2.25 D, 3.00 D, 3.75 D, 4.50 D, 5.25 D, 6.00 D
Diopter power (increments)	AA4203TF: +24.00 D to +28.50 D (0.50) AA4203TL: +9.50 D to +23.50 D (0.50)	+6.00 D to +30.00 D (0.50)
Optic diameter	6.0 mm	6.0 mm
Overall length	AA4203TF: 10.8 mm AA4203TL: 11.2 mm	13.0 mm
Suggested A-constant	118.5	119.0
IOL design	Single piece	Single piece
Manufacturer	STAAR Surgical	Alcon Surgical

In summary, the addition of a toric optic to IOLs provides meaningful clinical benefit to cataract patients by substantially improving UCVA and decreasing spectacle dependence. A key component of the toric IOL's effectiveness is its rotational stability.

3.0 TRULIGN TORIC ACCOMMODATING INTRAOCULAR LENS

Since approval of the parent Crystalens Accommodating IOL (Model AT45) in 2003, more than 315,000 eyes have been implanted with the Crystalens Accommodating IOL. For patients who, with the counsel of their surgeon, decide that the Crystalens Accommodating IOL is their best option, the goal is to provide them with good distance and intermediate vision with minimal spectacle dependence at near. Currently, the Crystalens Accommodating IOL does not correct astigmatism; therefore, Crystalens patients with astigmatism typically need spectacle or contact lens overcorrection, or they must undergo an additional surgical procedure to manage the astigmatism.

The Trulign Toric Accommodating IOL was developed to provide safe and effective correction of postoperative refractive astigmatism. The Trulign Toric Accommodating IOL (Models AT50T/AT52T) is a modified version of the currently approved Crystalens Five-O (spherical) Accommodating IOL (Models AT50SE/AT52SE). The only differences between the 2 lenses are that the Trulign Toric Accommodating IOL incorporates a toric posterior optic surface and axis marks on the anterior surface.

The parent Crystalens Accommodating IOL is approved in the US under PMA P030002. In accordance with US FDA recognized standards, ISO/TR 22979 [2006] and ISO 11979-7 [2006], Bausch + Lomb confirmed with FDA that addition of the toric optic and axis marks to the already approved IOL design to create the Trulign Toric Accommodating IOL could be considered like a Level B modification of the parent IOL. As identified in ISO/TR 22979 [2006], the safety or performance questions raised by a “Level B” modification of a monofocal IOL can “be adequately addressed with a limited clinical investigation.” Since there are no recognized standards that address modifications to accommodating or toric IOLs, the Study 650 clinical plan was developed with input from FDA, in accordance with consensus standard ISO 11979-7 [2006], and considering ANSI Toric Z80.30 standard [June 7, 2009]. Clinical Study 650 was approved under IDE [redacted] on April 23, 2010.

3.1 Device Description

The Trulign Toric Accommodating IOL is a modified haptic plate lens with hinges across the plates adjacent to the optic (**Figure 2**). The lens is foldable, with a biconvex silicone optic and fused polyimide loops. Models AT50T and AT52T have a spherical anterior surface with axis marks and a toric posterior surface, with an overall diameter of 11.5 mm (AT50T) or 12.0 mm (AT52T) and an optic body diameter of 5.0 mm. The lens possesses a mean spherical dioptric power range of 4.00 D to 33.00 D (in 0.50 D increments) and is available in 3 cylinder powers to address varying degrees of corneal astigmatism: 1.25 D, 2.00 D, and 2.75 D.

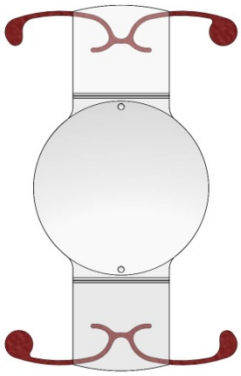


Figure 2 Trulign Toric Accommodating Intraocular Lens.

3.2 Proposed Indication for Use

The Trulign Toric Accommodating Posterior Chamber Intraocular Lens is intended for primary implantation in the capsular bag of the eye for the visual correction of aphakia and postoperative refractive astigmatism secondary to removal of a cataractous lens in adult patients with or without presbyopia who desire improved uncorrected distance vision and reduction of residual refractive cylinder. The Trulign Toric Accommodating Posterior Chamber Intraocular Lens provides approximately one diopter of monocular accommodation, which allows for near, intermediate, and distance vision without spectacles.

4.0 SUMMARY OF NONCLINICAL STUDIES

Since the parent model and subsequent models are approved under PMA P030002 and subsequent supplements, much of the preclinical information relating to the materials, design, and finished process has previously been submitted and approved under PMA P030002. Overall, the Trulign Toric Accommodating IOLs are biocompatible and provided in a sterile state. Based on the available data, packaging is sufficient to maintain the sterility and stability of the IOL throughout the 5-year shelf-life. The nonclinical studies further demonstrate that the IOLs comply with the requirements for physical and mechanical properties.

4.1 Biocompatibility and Toxicologic Testing

The proposed Trulign Toric Accommodating IOL models are composed of identical materials as the currently approved Crystalens Accommodating IOLs. Therefore, no new biocompatibility/toxicological data were provided. Biocompatibility and physical-chemical testing consistent with ISO 10993 (*Biological Evaluation of Medical Devices*) and ISO 11979-5 (*Ophthalmic Implants - Intraocular Lenses - Part 5: Biocompatibility*) was provided in the approved PMA P030002 (November 14, 2003) and PMA P030002/S020 (August 5, 2011).

4.2 Chemical Testing

Chemical testing was performed on the materials used in the Trulign Toric Accommodating IOL. Characterization tests confirmed that the material meets the requirements of ISO 11979-5 (*Ophthalmic Implants – Intraocular Lenses – Part 5: Biocompatibility*) and was provided in the approved PMA P030002 (November 14, 2003) and PMA P030002/S020 (August 5, 2011).

4.3 Optical/Mechanical Testing

The nonclinical optical/mechanical tests were performed with the Trulign Toric Accommodating IOL raw material and previously qualified Crystalens Accommodating IOL models and were measured in accordance with the FDA Guidance Document for Multifocal Intraocular Lenses (May 29, 1997), EN ISO 11979-2 (*Ophthalmic Implants – Intraocular Lenses – Part 2: Optical Properties and Test Methods*), and EN ISO 11979-3 (*Ophthalmic Implants – Intraocular Lenses – Part 3: Mechanical Properties and Test Methods*).

The optical/mechanical tests performed and passed are listed in **Table 2**.

Table 2 Optical/Mechanical Tests Performed and Passed

Tests	
Dioptric power	Optic tilt
Cylinder power	Loop pull strength
Cylinder axis	Dynamic fatigue durability
Imaging quality	Folding/injection
Spectral transmittance	Surface and bulk homogeneity
Clear optic diameter	Mechanical characterization
Overall diameter	Compression force/compression force decay
Vault height	Axial displacement in compression
Sagitta	Angle of contact
Optic decentration	Mechanical data analysis

Source: PMA P030002/180 Day Supplement, p17.

4.4 Sterilization, Packaging, and Shelf-Life

4.4.1 Sterilization

The Trulign Toric Accommodating IOLs are sterilized using a validated steam sterilization process, which is used for all currently approved Crystalens Accommodating IOL models. Supporting data were provided in the approved PMA P030002 (November 14, 2003).

4.4.2 Packaging

The packaging components for the Trulign Toric Accommodating IOLs are identical to the packaging components for the currently approved Crystalens Accommodating IOL models. The packaging components include a polycarbonate lens case, Tyvek pouch, and carton. The finished product includes the directions for use (DFU) and other pertinent labeling (chart stickers, patient information card, and patient registration card). Supporting data were provided in the approved PMA P030002 (November 14, 2003).

4.4.3 Shelf-Life

The proposed Trulign Toric Accommodating IOLs have the same 5-year shelf-life as the parent Crystalens Accommodating IOL model (AT45) and the approved Crystalens UVAM material models (AO1UV and AO2UV). Supporting data were provided in the approved PMA P030002 (November 14, 2003) and in PMA P030002/S020 (August 5, 2011).

5.0 CLINICAL STUDY 650

Study 650 evaluated the safety and effectiveness of the Trulign Toric Accommodating IOL (Models AT50T/AT52T[ii]) in providing near, intermediate, and distance vision and a reduction of the effects of preoperative corneal astigmatism in subjects undergoing cataract extraction and IOL placement. The study was designed and conducted in accordance with international standards for toric IOLs (ISO 11979-7 [2006] and ANSI Toric Z80.30 standard [June 7, 2009]), and GCP guideline.

Data presented from Study 650 are based on the interim clinical study report submitted with PMA Application P030002 (March 2012; database lock December 16, 2011).

5.1 Study Design and Plan

This was a prospective, randomized, single-masked clinical trial of the Trulign Toric Accommodating IOL, with study duration of up to 1 year. Subjects scheduled for cataract surgery with phacoemulsification cataract extraction were screened. Eligible subjects were evaluated preoperatively to obtain a medical history and to establish a baseline for their ocular condition. Subjects in the lowest astigmatic power cohort were randomized to undergo implantation of either the toric test lens or the non-toric spherical control lens in one eye. Subjects in the higher astigmatic power cohorts were implanted with the test lens in one eye. Postoperatively, subjects received an ophthalmic examination at regular intervals per the study visit schedule (up to 330-420 days postoperative or until rotational stability had been achieved):

- Form 1 Postoperative Days 1-2
- Form 2 Postoperative Days 7-14
- Form 3 Postoperative Days 30-60
- Form 4 Postoperative Days 120-180
- Form 5 Postoperative Days 245-301
- Form 6 Postoperative Days 330-420

5.1.1 Rotational Stability

Rotational stability, using photographic assessment performed by an independent reading center, was measured at Day 0 (Operative Day) and at Forms 3 through 6. The device was deemed stable when 90% of the eyes showed axial rotational stability ≤ 5° between consecutive scheduled visits at least 3 months apart, with stability being achieved at the latter of the 2 consecutive scheduled visits.

[ii] Bausch + Lomb believed that the AT52SE (control lens) and AT52T (test lens) IOLs had been approved for inclusion in Clinical Study 650. After submission of the PMA Supplement, FDA informed Bausch + Lomb that the AT52SE and AT52T IOLs were not approved for use in the study. Further discussions are presented in "Population and Study Cohorts" in Section 1.0 (Executive Overview) and in Section 5.2.2 (Protocol Deviations).

5.1.2 Subject Eligibility

5.1.2.1 Inclusion Criteria

Subjects were included in the study if they met the following criteria:

1. Clinically documented diagnosis of age-related cataract (cortical, nuclear, subcapsular, or a combination) considered amenable to treatment with standard phacoemulsification/ extracapsular cataract extraction
2. 18 years of age or older and met any applicable local minimum age requirements for IOL implantation following cataract surgery
3. Underwent primary IOL implantation for correction of aphakia following continuous curvilinear anterior capsulotomy and phacoemulsification cataract extraction
4. Ability to return for scheduled follow-up examinations and had mental capacity to cooperate when undergoing a detailed postoperative exam
5. Required spherical lens power of 16.00 D to 27.00 D
6. Predicted postoperative corneal astigmatism between 0.83 D and 2.50 D, as determined by the toric calculator (**Section 5.1.3.3**)
7. Potential for BCVA of 20/32 or better in the operated eye (as measured by retinal acuity meter/potential acuity meter testing)
8. BCVA equal to or worse than 20/40, with or without a glare source

5.1.2.2 Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study:

1. Anterior segment pathology for which extracapsular phacoemulsification cataract surgery would be contraindicated (e.g., chronic uveitis, iritis, iridocyclitis rubeosis, iridis, clinically significant corneal dystrophy, clinically significant Fuch's dystrophy, clinically significant anterior membrane dystrophy)
2. Corneal pathology potentially affecting topography
3. Diagnoses of degenerative visual disorders (e.g., macular degeneration or other retinal disorders) predicted to cause future acuity losses to a level of 20/32 or worse
4. Conditions associated with increased risk of zonular rupture (zonule rupture during cataract extraction procedure that may affect postoperative rotation, centration, or tilt of the lens)
5. Inability to achieve pupil dilation of 5.0 mm
6. Any inflammation or edema (swelling) of the cornea, including but not limited to keratitis, keratoconjunctivitis, and keratouveitis
7. Uncontrolled glaucoma
8. Prior retinal detachment
9. Diabetic retinopathy (proliferative or nonproliferative)
10. Presence of rubella, bilateral congenital, traumatic, or complicated cataract
11. Marked microphthalmos or aniridia
12. Prior corneal surgery in the planned operative eye
13. Irregular corneal astigmatism
14. Presence of amblyopia
15. Clinically significant retinal pigment or epithelium/macular changes

16. Iris or chorioretinal neovascularization
17. Presence of optic atrophy
18. Chronic use of systemic steroids or immunosuppressive medications
19. Concurrent participation in another clinical trial or participation in another clinical trial within 60 days prior to enrollment in this study
20. Difference in corneal astigmatism measured with the IOL Master and the topographer greater than 0.50 D using vector analysis

5.1.3 Study Materials and Methods

5.1.3.1 Test and Control Devices

The test lens, Trulign Toric Accommodating IOL (Models AT50T/AT52T), is a toric version of the Crystalens Accommodating IOL, as described in **Section 3.1** of this document. The available spherical equivalent powers range from +16.00 D to +16.50 D for Model AT52T and +17.00 D to +27.00 D for Model AT50T, with cylindrical powers at the lens plane of 1.25 D, 2.00 D, and 2.75 D. The effective corneal powers for each of the lens plane cylindrical powers of the test IOLs are shown in **Table 3**.

Table 3 Trulign Toric Accommodating IOL Cylinder Power

Cylinder Power at IOL Plane (D)	Cylinder Power at Corneal Plane (D)	Predicted Postoperative Cylinder Range (D)
1.25	0.83	0.83 – 1.32
2.00	1.33	1.33 – 1.82
2.75	1.83	1.83 – 2.50

Abbreviations: D, diopter; IOL, intraocular lens.
Source: 650-CSR-PMA-20feb2012, p19.

The Crystalens Accommodating IOL Models AT50SE/AT52SE (non-toric optic) were used as the control lenses. The available spherical equivalent powers range from +16.00 D to +16.50 D for Model AT52SE and +17.00 D to +27.00 D for Model AT50SE in 0.50 D increments.

5.1.3.2 Treatment Assignment

Eyes within the lowest cylinder range (i.e., predicted postoperative corneal astigmatism ranging from 0.83 D to 1.32 D, **Table 3**) were randomly assigned (1:1) to be implanted with the Toric IOL with the lowest IOL cylinder power (1.25 D; 0.83 D at the corneal plane) or the Control IOL. Randomization occurred at the time of surgery after Toric IOL calculations were completed, and eligibility based on toric lens power availability was established using the toric calculator. Eyes within the higher cylinder ranges (i.e., 1.33 D to 1.82 D or 1.83 D to 2.50 D, **Table 3**) were implanted with the Toric IOL with cylinder power 2.00 D or 2.75 D, respectively.

5.1.3.3 Toric Calculator

The Trulign toric calculator was used to calculate the predicted postoperative corneal astigmatism using preoperative keratometry, phaco/insertion incision location, and predicted

magnitude of surgically induced astigmatism (SIA) inputs entered by the physician. The calculator accounted for SIA, incision location, and the subject's preoperative corneal astigmatism, and determined the Toric IOL cylinder power needed and placement orientation to best correct a subject's predicted postoperative corneal astigmatism. A fixed SIA value of 0.50 D was used in the toric calculator for all study subjects.

Clinical Perspective: *Uniform on-axis incisions were implemented to reduce expected variability of technique among Investigators and generate study outcomes more similar to those an individual surgeon with a consistent technique might expect to achieve.*

5.1.3.4 Surgical Procedure

Surgery to implant either the Toric IOL (Models AT50T/AT52T) or Control IOL (Models AT50SE/AT52SE) was performed on Day 0 of the study, using standard microsurgical techniques. Surgery was performed under either local or topical ophthalmic anesthesia. The test and control lenses were not implanted if the following intraocular exclusion criteria were met: presence of zonular rupture or compromised anterior or posterior capsule.

All cataract incisions were to be placed on the preoperative keratometric steep axis for all test and control eyes to minimize postoperative corneal astigmatism. The cataract was extracted by phacoemulsification. The IOL, test (Model AT50T/AT52T) or control (Model AT50SE/AT52SE), was inserted using a validated insertion device, Crystalsert CI-28 injector, which was provided to all sites with each study IOL. The markings on the lens were aligned with the placement markings on the cornea, which were made prior to the incision to aid in IOL placement.

5.1.3.5 Clinical Assessments

The clinical parameters assessed in this study are described below.

- UCVA
  - UCDVA measured at 20 feet (6 m)
  - UCIVA measured at 32 inches (80 cm)
  - UCNVA measured at 16 inches (40 cm)
- Manifest refraction (autorefraction was not permitted)
- BCVA
  - Without glare
  - With glare (only if BCVA without glare < 20/40)
  - Near with Add at 16 inches (40 cm)
- DCVA
  - DCIVA at 32 inches (80 cm)
  - DCNVA at 16 inches (40 cm)
- Subject questionnaire for assessment of visual disturbance
- Rotational stability photographs

- IOL tilt and decentration
- Intraocular pressure (IOP)
- Corneal topography
- Keratometry (IOL Master)
- Cycloplegic refraction
- Slit lamp examination
- Dilated fundus exam
- AEs/complications

Standardized testing equipment was used for all evaluations. Distance visual acuity was measured using the [redacted] vision tester. This vision tester is a single-letter acuity tester calibrated for distance vision at 20 feet. Near and intermediate acuities were measured using the MN text reading card. This card is calibrated for near vision at 16 inches (40 cm). Intermediate vision was recorded using the same MN card with a test distance of 32 inches (80 cm). Axial length measurements and keratometry were performed using the [redacted] Lens orientation was verified using a slit lamp and digital camera system. All Investigators were supplied with a slit lamp/digital camera system.

5.1.3.6 Concomitant Therapy

All medical treatment and medications that were considered necessary for the subject's welfare were allowed at the investigator's discretion.

According to the clinical protocol, Nd:YAG posterior capsulotomy should have been delayed until after Form 4 was completed and only performed by the Investigator in response to spontaneous subject complaints of reduced visual acuity or glare that affected functional vision and which may have been associated with PCO or striae.

5.1.4 Study Endpoints

5.1.4.1 Safety Endpoints

- Preservation of BCVA (distance and near)
- Incidences of complications and AEs

5.1.4.2 Effectiveness Endpoints

Primary

- Percent reduction in absolute cylinder, expressed as a percentage of the intended reduction in cylinder, calculated as

$$\frac{\text{(Postoperative Manifest Refractive Cylinder – Preoperative Keratometric Cylinder)}}{\text{(Intended Postoperative Manifest Refractive Cylinder – Preoperative Keratometric Cylinder)}} \times 100$$

  - Percent reduction in absolute cylinder is defined as the difference between the postoperative magnitude of the subjective manifest refractive cylinder (converted to the corneal plane) and the preoperative magnitude of the keratometric cylinder divided by the intended reduction in cylinder expressed as a percentage. The intended reduction in cylinder is the difference between the "intended" magnitude of the posterior manifest refractive cylinder (converted to the corneal plane) and the magnitude of the preoperative keratometric cylinder.
- Percent of eyes with reduction of cylinder within 0.50 D and within 1.00 D of intended reduction in cylinder
- Lens axis misalignment as determined by a photographic method

Secondary

- Lens misalignment as determined by postoperative manifest refraction and vector analysis
- DCIVA at 32 inches (80 cm)
- DCNVA at 16 inches (40 cm), with and without the minimal reading Add for DCNVA
- BCDVA
- UCDVA, UCIVA, and UCNVA

5.1.5 Statistical Methods

5.1.5.1 Statistical Analysis

Continuous measures are described by mean, SD, median, minimum, and maximum. Categorical and incidence measures were tabulated by both count and by percentage of occurrence. Adverse events and complications were reported as both cumulative (occurred at any time through Form 6) and persistent (present at Form 6). Unless otherwise specified, all summaries were presented separately for eyes implanted with Toric IOL cylinder power 1.25 D, 2.00 D, or 2.75 D, as well as the sum of 1.25 D, 2.00 D, or 2.75 D (referred to as All Toric IOL), and eyes implanted with the Control IOL, by visit.

Analysis of the percent reduction in absolute cylinder included continuous summary statistics and 95% confidence intervals (CIs) around the mean. Additionally, a 2-sample *t*-test assuming unequal variance was performed using the Effectiveness Cohort to test the null hypothesis that the percent reduction of cylinder within the eyes implanted with IOL cylinder power 1.25 D was less than or equal to the percent reduction of cylinder within the eyes implanted with the control IOL.

Analysis of the percent of eyes with reduction of cylinder within 0.50 D and 1.00 D of intended reduction in cylinder included categorical summary statistics, including exact 95% binomial CI around the percent of eyes within 0.50 D and 1.00 D.

Analysis of lens axis misalignment included continuous summaries of the absolute value of the misalignment, the signed value of the misalignment (including a 2-sided 95% tolerance interval, which contains at least 90% of the population), and the proportion of lenses with axis misalignment in the following categories: $< 5°$, $< 10°$, $< 20°$, $\leq 30°$, and $> 30°$. These analyses

were completed using measurements as determined by photographic method and manifest refraction and vector analysis.

Safety measures were presented separately for implanted eyes and eyes not implanted due to surgical complications. Subjects who discontinued prior to surgery were excluded from all safety analyses.

The statistical analysis plan (SAP) for Study 650 was initially provided to FDA in the original study protocol (dated March 22, 2010) and approved by FDA in IDE G990163. Bausch + Lomb subsequently produced a SAP (dated November 29, 2011) as a separate document to provide additional detail on the planned analyses presented originally in the study protocol. Although Bausch + Lomb conducted two unplanned interim analyses prior to finalization of the November 29, 2011 SAP, the secondary effectiveness endpoints and AE rates and methods of analysis were unchanged from the study protocol. The SAP was amended prior to the primary analysis for PMA submission to provide further clarification of the analysis and to ensure alignment with the required ISO and ANSI standards for toric IOLs. Therefore, the interim analyses did not affect the original planned analyses for this study.

5.1.5.2 Sample Size Determination

The sample size calculations were performed according to ANSI Z80.30 standard for toric IOLs.

To evaluate the percent reduction in absolute cylinder (for eyes implanted with the lowest IOL cylinder power, 1.25 D), a sample size of 62 eyes yielded 95% CIs with half-widths of 10%, assuming the SD of percent reduction is 40%.

Moreover, with a sample size of 62 eyes implanted with the lowest IOL cylinder power (1.25 D), a sample size of 65 control eyes within the same cylinder power range as the eyes implanted with the lowest IOL cylinder power implanted with control IOL yielded 90% power to detect a difference in the percent reduction in absolute cylinder between the eyes implanted with the lowest IOL cylinder and eyes implanted with the control IOL. This sample size calculation assumes a *t*-test with unequal variances of the following hypotheses:

- **H0**: Percent reduction of cylinder in low-cylinder test cohort ≤ Percent reduction of cylinder in control cohort,
- **H1**: Percent reduction of cylinder in low-cylinder test cohort > Percent reduction of cylinder in control cohort,
  Where the assumed difference in percent reduction of cylinder (low-cylinder test minus control) is (67% – 33%) = 34%, and the SDs for low-cylinder test and control lenses are 40% and 80%, respectively.

To allow for 1:1 randomization within the lowest cylinder power range, the sample size required for the lowest IOL cylinder power was to be increased from 62 to 65 subjects.

To evaluate the proportion of eyes with significant visual disturbances in the highest cylinder cohort (i.e., eyes implanted with IOL cylinder powers of 2.00 D or 2.75 D), a sample size of 50 eyes yielded 95% probability of detecting an eye with significant visual disturbances if the

true rate of eyes with these disturbances was 6% or greater. That is, within 50 eyes implanted, if no eyes showed significant visual disturbances, there was 95% confidence that the true rate of eyes with these disturbances was less than 6%. At least 10 eyes were to be implanted with the 2.75 D cylinder power lens.

The minimum sample size required for the study was 130 eyes in the lowest cylinder range (65 eyes randomized to the lowest Toric IOL cylinder power and 65 eyes randomized to the Control IOL) and 50 eyes within the higher cylinder ranges, yielding 180 eyes. To account for subject discontinuation, missing data, and repositioning, up to 230 eyes were to be implanted (150 Toric IOLs and 80 Control IOLs).

5.2 Study Subjects

5.2.1 Disposition and Accountability of Subjects

Subject disposition and accountability are depicted in **Table 4** and **Table 5**, respectively.

A total of 229 subjects were enrolled: 220 subjects at 8 sites in the US and 9 subjects at a single site in Canada (**Table 4**). Two subjects (0.9%) discontinued prior to implantation and another 2 subjects (0.9%) discontinued after implantation. Reasons for withdrawal before implantation were mild capsulorhexis tear and moderate posterior capsular rupture. Reasons for discontinuation after implantation were withdrawal of consent and death.

Table 4 Subject Disposition (All Enrolled Cohort)

Subject Status	Overall n (%)
Number enrolled	229
Still active in trial	225
Completed entire trial	0
Discontinued *after* implant	2 (0.9)
Subject lost to follow-up	0
Subject withdrew consent	1 (0.4)
Subject explanted	0
Subject death	1 (0.4)[a]
Discontinued *before* implant	2 (0.9)[b]
Surgical complications	2 (0.9)

[a] Subject [redacted] attended the Form 4 visit, but discontinued study soon afterwards (death), so is counted only once in Table 4 as a discontinuation.
[b] Subjects were not implanted due to mild capsulorhexis tear and moderate posterior capsular rupture, respectively.
Source: 065 CSR-PMA-20feb2012.pdf, Table 5.

As shown in **Table 5**, accountability was 100% at Form 4.

Table 5 Subject Accountability by Each Scheduled Visit (All Enrolled Cohort)

Subject Status	Preop Exam n (%)	Op Report n (%)	Form (Postoperative) Visits, n (%)			
			1	2	3	4
Available for analysis	229 (100.0)	229 (100.0)	227 (99.1)	223 (97.4)	219 (95.6)	211 (92.1)
Discontinued	0	0	2 (0.9)	3 (1.3)	3 (1.3)	3 (1.3)
Missing at scheduled visit but seen later	0	0	0	3 (1.3)	7 (3.1)	0
Not seen but accounted for	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Active	0	0	0	0	0	15 (6.6)
% Accountability	–	–	(100.0)	(98.7)	(96.9)	(100.0)

Note: Percentages are based on the number of enrolled subjects.
Percent accountability = 100 x Available for Analysis / (Enrolled – Discontinued – Active)
Source: 065 CSR-PMA-20feb2012.pdf, Table 6.

5.2.2 Protocol Deviations

The recent FDA guidance to industry, International Conference on Harmonisation (ICH) E3 Guidance on the Structure and Content of Clinical Study Reports (R1), provides guidance on the reporting and categorization of protocol deviations, particularly accounting of protocol deviations.[26] According to this guidance, the definition of important/major protocol deviations for a particular trial is determined in part by the study design, critical procedures, study data, subject protections described in the protocol, and the planned analyses of study data. Furthermore, important/major protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. For example, important/major protocol deviations might include enrolling subjects in violation of key eligibility criteria designed to ensure a specific subject population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial.

On the basis of this guidance document, protocol deviations observed in Study 650 have been identified as either major/important or minor. Major/important protocol deviations constituted enrollment of ineligible patients and noncompliance with the surgical procedure for Toric IOL implantation described in the study protocol. Minor protocol deviations included out-of-window visits, missed measurements in subjects who did not return for visits, assessments performed incorrectly, and other findings.

Protocol deviations recorded during Study 650 up to the time of PMA submission affecting the primary effectiveness endpoint (Form 4) are summarized in **Table 6**, and additional detail on specific types of protocol deviations (important/major and minor) is presented after the table. Fourteen of 391 total protocol deviations were considered important/major deviations according to the FDA guidance; however, none of these involved Form 4 assessments.[26] The remainder of the events was considered to be minor. Only 29 of the 377 minor deviations involved Form 4 assessments.

Table 6 Summary of Protocol Deviations

Type of Deviation	% at Form 4 (n at Form 4/total)
Major	**0 (0/14)**
Failed to meet inclusion criteria	(0/11)
Noncompliance with surgical procedure	(0/3)
Minor	**7.7 (29/377)**
Protocol assessments not performed	(20/151)
Protocol procedures/assessments done incorrectly/incompletely	(2/105)
Documentation practices	(0/82)
Out-of-window visit	(6/22)
Informed consent issues	(0/15)
Missed visit	(1/2)
Total	**7.4 (29/391)**

As corrective action and to avoid/reduce the occurrence of these types of protocol deviations, the sponsor's trained study monitors re-educated the clinical site personnel during monitoring visits on the specific areas of the protocol wherein deviations were observed. In addition, training on the importance of adhering to ICH and GCP guidelines was provided during site visits. Clinical sites were trained repeatedly during monitoring visits and via monitoring visit follow-up letters.

Important/Major Protocol Deviations

A total of 14 important/major protocol deviations in 12 subjects were identified, consisting of enrollment of ineligible subjects (n = 11) and subjects in whom the surgical procedure was not performed in accordance with the study protocol and instructions for use (n = 3). None of these important/major protocol deviations involved Form 4 assessments. Reasons for ineligibility included a history of amblyopia, not meeting the preoperative BCDVA requirements, enrollment based on incorrect keratometry values, and chronic use of systemic steroids. The important/major deviations related to surgical procedure included implantation of the study IOL in the presence of either an anterior capsular tear or a posterior capsular tear per study protocol exclusion criteria.

Minor Protocol Deviations

Protocol deviations were considered minor if they were procedural or administrative in nature with no impact on the study safety and/or effectiveness endpoints (did not affect the scientific validity of the study). The minor protocol deviations included missed study visits; procedures not performed at visits where the patients did return for examination or performed incorrectly; minor informed consent issues; and deviations related to documentation practices (e.g., California Bill of Rights or Health Insurance Portability and Accountability Act release).

Assessment of Impact of Protocol Deviations

Of the 391 protocol deviations reported at the time of PMA submission in March 2012, only a small number were significant; and none compromised the safety of the study subjects or resulted in early discontinuation of subjects from the study for safety reasons.

All protocol deviations were reviewed with the Medical Monitor and the Institutional Review Board to assess impact to safety and welfare of subjects, as well as integrity of the study. Bausch + Lomb clinical personnel reviewed the deviations prior to database lock for the primary analysis for this study to support PMA submission. It was determined that 14 of these deviations were to be classified as important/major as they included enrollment and implantation of eyes of 12 subjects who either did not meet eligibility criteria or should not have had a study lens implanted due to an intraoperative event. Although the visual acuity outcomes for each of these 12 subjects were consistent with outcomes for the remainder of the study population, these subjects were excluded from the effectiveness analyses based on the potential to confound the clinical outcomes.

Statistical Impact of Protocol Deviations

Results of the analyses shown in **Table 7** indicate that removal or inclusion of protocol deviations and conservative imputation does not change the conclusion that the Trulign Toric 1.25 IOL is superior to the Control IOL in reducing targeted cylinder.

Table 7 Statistical Impact of Protocol Deviations and Conservative Imputation on Effectiveness

Analyses	Percentage Reduction in Targeted Cylinder		p value
	Control IOL	Toric 1.25 D IOL	
Current effectiveness analyses			
n	66	71	
%	46.3	81.1	<0.001
Inclusive of all measured Form 4 data (including out-of-window data), regardless of the presence of protocol deviations			
n	71	75	
%	46.0	80.8	<0.001
ITT analysis with all 229 subjects enrolled and imputed[a] a very conservative 11% reduction for Toric 1.25 D IOL and 89% reduction for Control IOL when data are missing or if any minor or important/major protocol deviation was recorded			
n	76	82	
%	56.7	70.0	0.044

Abbreviations: D, diopter; IOL, intraocular lens; ITT, intent to treat.
[a] These imputation values were selected as they represent the "tipping point" for the final analyses (i.e., a percentage reduction of 90% for control IOL and 10% for the Toric 1.25 D IOL would have "tipped" the p value >0.05.

The FDA has indicated that they consider the use of the AT52 lenses to be a major protocol deviation. Ten eyes were implanted with either the AT52SE (Control) or the AT52T (Toric) lenses. To address this concern, Form 4 data for the primary effectiveness endpoint (percent reduction of absolute cylinder) for these 10 lenses was replaced by conservatively imputed values, 81% for the Control lens and 19% for the Toric 1.25 D lens. Using these imputed values, the Toric 1.25 D lens remained significantly better than the Control lens (p=0.049). To restate, even if imputation of the astigmatic reduction for the Control lens is almost doubled (from 46% to 81%) and the astigmatic reduction for the Toric 1.25 D lens is reduced by one

fourth (from 81% to 19%), a statistically significant advantage in ability of the Toric 1.25 D lens to reduce astigmatism over the Control lens is still maintained.

Taken together, the 14 (or 24, if we consider the AT52 lenses) important/major protocol deviations and the low rate of minor deviations related to Form 4 assessments have had a minimal impact on the primary effectiveness endpoint of Study 650. The inclusion of data from protocol deviations as well as the robustness of the results to conservative imputation methods supports the scientific validity of the trial. All data for patients with important/major deviations were included in the Safety Cohort (ensuring all safety events were assessed). Data for patients with important/major deviations were excluded from the effectiveness population. This assessment confirms the scientific validity of the safety and effectiveness data from Study 650.

Clinical Perspective: *Detailed and thorough review and analysis of important/major and minor protocol deviations demonstrate the integrity of the data and the scientific validity of the conclusions.*

5.2.3 Analysis Populations

Analyses presented in this document are based on the following study populations: All Enrolled Cohort, Safety Cohort, Effectiveness Cohort, and Consistent Cohort. The number of subjects included in these populations is shown in **Figure 3**.

The All Enrolled Cohort (N = 229) included all subjects who were enrolled in the study, regardless of whether they underwent cataract surgery. Of the 229 enrolled subjects, 227 who underwent surgery and were implanted with study lens (test or control) were included in the Safety Cohort. Two subjects were not implanted with the study lens at the time of surgery due to either mild capsulorhexis tear or posterior capsular rupture. The Effectiveness Cohort (N = 215) excludes 14 subjects: 2 not implanted with the study lens and 12 who had major protocol deviations. The Consistent Cohort (N = 121) included the All Toric IOL-implanted subjects from the Effectiveness Cohort who did not miss any follow-up visits and was used for the rotational stability analysis.

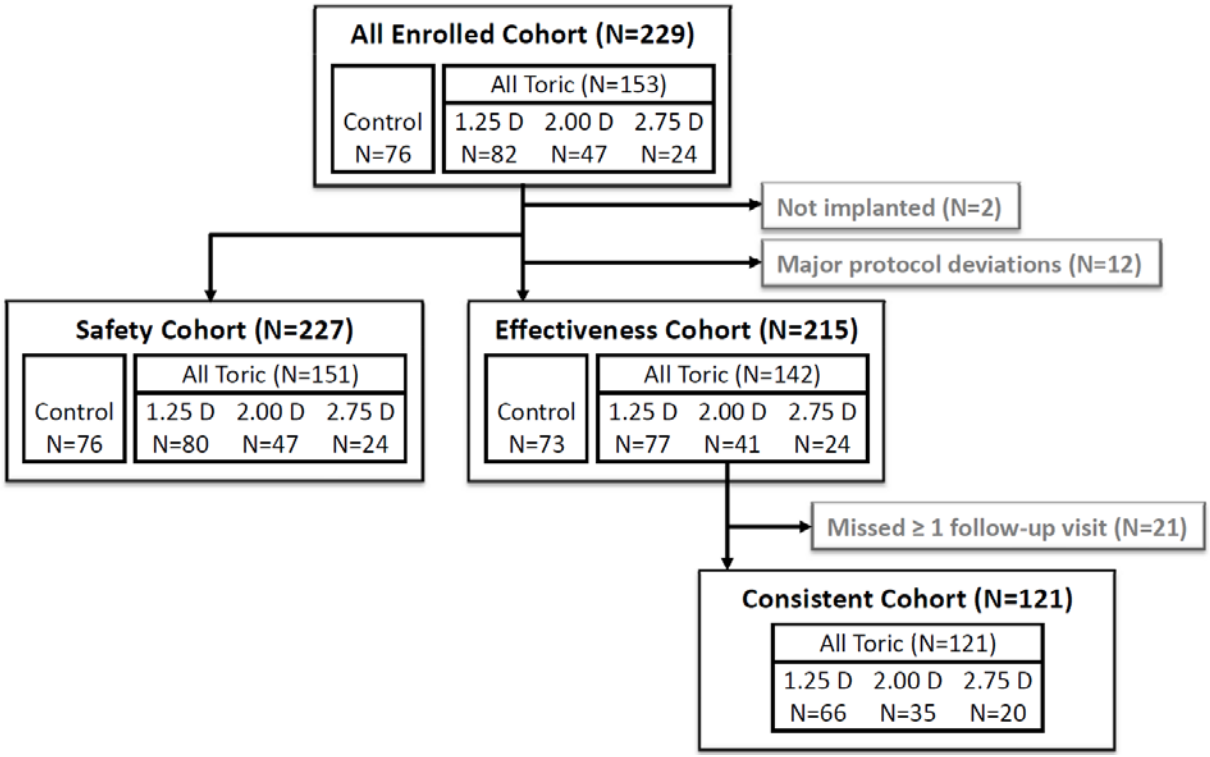


Figure 3 Number of Subjects Included in Each Analysis Cohort.
Abbreviation: D, diopter.
Note: All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, p26, Figure 1.

5.2.4 Demographics

Demographic characteristics of the study population are presented in **Table 8**. In both the Control IOL and All Toric IOL (sum of Toric 1.25 D, 2.00 D, and 2.75 D) groups, approximately 50% of subjects were female, with a mean age of 69.8 and 70.1 years, respectively. The age range for the study population was 47 to 89 years.

Table 8 Demographics of Study Population (All Enrolled Cohort)

Characteristic	Control IOL (N = 76)	Toric IOL 1.25 D (N = 82)	Toric IOL 2.00 D (N = 47)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 153)
Age, years					
n	76	82	47	24	153
Mean (SD)	69.8 (9.2)	69.9 (8.8)	70.4 (8.4)	70.4 (10.8)	70.1 (9.0)
Category, n (%)					
< 60	13 (17.1)	8 (9.8)	3 (6.4)	5 (20.8)	16 (10.5)
60 to 69	20 (26.3)	32 (39.0)	20 (42.6)	5 (20.8)	57 (37.3)
70 to 79	34 (44.7)	27 (32.9)	15 (31.9)	7 (29.2)	49 (32.0)
≥ 80	9 (11.8)	15 (18.3)	9 (19.1)	7 (29.2)	31 (20.3)
Gender, n (%)					
n	76	82	47	24	153
Male	34 (44.7)	35 (42.7)	27 (57.4)	10 (41.7)	72 (47.1)
Female	42 (55.3)	47 (57.3)	20 (42.6)	14 (58.3)	81 (52.9)
Operative eye, n (%)					
n	76	82	47	24	153
Right	42 (55.3)	37 (45.1)	25 (53.2)	12 (50.0)	74 (48.4)
Left	34 (44.7)	45 (54.9)	22 (46.8)	12 (50.0)	79 (51.6)

Abbreviations: D, diopter; IOL, intraocular lens; n, eyes available for analysis; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 9.

5.3 Safety

5.3.1 Safety Outcomes

The addition of the toric optic did not introduce any new safety concerns compared with the parent lens or the historical performance of IOLs. All safety endpoints of Study 650 (i.e., preservation of BCVA [at distance and near] and incidence of complications and AEs) were met.

5.3.1.1 Preservation of Best-Corrected Visual Acuity

BCDVA and BCNVA are presented for the All Toric IOL eyes in **Table 9** and **Table 10**, respectively.

BCDVA was 20/40 or better in the majority (> 97%) of All Toric IOL eyes at the postoperative visits, including unscheduled visits (**Table 9**). All postoperative results exceeded the 92.5% value provided in the FDA Grid for BCDVA of 20/40 or better.

Table 9 BCDVA at Each Examination (All Toric IOL; Safety Cohort)

Parameter	Study Visit, n (%) Preop	Form 3	Form 4	Unscheduled
20/40 or better	108 (72.0)	143 (99.3)	139 (97.9)	32 (97.0)
Worse than 20/40	42 (28.0)	1 (0.7)	3 (2.1)	1 (3.0)

Abbreviations: BCDVA, best-corrected distance visual acuity; IOL, intraocular lens.
Source: 650 CSR-PMA-20feb2012.pdf, Table 10.

Consistent with the BCDVA findings, BCNVA of 20/40 or better was reported in the majority (> 98%) of eyes at the postoperative visits, including unscheduled visits (**Table 10**).

Table 10 BCNVA at Each Examination (All Toric IOL; Safety Cohort)

Parameter	Study Visit, n (%)			
	Preop	Form 3	Form 4	Unscheduled
20/40 or better	124 (89.2)	141 (98.6)	142 (100.0)	24 (100.0)
Worse than 20/40	15 (10.8)	2 (1.4)	0	0

Abbreviations: BCNVA, best-corrected near visual acuity; D, diopter; IOL, intraocular lens.
Source: 650 CSR-PMA-20feb2012.pdf, Table 12.

5.3.1.2 Adverse Events

Surgical Adverse Events

The frequency of surgical AEs in the Safety Cohort is presented in **Table 11**. A total of 7 subjects reported 8 AEs. All AEs were mild and assessed as unrelated to the study device. Six AEs were judged by the investigator as related to the study procedure.

Table 11 Frequency of Surgical Adverse Events, Implanted Subjects (Safety Cohort)

System Organ Class Preferred Term	n (%)				
	Control IOL (N = 76)	Toric IOL			
		1.25 D (N = 80)	2.00 D (N = 47)	2.75 D (N = 24)	All Toric[a] (N = 151)
Total number of AEs	3	2	3	0	5
Number of subjects with ≥ 1 AE	2 (2.6)	2 (2.5)	3 (6.4)	0	5 (3.3)
Eye Disorders	**1 (1.3)**	**1 (1.3)**	**2 (4.3)**	**0**	**3 (2.0)**
Corneal disorder	1 (1.3)	0	0	0	0
Foreign body sensation in eyes	0	0	1 (2.1)	0	1 (0.7)
Hordeolum	0	0	1 (2.1)	0	1 (0.7)
Iris atrophy	0	1 (1.3)	0	0	1 (0.7)
Injury, Poisoning, and Procedural Complications	**2 (2.6)**	**1 (1.3)**	**1 (2.1)**	**0**	**2 (1.3)**
Cataract operation complication	2 (2.6)	0	0	0	0
Incision site complication	0	0	1 (2.1)	0	1 (0.7)
Posterior capsule rupture	0	1 (1.3)	0	0	1 (0.7)

Abbreviations: AE, adverse event; D, diopter; IOL, intraocular lens.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
The total number of AEs includes all AEs for subjects. Subjects may have > 1 AE per system organ class and preferred term. At each level of subject summarization, a subject was counted once if he/she reported ≥ 1 events.
Source: 650 CSR-PMA-20feb2012.pdf, Table 13.

FDA Grid Adverse Events

Table 12 and **Table 13** display the rates of cumulative AEs reported through study exit for the Control IOL and All Toric IOL groups, respectively, compared with the FDA Grid. Cumulative AEs were defined as AEs that occurred at any time throughout the study.

A total of 4 cumulative AEs were reported through Form 4. Two of these AEs occurred in the All Toric IOL group: 1 AE (0.7%) of macular edema and 1 AE (0.7%) of SSI (**Table 13**). In the Control IOL group, 1 AE (1.3%) of macular edema and 1 AE (1.3%) of SSI were reported (**Table 12**). The SSI events are described below.

The 2 cases of SSI involved lens repositioning that was not related to lens axis misalignment or rotation. One eye in the Control IOL cohort [redacted]) experienced lens malposition at postoperative Day 1. The eye in the Toric 2.00 IOL cohort ([redacted] experienced lens vaulting at Form 4; however, the Investigator determined this event was due to subject noncompliance with medications. Both lenses were repositioned without sequelae.

When comparing FDA Grid AEs occurring through Form 4 in the All Toric IOL group (**Table 13**), the cumulative rate of reported macular edema (1/151 [0.7%]) is below the FDA Grid rate (3.0%) and the rates presented in PMA P030002 for Crystalens Accommodating IOL Model AT45 (3.7%). The cumulative rate of reported SSI (1/151 [0.7%]) is comparable with the rate reported in the FDA Grid (0.8%) and the rate reported in PMA P030002 (0.6%).

Table 12 FDA Grid Cumulative Adverse Events Reported at Each Postoperative Visit (Control IOL; Safety Cohort)

Adverse Event	n/N (%)						FDA Grid, %	p value	Reason for SSI
	Unscheduled	Form 1	Form 2	Form 3	Form 4	Cumu-lative			
Endophthalmitis	0/34	0/76	0/75	0/74	0/69	0/76	0.1	>0.999	--
Hypopyon	0/34	0/76	0/75	0/74	0/69	0/76	0.3	>0.999	--
Lens dislocated from posterior chamber	0/34	0/76	0/75	0/74	0/69	0/76	0.1	>0.999	--
Macular edema	0/34	0/76	0/75	1/74 (1.4)	1/70 (1.4)	1/76 (1.3)	3.0	0.901	--
Pupillary block	0/34	0/76	0/75	0/74	0/69	0/76	0.1	>0.999	--
Retinal detachment	0/34	0/76	0/75	0/74	0/69	0/76	0.3	>0.999	--
Secondary surgical intervention	0/34	0/76	1/75 (1.3)	0/74	0/69	1/76 (1.3)	0.8	0.457	IOL reposition due to IOL malposition

Abbreviations: FDA, US Food and Drug Administration; IOL, intraocular lens; SSI, secondary surgical intervention.
The p value was calculated from the exact binomial test comparing the cumulative or persistent (at Form 6) proportion of eyes with each adverse event to the FDA Grid proportion (1-sided test).
Source: 650 CSR-PMA-20feb2012.pdf, Table 15.

Table 13 FDA Grid Cumulative Adverse Events Reported at Each Postoperative Visit (All-Toric IOL; Safety Cohort)

Adverse Event	n/N (%)						FDA Grid, %	p value	Reason for SSI
	Unscheduled	Form 1	Form 2	Form 3	Form 4	Cumu-lative			
Endophthalmitis	0/63	0/151	0/148	0/145	0/142	0/151	0.1	>0.999	--
Hypopyon	0/63	0/151	0/148	0/145	0/142	0/151	0.3	>0.999	--
Lens dislocated from posterior chamber	0/63	0/151	0/148	0/145	0/142	0/151	0.1	>0.999	--
Macular edema	0/63	0/151	0/148	1/145 (0.7)	1/142 (0.7)	1/151 (0.7)	3.0	0.990	--
Pupillary block	0/63	0/151	0/148	0/145	0/142	0/151	0.1	>0.999	--
Retinal detachment	0/63	0/151	0/148	0/145	0/142	0/151	0.3	>0.999	--
Secondary surgical intervention	0/63	0/151	0/148	0/145	1/142 (0.7)	1/151 (0.7)	0.8	0.703	IOL reposition due to anterior vaulted IOL (Toric 2.00 cohort)

Abbreviations: FDA, US Food and Drug Administration; IOL, intraocular lens; SSI, secondary surgical intervention.
The p value was calculated from the exact binomial test comparing the cumulative or persistent (at Form 6) proportion of eyes with each adverse event to the FDA Grid proportion (1-sided test).
Source: 650 CSR-PMA-20feb2012.pdf, Table 19.

5.3.1.3 Serious Adverse Events

Two ocular serious adverse events (SAEs) in study eyes were reported. Brief narratives of these events are provided below.

- One ocular SAE occurred in the Toric 2.00 IOL group. Subject [redacted] experienced anterior vault, noted at Form 4, which was determined by the investigator to be of "mild" intensity. The orientation of the Toric IOL axis was 86.74° at the conclusion of surgery, 86.90° at Form 3, and 88.02° at Form 4. At the Form 3 (postoperative Days 30-60) visit, the UCDVA was 20/25 with a manifest refraction of –0.50 + 0.50 @ 10 and BCDVA of 20/20. Compromise to both UCDVA and BCDVA was noted at the Form 4 (postoperative Days 120-180) visit. The UCDVA had worsened to 20/63 due to a 2.00 D myopic shift in the manifest refraction (–2.50 +0.50 @ 08) with minimal change in refractive cylinder. The BCDVA had worsened to 20/32. The etiology for both the myopic shift and change in BCDVA was revealed by the slit lamp examination at this visit, where anterior vault of the IOL and grade 2 PCO were identified. The Investigator determined that the event was due to the subject's noncompliance with postoperative anti-inflammatory medications, which resulted in atypical fibrosis of the capsular bag, excessive capsular contraction, and subsequent anterior vault of the IOL. The Investigator performed an SSI to reposition the IOL.
- One ocular SAE occurred in the Control IOL group. Subject [redacted] experienced IOL malposition, noted at postoperative Day 1, with the superior haptic placed in the capsular bag and the inferior haptic placed in the sulcus. The event was assessed by the Investigator to be unrelated to the control device and probably related to study procedure. The Investigator determined that the incorrect placement of the inferior haptic could create a potential for iris contact and, thus, an SSI to reposition the inferior haptic in the capsular bag was performed. At the Form 4 (postoperative Days 120-180) visit, the UCDVA was 20/50 with a myopic manifest refraction of –1.00 +0.50 @ 11 and BCDVA of 20/32.

Clinical Perspective: *Anterior vault is a known complication of the parent accommodating lens. Prevention and treatment strategies for this event have been implemented. Inaccurate positioning is a known complication of all IOLs. Neither SAE (and, in fact, no AE) related specifically to the addition of a toric correction to the accommodating platform.*

5.3.1.4 Other Safety Analyses

Posterior Capsular Opacification

The dilated assessment of PCO grade for the Safety Cohort at Forms 3 and 4 is presented in **Table 14**. At Form 4, 72.5% of subjects in the Control IOL group and 77.9% of subjects in the All Toric IOL group had a PCO grade ≤ 1.

Table 14 Dilated Assessment of PCO Grade—Forms 3 and 4 (Postoperative Days 30 – 60 and 120 – 180; Safety Cohort)

Study Visit PCO Grade	n (%)				
		Toric IOL			
	Control IOL (N = 76)	1.25 D (N = 80)	2.00 D (N = 47)	2.75 D (N = 24)	All Toric[a] (N = 151)
Form 3					
n	74	78	45	22	145
0	42 (56.8)	47 (60.3)	25 (55.6)	12 (54.5)	84 (57.9)
1	24 (32.4)	28 (35.9)	16 (35.6)	10 (45.5)	54 (37.2)
2	8 (10.8)	3 (3.8)	3 (6.7)	0	6 (4.1)
3	0	0	1 (2.2)	0	1 (0.7)
4	0	0	0	0	0
Form 4					
n	69	73	45	22	140
0	20 (29.0)	20 (27.4)	19 (42.2)	10 (45.5)	49 (35.0)
1	30 (43.5)	36 (49.3)	15 (33.3)	9 (40.9)	60 (42.9)
2	18 (26.1)	17 (23.3)	10 (22.2)	2 (9.1)	29 (20.7)
3	1 (1.4)	0	1 (2.2)	0	1 (0.7)
4	0	0	0	1 (4.5)	1 (0.7)

Abbreviations: D, diopter; IOL, intraocular lens; PCO, posterior capsule opacification.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
PCO Grade 0 = none, 1 = trace or mild, 2 = moderate, 3 = severe, 4 = very severe.
Source: 650 CSR-PMA-20feb2012.pdf, Table 26.

Nd:YAG Capsulotomy

Nd:YAG capsulotomy rates for the Safety Cohort are presented in **Table 15**. A total of 24 eyes (14 [18.4%] Control IOL and 10 [6.6%] All Toric IOL) underwent Nd:YAG capsulotomy through Form 4.

Table 15 Nd:YAG Capsulotomy (Safety Cohort)

Parameter	n (%)				
		Toric IOL			
	Control IOL (N = 76)	1.25 D (N = 80)	2.00 D (N = 47)	2.75 D (N = 24)	All Toric[a] (N = 151)
Eyes with capsulotomies	14 (18.4)	6 (7.5)	4 (8.5)	0	10 (6.6)
Capsulotomies performed by time period (days postop)					
0 to 29	0	1 (1.3)	0	0	1 (0.7)
30 to 119	2 (2.6)	0	1 (2.1)	0	1 (0.7)
120 to 329	12 (15.8)	5 (6.3)	3 (6.4)	0	8 (5.3)

Abbreviations: D, diopter; IOL, intraocular lens.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 27.

Intraocular Pressure

Intraocular pressure for subjects in the Safety Cohort is presented for the preoperative visit and Form 4 in **Table 16**. None of the Control IOL or Toric IOL eyes had IOP > 27 mm Hg.

Table 16 Intraocular Pressure—Preoperative Visit and Form 4 (Postoperative Days 120 – 180; Safety Cohort)

	n (%)				
		Toric IOL			
Study Visit IOP (mm Hg)	Control IOL (N = 76)	1.25 D (N = 80)	2.00 D (N = 47)	2.75 D (N = 24)	All Toric[a] (N = 151)
Preoperative Visit					
n	76	79	47	24	150
Mean (SD)	15.3 (3.1)	14.7 (3.1)	14.6 (2.9)	15.8 (3.2)	14.9 (3.1)
< 5	0	0	0	0	0
5 - 9	0	1 (1.3)	0	0	1 (0.7)
10 - 15	42 (55.3)	48 (60.8)	31 (66.0)	12 (50.0)	91 (60.7)
16 -21	32 (42.1)	28 (35.4)	15 (31.9)	12 (50.0)	55 (36.7)
22 - 27	2 (2.6)	2 (2.5)	1 (2.1)	0	3 (2.0)
> 27	0	0	0	0	0
Form 4					
n	69	74	46	22	142
Mean (SD)	13.0 (2.8)	12.7 (2.5)	13.6 (2.7)	13.7 (2.7)	13.2 (2.6)
< 5	0	0	0	0	0
5 - 9	3 (4.3)	2 (2.7)	1 (2.2)	2 (9.1)	5 (3.5)
10 - 15	52 (75.4)	64 (86.5)	33 (71.7)	15 (68.2)	112 (78.9)
16 -21	13 (18.8)	7 (9.5)	12 (26.1)	5 (22.7)	24 (16.9)
22 - 27	1 (1.4)	1 (1.4)	0	0	1 (0.7)
> 27	0	0	0	0	0

Abbreviations: D, diopter; IOL, intraocular lens; IOP, intraocular pressure; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 24.

Fellow Eye Serious Adverse Events

One ocular SAE occurred in the fellow eye of a study subject. This eye was not enrolled in the study and not included in the safety or effectiveness cohorts. Subject [redacted] experienced anterior vault that was determined by the Investigator to be of "moderate" intensity. The event was assessed by the Investigator to be possibly due to zonular dehiscence and unrelated to the study device or study procedure. The Investigator performed an SSI to replace the IOL with a sulcus fixated monofocal IOL.

5.3.2 Safety Conclusions

All safety endpoints of Study 650 were met. The addition of a toric optic did not introduce any new safety concerns compared with the parent Crystalens Accommodating IOL. The Trulign Toric Accommodating IOL demonstrated preservation of BCDVA and BCNVA, and the incidences of complications and AEs reported for the All Toric population did not exceed the FDA Grid of historical controls or those reported with the parent Crystalens Accommodating IOL, Model AT45 (PMA P030002). No SSIs were related to rotational instability.

5.4 Effectiveness

5.4.1 Surgical Parameters

Surgical parameters are summarized in **Table 17**. In the majority of subjects (> 84%), in both the Control IOL and All Toric IOL groups, the incision was made in the cornea. The mean incision location was 84.4° in the Control IOL group and 89.5° in the All Toric IOL group. The Control IOL and All-Toric IOL groups were comparable with respect to the mean initial incision size (2.6 mm each) and mean capsulorhexis size (5.4 mm each). In the All-Toric IOL eyes, mean target axis orientation and mean actual axis orientation were 89.0° and 89.1°, respectively.

Table 17 Surgical Parameters (Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
Incision location, n (%)					
n	73	77	41	24	142
Cornea	65 (89.0)	71 (92.2)	31 (75.6)	18 (75.0)	120 (84.5)
Limbus	3 (4.1)	2 (2.6)	1 (2.4)	0	3 (2.1)
Sclera	5 (6.8)	4 (5.2)	9 (22.0)	6 (25.0)	19 (13.4)
Incision location (°)					
n	73	77	41	24	142
Mean (SD)	84.4 (55.7)	91.6 (64.9)	85.6 (64.9)	89.3 (55.2)	89.5 (63.0)
Initial incision size (mm)					
n	73	77	41	24	142
Mean (SD)	2.58 (0.36)	2.62 (0.32)	2.55 (0.37)	2.74 (0.15)	2.62 (0.32)
Capsulorhexis size (mm)					
n	73	77	41	24	142
Mean (SD)	5.44 (0.50)	5.46 (0.54)	5.25 (0.48)	5.32 (0.62)	5.38 (0.54)
Target axis orientation (°)					
n	0	77	41	24	142
Mean (SD)	NA	91.7 (63.5)	83.1 (62.6)	90.5 (54.5)	89.0 (61.5)
Actual axis orientation (°)					
n	0	77	41	24	142
Mean (SD)	NA	91.8 (63.5)	83.2 (62.8)	90.5 (54.5)	89.1 (61.6)

Abbreviations: D, diopter; IOL, intraocular lens; NA, not applicable; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2013.pdf, Table 29.

5.4.2 Effectiveness Outcomes

5.4.2.1 Percent Reduction in Cylinder

The primary statistical analysis consists of a comparison of reduction in cylinder between the low cylinder Toric IOL (1.25 D) eyes and Control IOL eyes at the time point at which rotational stability was achieved (i.e., Form 4, Days 120-180). The mean percent reduction in absolute cylinder, as defined in **5.1.4**, was 85.8% in the All Toric eyes (**Table 18**). The mean percent reduction in absolute cylinder was significantly greater in the Toric 1.25 IOL eyes compared with the Control IOL eyes (81.1% vs 46.3%, respectively; $p<0.001$).

Table 18 Percent Reduction in Absolute Cylinder Expressed as Percentage of Intended Reduction in Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL			
		1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
n	66	71	40	22	133
Mean (SD)	46.3 (44.16)	81.1 (31.77)	87.9 (26.69)	97.2 (18.73)	85.8 (28.93)
95% CI	(35.46, 57.17)	(73.53, 88.57)	(79.35, 96.43)	(88.92, 105.53)	(80.82, 90.75)
p value		<0.001			

Abbreviations: CI, confidence interval; D, diopter; n, eyes available for analysis; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 31.

5.4.2.2 Percentage of Eyes With Reduction in Cylinder Within 0.50 D and 1.00 D of Intended Reduction in Cylinder

The percentage of eyes with a reduction in cylinder within ± 0.50 D and within ± 1.00 D of intended reduction in cylinder at Form 4 is presented in **Table 19**. The intended reduction in cylinder was calculated under the assumption that a toric lens would be implanted. A higher percent reduction in cylinder within ± 0.50 D (79.7% vs 45.5%, respectively) and within ± 1.00 D (95.5% vs 72.7%, respectively) of the intended reduction in cylinder was observed for the All Toric IOL eyes compared with the Control IOL eyes.

Table 19 Percent of Eyes With Reduction in Cylinder Within 0.50 D and 1.00 D of Intended Reduction in Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL			
		1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
n	66	71	40	22	133
Within 0.50 D of intended, n (%) 95% CI	30 (45.5) (33.1, 58.2)	58 (81.7) (70.7, 89.9)	32 (80.0) (64.4, 90.9)	16 (72.7) (49.8, 89.3)	106 (79.7) (71.9, 86.2)
Within 1.00 D of intended, n (%) 95% CI	48 (72.7) (60.4, 83.0)	68 (95.8) (88.1, 99.1)	37 (92.5) (79.6, 98.4)	22 (100.0) (84.6, 100.0)	127 (95.5) (90.4, 98.3)

Abbreviations: CI, confidence interval; D, diopter; IOL, intraocular lens.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Note: 95% CIs are exact binomial CIs.
Source: 650 CSR-PMA-20feb2012.pdf, Table 32.

5.4.2.3 Lens Axis Misalignment as Determined by a Photographic Method

Lens axis misalignment, as determined by photographic method performed by an independent reading center, was measured relative to both surgical markings and target axis. Misalignment of the Toric IOL was assessed using a validated image analysis technique with repeatability of ± 0.79°.[27] The absolute lens axis misalignment from surgical markings and target are determined on the day of surgery or at the preoperative visit, respectively, and compared with the Toric IOL orientation at Form 4 (4-6 months postoperatively). Three factors contribute to lens axis

misalignment between the day of surgery and Form 4: (1) accuracy of marking the steep axis of the cornea prior to surgery; (2) accuracy of Toric IOL orientation at the time of surgery; and (3) Toric IOL rotational stability. It is important to note that the first 2 factors are surgeon dependent and the last factor is dependent on the IOL.

As shown in **Table 20**, the mean absolute lens axis misalignment from surgical markings and target were 2.57° and 4.76°, respectively.

Table 20 Absolute Lens Axis Misalignment From Surgical Markings and Target—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Toric IOL			
	1.25 D (N = 77)	**2.00 D (N = 41)**	**2.75 D (N = 24)**	**All Toric[a] (N = 142)**
Surgical Markings				
n	69	37	20	126
Mean (SD)	2.59 (2.578)	2.14 (1.988)	3.24 (2.729)	2.57 (2.452)
Degree of lens axis misalignment, n (%)				
< 5°	59 (85.5)	32 (86.5)	16 (80.0)	107 (84.9)
< 10°	67 (97.1)	37 (100.0)	19 (95.0)	123 (97.6)
< 20°	69 (100.0)	37 (100.0)	20 (100.0)	126 (100.0)
≤ 30°	69 (100.0)	37 (100.0)	20 (100.0)	126 (100.0)
> 30°	0	0	0	0
Target				
n	70	38	21	129
Mean (SD)	5.06 (3.862)	3.79 (2.362)	5.51 (4.650)	4.76 (3.668)
Degree of lens axis misalignment, n (%)				
< 5°	38 (54.3)	26 (68.4)	12 (57.1)	76 (58.9)
< 10°	62 (88.6)	38 (100.0)	18 (85.7)	118 (91.5)
< 20°	70 (100.0)	38 (100.0)	21 (100.0)	129 (100.0)
≤ 30°	70 (100.0)	38 (100.0)	21 (100.0)	129 (100.0)
> 30°	0	0	0	0

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 33 and Table 35.

5.4.2.4 Absolute Rotation Since Implantation

As shown in **Table 21**, the mean (SD) absolute rotation since implantation was 1.78° (1.971°) for the Toric 1.25 IOL eyes, 1.35° (1.083°) for the Toric 2.00 IOL eyes, and 1.68° (1.628°) for the Toric 2.75 IOL eyes. The majority (> 96%) of eyes demonstrated ≤ 5.00° of absolute rotation since implantation.

Table 21 Absolute Rotation Since Implantation—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Toric IOL			
	1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
n	69	37	21	127
Mean (SD)	1.78 (1.971)	1.35 (1.083)	1.68 (1.628)	1.64 (1.699)
Degree of absolute rotation, n (%)				
≤ 5.00°	66 (95.7)	37 (100.0)	20 (95.2)	123 (96.9)
5.01° to 10.00°	3 (4.3)	0	1 (4.8)	4 (3.1)

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 54.

5.4.2.5 Rotational Stability Between Consecutive Visits

According to the ANSI standard, stability of the Toric IOL axis is achieved when 90% of the implanted lenses rotate ≤ 5.00° between 2 consecutive visits at least 3 months apart. As shown for the Consistent Cohort in **Table 22**, 99.2% of Toric IOLs demonstrated ≤ 5.00° of rotation since the last visit.

Table 22 Rotational Stability Between Consecutive Visits—Form 4 (Postoperative Days 120 – 180; Consistent Cohort)

Parameter	Toric IOL			
	1.25 D (N = 66)	2.00 D (N = 35)	2.75 D (N = 20)	All Toric[a] (N = 121)
Absolute value of rotation (°)				
n	66	35	20	121
Mean (SD)	1.14 (1.081)	1.15 (0.914)	1.64 (1.316)	1.22 (1.086)
Lens rotating ≤ 5.00° since last visit, n (%)	65 (98.5)	35 (100.0)	20 (100.0)	120 (99.2)

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 55.

Clinical Perspective: *Alignment on axis and rotational stability, together with accurate preoperative keratometry and toric power calculation, represent the critical factors that contribute to the percent reduction in manifest refractive cylinder.*

5.4.2.6 Best-Corrected Distance Visual Acuity Without Glare

BCDVA without glare at Form 4 is presented in **Table 23**. The mean (SD) logMAR BCDVA without glare was 0.011 (0.097) for the Control IOL eyes and 0.007 (0.090) for the All Toric IOL eyes. Of the All Toric IOL eyes, 99.2% achieved BCDVA without glare of 20/40 or better, which exceeded the FDA Grid value of 92.5% for BCDVA without glare of 20/40 or better. Overall, no statistically significant difference in mean logMAR BCDVA without glare was observed between the Control IOL and All Toric IOL eyes (p=0.947).

Table 23 BCDVA Without Glare—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
BCDVA (logMAR)					
n	66	71	40	22	133
Mean (SD)	0.011 (0.097)	0.006 (0.072)	0.002 (0.082)	0.018 (0.146)	0.007 (0.090)
BCDVA (Snellen), n (%)					
n	66	71	40	22	133
20/20 or better	47 (71.2)	55 (77.5)	29 (72.5)	14 (63.6)	98 (73.7)
20/25 or better	61 (92.4)	69 (97.2)	39 (97.5)	20 (90.9)	128 (96.2)
20/32 or better	64 (97.0)	71 (100.0)	40 (100.0)	21 (95.5)	132 (99.2)
20/40 or better	66 (100.0)	71 (100.0)	40 (100.0)	21 (95.5)	132 (99.2)
Worse than 20/40	0	0	0	1 (4.5)	1 (0.8)
p value[b]					
Control vs All Toric	0.947	--	--	--	--

Abbreviations: BCDVA, best-corrected distance visual acuity; D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
[b] p value comparing logMAR.
Source: 650 CSR-PMA-20feb2012.pdf, Table 40.

5.4.2.7 Distance-Corrected Intermediate Visual Acuity at 32 Inches (80 cm)

DCIVA at 32 inches at Form 4 is presented in **Table 24**. The mean (SD) logMAR DCIVA was 0.07 (0.143) in the Control IOL eyes and 0.06 (0.127) in the All Toric IOL eyes. There was no statistically significant difference in mean logMAR DCIVA between the Control IOL and All Toric IOL eyes (p=0.760).

Table 24 DCIVA at 32 inches (80 cm)—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
DCIVA (logMAR)					
n	65	71	39	22	132
Mean (SD)	0.07 (0.143)	0.06 (0.107)	0.06 (0.147)	0.04 (0.148)	0.06 (0.127)
DCIVA (Snellen), n (%)					
n	65	71	39	22	132
20/20 or better	31 (47.7)	33 (46.5)	13 (33.3)	13 (59.1)	59 (44.7)
20/25 or better	50 (76.9)	61 (85.9)	31 (79.5)	17 (77.3)	109 (82.6)
20/32 or better	58 (89.2)	66 (93.0)	36 (92.3)	20 (90.9)	122 (92.4)
20/40 or better	62 (95.4)	71 (100.0)	39 (100.0)	22 (100.0)	132 (100.0)
Worse than 20/40	3 (4.6)	0	0	0	0
p value[b]					
Control vs All Toric	0.760	--	--	--	--

Abbreviations: D, diopter; DCIVA, distance-corrected intermediate visual acuity; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
[b] p value comparing logMAR.
Source: S650 Intermediate VA Revision 17 Aug 2012, Table 4.

5.4.2.8 Near Visual Acuity With Distance Correction at 16 Inches (40 cm) With and Without the Minimal Reading Add

DCNVA at 16 inches without and with Add are presented in **Table 25** and **Table 26**, respectively. The mean (SD) logMAR DCNVA was 0.30 (0.138) in the Control IOL eyes and 0.30 (0.144) in the All Toric IOL eyes (**Table 25**). There was no statistically significant difference in mean logMAR DCNVA between the Control IOL and All Toric IOL eyes (p=0.912). However, a statistically significant mean difference between the Control IOL and All Toric IOL eyes were reported for Add (p=0.046; **Table 26**).

Table 25 DCNVA at 16 inches (40 cm)—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
DCNVA (logMAR)					
n	65	71	39	22	132
Mean (SD)	0.30 (0.138)	0.30 (0.131)	0.31 (0.152)	0.26 (0.170)	0.30 (0.144)
DCNVA (Snellen), n (%)					
n	65	71	39	22	132
20/20 or better	1 (1.5)	0	3 (7.7)	4 (18.2)	7 (5.3)
20/25 or better	9 (13.8)	7 (9.9)	7 (17.9)	5 (22.7)	19 (14.4)
20/32 or better	23 (35.4)	28 (39.4)	10 (25.6)	9 (40.9)	47 (35.6)
20/40 or better	42 (64.6)	45 (63.4)	22 (56.4)	16 (72.7)	83 (62.9)
Worse than 20/40	23 (35.4)	26 (36.6)	17 (43.6)	6 (27.3)	49 (37.1)
p value[b]					
Control vs All Toric	0.912	--	--	--	--

Abbreviations: D, diopter; DCNVA, distance-corrected near visual acuity; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
[b] p value comparing logMAR.
Source: 650 CSR-PMA-20feb2012.pdf, Table 38.

Table 26 DCNVA at 16 inches (40 cm) With Add—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
DCNVA with Add (logMAR)					
n	66	71	40	22	133
Mean (SD)	0.05 (0.073)	0.04 (0.075)	0.03 (0.066)	0.04 (0.073)	0.04 (0.071)
DCNVA with Add (Snellen)					
n	66	71	40	22	133
20/20 or better	41 (62.1)	48 (67.6)	29 (72.5)	15 (68.2)	92 (69.2)
20/25 or better	60 (90.9)	65 (91.5)	37 (92.5)	20 (90.9)	122 (91.7)
20/32 or better	65 (98.5)	69 (97.2)	40 (100.0)	22 (100.0)	131 (98.5)
20/40 or better	66 (100.0)	71 (100.0)	40 (100.0)	22 (100.0)	133 (100.0)
p value					
Control vs All Toric	0.338	--	--	--	--
Add (D)					
Mean (SD)	1.60 (0.580)	1.45 (0.446)	1.39 (0.537)	1.46 (0.630)	1.43 (0.505)
p value					
Control vs All Toric	0.046	--	--	--	--

Abbreviations: D, diopter; DCNVA, distance-corrected near visual acuity; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 39.

Clinical Perspective: *The minimal reading add for near vision at 40 cm reflects 1.00 D of accommodative amplitude provided by both the parent platform accommodating IOL and the Trulign Toric Accommodating IOL (i.e., 2.50 D – 1.00 D = 1.50 D).*

5.4.2.9 Uncorrected Distance, Intermediate, and Near Visual Acuity

UCDVA (20 feet), UCIVA (32 inches), and UCNVA (16 inches) results at Form 4 are presented in **Table 27**, **Table 28**, and **Table 29**, respectively. The mean logMAR (Snellen) visual acuity was 0.10 (20/25) at distance, 0.04 (20/20) at intermediate, and 0.29 (20/40) at near.

Table 27 UCDVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
UCDVA (logMAR)					
n	66	71	40	22	133
Mean (SD)	0.19 (0.181)	0.10 (0.128)	0.09 (0.135)	0.10 (0.134)	0.10 (0.130)
UCDVA (Snellen)					
n	66	71	40	22	133
20/20 or better	17 (25.8)	27 (38.0)	14 (35.0)	7 (31.8)	48 (36.1)
20/25 or better	30 (45.5)	50 (70.4)	30 (75.0)	15 (68.2)	95 (71.4)
20/32 or better	44 (66.7)	61 (85.9)	35 (87.5)	18 (81.8)	114 (85.7)
20/40 or better	50 (75.8)	69 (97.2)	39 (97.5)	22 (100.0)	130 (97.7)
Worse than 20/40	16 (24.2)	2 (2.8)	1 (2.5)	0	3 (2.3)
p value					
Control vs Toric 1.25 D	0.004	--	--	--	--
Control vs All Toric	< 0.001				

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation; UCDVA, uncorrected distance visual acuity.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 43.

Table 28 UCIVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
UCIVA (logMAR)					
n	66	71	40	22	133
Mean (SD)	0.07 (0.155)	0.04 (0.117)	0.06 (0.153)	0.01 (0.115)	0.04 (0.129)
UCIVA (Snellen)					
n	66	71	40	22	133
20/20 or better	38 (57.6)	43 (60.6)	18 (45.0)	15 (68.2)	76 (57.1)
20/25 or better	49 (74.2)	62 (87.3)	33 (82.5)	21 (95.5)	116 (87.2)
20/32 or better	57 (86.4)	66 (93.0)	38 (95.0)	21 (95.5)	125 (94.0)
20/40 or better	62 (93.9)	70 (98.6)	38 (95.0)	22 (100.0)	130 (97.7)
Worse than 20/40	4 (6.1)	1 (1.4)	2 (5.0)	0	3 (2.3)
p value					
Control vs Toric 1.25 D	0.465	--	--	--	--
Control vs All Toric	0.457	--	--	--	--

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation; UCIVA, uncorrected intermediate visual acuity.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: S650 Intermediate VA Revision 17 Aug 2012, Table 2.

Table 29 UCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
UCNVA (logMAR)					
n	66	71	40	22	133
Mean (SD)	0.28 (0.138)	0.29 (0.148)	0.30 (0.144)	0.27 (0.146)	0.29 (0.146)
UCNVA (Snellen)					
n	66	71	40	22	133
20/20 or better	1 (1.5)	1 (1.4)	1 (2.5)	3 (13.6)	5 (3.8)
20/25 or better	10 (15.2)	14 (19.7)	6 (15.0)	3 (13.6)	23 (17.3)
20/32 or better	29 (43.9)	28 (39.4)	14 (35.0)	8 (36.4)	50 (37.6)
20/40 or better	48 (72.7)	51 (71.8)	25 (62.5)	18 (81.8)	94 (70.7)
Worse than 20/40	18 (27.3)	20 (28.2)	15 (37.5)	4 (18.2)	39 (29.3)
p value					
Control vs Toric 1.25 D	0.947	--	--	--	--
Control vs All Toric	0.725	--	--	--	--

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation; UCNVA, uncorrected near visual acuity.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D; and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 45.

At FDA's request, additional unplanned analyses were performed assessing UCDVA (20 feet), UCIVA (32 inches), and UCNVA (16 inches) at Form 4 with adjustment for MRSE, which are presented in **Table 30**, **Table 31**, and **Table 32**, respectively. These analyses demonstrate a statistically significant superiority in MRSE-adjusted UCDVA of the Toric 1.25 IOL versus the Control IOL (p=0.007; **Table 30**). For MRSE-adjusted UCIVA, a trend was evident for the superiority of the Toric 1.25 IOL over the Control IOL (p=0.062; **Table 31**). However, adjustment for MRSE had no effect on UCNVA (p=0.579; **Table 32**).

Table 30 UCDVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

	Control IOL	Toric 1.25 D IOL	Difference[a]	p value
UCDVA (logMAR)				
Adjusted mean (SE)	0.17 (0.018)	0.11 (0.017)	–0.07 (0.025)	0.007
95% CI	(0.139, 0.208)	(0.073, 0.140)	(–0.019, –0.116)	--

Abbreviations: D, diopter; IOL, intraocular lens; MRSE, manifest refractive spherical equivalent; SE, standard error; UCDVA, uncorrected distance visual acuity.
[a] Toric 1.25 D IOL minus Control IOL.
Source: S650/Adhoc/va_mrse.sas with analysis based on primary effectiveness cohort.

Table 31 UCIVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

	Control IOL	Toric 1.25 D IOL	Difference[a]	p value
UCIVA (logMAR)				
Adjusted mean (SE)	0.08 (0.015)	0.04 (0.015)	–0.04 (0.021)	0.062
95% CI	(0.047, 0.107)	(0.007, 0.066)	(–0.083, 0.002)	--

Abbreviations: D, diopter; IOL, intraocular lens; MRSE, manifest refractive spherical equivalent; SE, standard error; UCIVA, uncorrected intermediate visual acuity.
[a] Toric 1.25 D IOL minus Control IOL.
Source: S650/Adhoc/va_mrse.sas with analysis based on primary effectiveness cohort.

Table 32 UCNVA With Adjustment for MRSE—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

	Control IOL	Toric 1.25 D IOL	Difference[a]	p value
UCNVA (logMAR)				
Adjusted mean (SE)	0.29 (0.016)	0.28 (0.016)	–0.01 (0.022)	0.579
95% CI	(0.261, 0.325)	(0.250, 0.311)	(–0.057, 0.032)	--

Abbreviations: D, diopter; IOL, intraocular lens; MRSE, manifest refractive spherical equivalent; SE, standard error; UCNVA, uncorrected near visual acuity.
[a] Toric 1.25 D IOL minus Control IOL.
Source: S650/Adhoc/va_mrse.sas with analysis based on primary effectiveness cohort.

Approved labeling for the Crystalens Accommodating IOL describes amplitude of accommodation of approximately 1.00 D. This magnitude of accommodation suggests that the uncorrected or distance-corrected visual acuity at a distance of 1 meter (39 inches) will be equivalent to the uncorrected or best-corrected visual acuity at 6 meters (20 feet).

In Study 650, intermediate vision was tested at 32 inches (80 cm), which nominally requires accommodative amplitude of 1.25 D. Therefore, when maintaining a constant MRSE to eliminate the impact of myopia or hyperopia, only a slight difference in uncorrected and distance-corrected visual acuity should occur at this range versus the visual acuity at 20 feet. Near vision was tested at 16 inches (40 cm), which would require accommodative amplitude of 2.50 D. Again, when maintaining a constant MRSE, a significant decline in uncorrected and distance-corrected visual acuity should occur at 16 inches (40 cm) compared with measurements of visual acuity at 20 feet.

When comparing the Toric 1.25 D IOL and Control IOL in Study 650, the greatest difference in performance would be expected at a range from 1 to 6 meters. Within this range, the magnitude of accommodation has no impact on visual acuity. In other words, since the accommodative amplitude of both IOLs is approximately 1.00 D, optimal uncorrected visual acuity will be achieved in this range. Visual acuity testing distances less than 1 meter (39 inches) will require a greater degree of accommodation than the Crystalens generally provides. At these closer distances, including 32 inches and 16 inches, the relative lack of accommodation will impact visual performance. The greater the blurring of vision from pseudophakic presbyopia, the less the astigmatic correction can aid visual performance.

Examination of the data from Study 650 supports this conclusion.

To evaluate the contribution of pseudophakic presbyopia compared with the contribution of astigmatic correction, the effect of uncorrected myopia and hyperopia must be eliminated. To accomplish this, analyses of mean UCDVA, UCIVA, and UCNVA were performed controlling for MRSE at Form 4. As expected, eyes with residual myopic error had significantly better UCNVA than eyes with residual hyperopic error.

As described above, the decrement in effectiveness at near is explained by the effect of the accommodative amplitude (approximately 1.00 D) of the Control IOL relative to the effect of the correction of astigmatism by the Toric IOL. In contrast, when controlling for MRSE, UCDVA and, to a lesser extent, UCIVA are primarily influenced by the astigmatic correction in the treatment group compared with the Control IOL group. At these ranges, the Toric IOL outperforms the Control IOL, as would be expected.

In contrast, UCNVA is primarily affected by the magnitude of accommodation of the Crystalens IOL at approximately 1.00 D, and the resulting effect of pseudophakic presbyopia. The magnitude of the spherical blur at near (1.50 D on average in both cohorts) is the primary source of compromise in UCNVA (approximately 20/40). The magnitude of this blur effectively prevents discrimination between the magnitude of residual astigmatism in UCNVA in the Toric 1.25 D IOL and Control IOL cohorts.

While spherical blur at near explains the lack of discrimination in UCNVA between the Toric IOL and Control IOL cohorts, another phenomenon may also play a role in this finding. Published reports show that uncorrected astigmatism may actually improve pseudo-accommodation in the pseudophakic eye.[28-30] In this case, the greater residual astigmatism in the Control IOL cohort may actually improve the performance of the control lens at near, and further diminish the difference in performance between the cohorts.

In summary, the accommodative amplitude (approximately 1.00 D) of both the Control IOL and the Toric IOL explains the relative reduction of the effect of astigmatic correction at reading distances closer than 1 meter. In contrast, the study results show that, when controlling for MRSE, the Toric IOL outperforms the Control IOL with regard to uncorrected visual acuities at distance and, to a lesser extent, at intermediate, as would be expected.

Clinical Perspective: *Correcting distance, intermediate, and near visual acuity for MRSE removes the effects of myopia and hyperopia. In this setting, the visual performance of the Toric Accommodating IOL at distance is significantly better than that of the non-toric accommodating parent platform IOL. However, at intermediate and near, closer than the accommodative range of either IOL (1 meter), the advantage of correcting astigmatism becomes relatively less significant, especially since residual against-the-rule astigmatism is known to be a factor in pseudoaccommodation.*

5.4.2.10 Manifest and Cycloplegic Refraction

The manifest refraction cylinder at Form 4 is shown in **Table 33**. A comparison of the mean cylinders of the Toric 1.25 IOL eyes and the Control IOL eyes revealed that the Toric 1.25 IOL eyes had a statistically significant lower mean (SD) absolute residual cylinder (–0.47 D [0.420 D]) compared with the Control IOL eyes (–0.90 D [0.617 D]). The mean difference (0.43) between these 2 groups was statistically significant ($p<0.001$). Seven All Toric IOL eyes (5.3%) exhibited refractive cylinder > 1.00 D. All but one of those eyes had BCDVA of 20/25 or better. One eye had BCDVA of 20/32. None of those eyes showed significant visual disturbances.

Table 33 Manifest Refraction Cylinder—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
n	66	71	40	22	133
Mean (SD) cylinder	–0.90 (0.617)	–0.47 (0.420)	–0.43 (0.497)	–0.34 (0.382)	–0.43 (0.438)
Refractive cylinder, n (%)					
–3.00 to –2.51 D	1 (1.5)	0	0	0	0
–2.50 to –2.01 D	2 (3.0)	0	1 (2.5)	0	1 (0.8)
–2.00 to –1.51 D	6 (9.1)	1 (1.4)	0	0	1 (0.8)
–1.50 to –1.01 D	13 (19.7)	3 (4.2)	2 (5.0)	0	5 (3.8)
–1.00 to –0.51 D	19 (28.8)	18 (25.4)	6 (15.0)	7 (31.8)	31 (23.3)
–0.50 to –0.01 D	17 (25.8)	27 (38.0)	18 (45.0)	4 (18.2)	49 (36.8)
0.00 D	8 (12.1)	22 (31.0)	13 (32.5)	11 (50.0)	46 (34.6)
Within 0.50 D of intended, n (%)	30 (45.5)	58 (81.7)	33 (82.5)	16 (72.7)	107 (80.5)
Within 1.00 D of intended, n (%)	48 (72.7)	68 (95.8)	37 (92.5)	22 (100.0)	127 (95.5)
Toric 1.25 D vs Control					
Mean (SD)	--	0.43 (0.524)	--	--	--
p value	--	< 0.001	--	--	--

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 47.

Manifest refraction spherical equivalent was calculated as the value of the sphere plus one-half of the value of the cylinder. At Form 4, the MRSE within 0.50 D and 1.00 D of intended MRSE target was 63.6% and 90.9%, respectively, for the Control IOL eyes and 73.7% and 93.2%, respectively, for the All Toric IOL eyes (**Table 34**).

Table 34 Manifest Refraction Spherical Equivalent—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL 1.25 D (N = 77)	Toric IOL 2.00 D (N = 41)	Toric IOL 2.75 D (N = 24)	Toric IOL All Toric[a] (N = 142)
n	66	71	40	22	133
Mean (SD)	–0.44 (0.547)	–0.27 (0.489)	–0.24 (0.572)	–0.40 (0.425)	–0.28 (0.505)
–2.99 to –2.00 D	0	0	1 (2.5)	0	1 (0.8)
–1.99 to –1.00 D	11 (16.7)	6 (8.5)	2 (5.0)	2 (9.1)	10 (7.5)
–0.99 to –0.01 D	40 (60.6)	36 (50.7)	22 (55.0)	12 (54.5)	70 (52.6)
0.00 D	5 (7.6)	17 (23.9)	9 (22.5)	6 (27.3)	32 (24.1)
0.01 to 0.99 D	9 (13.6)	11 (15.5)	5 (12.5)	2 (9.1)	18 (13.5)
1.00 to 1.99 D	1 (1.5)	1 (1.4)	1 (2.5)	0	2 (1.5)
Within 0.50 D of intended, n (%)	42 (63.6)	50 (70.4)	32 (80.0)	16 (72.7)	98 (73.7)
Within 1.00 D of intended, n (%)	60 (90.9)	67 (94.4)	37 (92.5)	20 (90.9)	124 (93.2)

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 49.

Clinical Perspective: *73.7% within 0.50 D and 93.2% within 1.00 D of intended postoperative MRSE fits within the top of the range of expected outcomes for cataract surgery.*

5.4.2.11 Lens Decentration and Tilt

Results of lens decentration and tilt at Form 4 are presented in **Table 35**. The mean (SD) of total decentration was 0.002 mm (0.012 mm) for the Control IOL eyes and 0.008 mm (0.087 mm) for the All Toric IOL eyes. The mean (SD) IOL tilt was 0.37° (1.040°) for the Control IOL eyes and 0.29° (1.089°) for the All Toric IOL eyes. One subject [redacted] with 8.74° of tilt also reported UCDVA and BCDVA of 20/20 at Form 4. This subject did not report significant visual disturbances at any postoperative visit.

Table 35 Lens Decentration and Tilt—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL			
		1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
Total decentration (mm)					
n	65	71	40	22	133
Mean (SD)	0.002 (0.012)	0.014 (0.119)	0.000 (0.000)	0.000 (0.000)	0.008 (0.087)
Tilt (°)					
n	65	71	40	22	133
Mean (SD)	0.37 (1.040)	0.43 (1.405)	0.16 (0.543)	0.09 (0.414)	0.29 (1.089)

Abbreviations: D, diopter; IOL, intraocular lens; SD, standard deviation.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 59.

5.4.2.12 Visual Disturbances From Subject Questionnaire

As reported by subject questionnaire, a single subject (0.8%) in the Toric 2.00 IOL group experienced a significant increase in visual disturbances (**Table 36**). This subject ([redacted]) was implanted with a lens that was 1.23° from its target axis orientation at Form 4. At that visit, the subject had developed moderate PCO. At the visit following Nd:YAG treatment, the subject reported via the questionnaire that the visual disturbances were resolved.

Table 36 Subjects Experiencing ≥ 1 Significant Visual Disturbances—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Parameter	Control IOL (N = 73)	Toric IOL			
		1.25 D (N = 77)	2.00 D (N = 41)	2.75 D (N = 24)	All Toric[a] (N = 142)
n	64	71	39	21	131
Significant visual disturbance, n (%)	5 (7.8)	0	1 (2.6)	0	1 (0.8)
No significant visual disturbance, n (%)	59 (92.2)	71 (100.0)	38 (97.4)	21 (100.0)	130 (99.2)

Abbreviations: D, diopter; IOL, intraocular lens.
[a] All Toric is the sum of Toric 1.25 D, 2.00 D, and 2.75 D.
Source: 650 CSR-PMA-20feb2012.pdf, Table 57.

5.4.2.13 Comparison Between UCIVA/UCNVA and DCIVA/DCNVA

Concerns related to the achievement of UCIVA and UCNVA due to residual refractive error (i.e., myopia or astigmatism) can be addressed by the outcomes reported for DCIVA and DCNVA. These outcomes represent the intermediate and near vision with full correction of any residual ametropia in place.

No significant differences were found when mean uncorrected and distance-corrected visual acuities were compared at intermediate and near (**Table 37**).

Table 37 Comparison Between UCIVA/UCNVA and DCIVA/DCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

Visual Acuity	UCIVA	DCIVA	UCNVA	DCNVA (without Add)
Mean logMAR (SD)	0.04 (0.129)	0.06 (0.127)	0.29 (0.146)	0.30 (0.144)
p value	0.457	0.760	0.725	0.912

Abbreviations: DCIVA, distance-corrected intermediate visual acuity; DCNVA, distance-corrected near visual acuity; UCIVA, uncorrected intermediate visual acuity; UCNVA, uncorrected near visual acuity.

5.4.2.14 Summary of Mean UCDVA, UCIVA, and UCNVA

The mean monocular uncorrected visual acuity for the All Toric IOL eyes were reported to be 20/25 at distance, 20/20 at intermediate, and 20/40 at near (**Table 38**).

Table 38 Summary of Mean UCDVA, UCIVA, and UCNVA—Form 4 (Postoperative Days 120 – 180; Effectiveness Cohort)

	All Toric IOL (N=142)		
Snellen, %	**UCDVA**	**UCIVA**	**UCNVA**
20/20 or better	36.1	57.1	3.8
20/25 or better	71.4	87.2	17.3
20/32 or better	85.7	94.0	37.6
20/40 or better	97.7	97.7	70.7
Median logMAR acuity	0.10 (20/25)	0.04 (20/20)	0.29 (20/40)

5.4.3 Effectiveness Conclusions

All effectiveness endpoints of Study 650 were met. The Trulign Toric Accommodating IOL demonstrated good predictability in both absolute reduction of cylinder and MRSE. The toric optic corrects the effect of corneal astigmatism, thereby providing good UCDVA. Moreover, the Trulign Toric Accommodating IOL is effective at providing good uncorrected distance, intermediate, and functional near vision.

6.0 RISK-BENEFIT ASSESSMENT

Many patients implanted with the Crystalens Accommodating IOL since its approval in 2003 have had preexisting corneal astigmatism. Since the Crystalens Accommodating IOL does not correct for astigmatism, patients typically need spectacle or contact lens overcorrection or undergo an additional surgical procedure, such as corneal relaxing incisions or astigmatic correction with the excimer laser, to manage the astigmatism. Therefore, the Trulign Toric Accommodating IOL was developed to provide safe and effective correction of preoperative keratometric astigmatism for those patients selecting the Crystalens Accommodating IOL.

6.1 Risks of Trulign Toric Accommodating IOL

The risks associated with the Trulign Toric Accommodating IOL are consistent with the risks of cataract surgery and implantation of currently approved IOLs. This is supported by the fact that all safety endpoints of Study 650 were met. Specifically, with regard to BCDVA, 97.9% of eyes had BCDVA of 20/40 or better at Form 4 (4-6 months postoperatively), exceeding the rate of 92.5% reported in the historical control ("FDA Grid") population for BCDVA of 20/40 or better. The occurrence of cumulative AEs (as defined by the FDA and ISO) in All Toric IOL subjects were within limits. The rate of reported macular edema (1/151 [0.7%]) is below the rates reported in the FDA grid (3.0%) and PMA P030002 (3.7%), and the rate of reported SSI in the All Toric cohort (1/151 [0.7%]) is below the rate reported in the FDA Grid (0.8%) and comparable with the rate reported in PMA P030002 (0.6%).

In Study 650, one event of anterior vault was reported in the study eye of a subject implanted with a Trulign Toric Accommodating IOL (2.00 D). This case represents the single SSI reported for the All Toric IOL cohort, and was not related to repositioning of the Toric IOL due to rotational instability. Although this event was assessed by the Investigator and Sponsor as related to the study device and procedure, the Investigator determined that the subject was not compliant with the postoperative anti-inflammatory topical medication regimen, which may have resulted in atypical fibrosis of the capsular bag. The fibrosis likely resulted in significant capsular contraction that caused the study device to vault in an anterior position.

Successful strategies have been developed and disseminated for the prevention and treatment of anterior and asymmetric vault. Management with postoperative medications (cycloplegics and anti-inflammatories) and Nd:YAG laser-selective capsulotomy has resulted in favorable outcomes.[31,32] Furthermore, there has been a substantial reduction in frequency of anterior and asymmetric vault observed over time, which can be attributed to enhanced lens design, established prevention strategies provided in the Crystalens DFU, and greater surgeon experience with these techniques. These improved strategies have also been incorporated into the Trulign Toric Accommodating IOL design, labeling, and training.

Additionally, to address any concerns of combining a toric correction on an accommodating IOL platform, it is important to note that only a single subject (0.8%) in the All Toric IOL cohort reported significant increase in visual disturbances during this trial. It was found that this subject had developed moderate PCO, and following Nd:YAG treatment, resolution of the visual disturbances was reported.

Therefore, the safety of the Trulign Toric Accommodating IOL was demonstrated by the preservation of best corrected visual acuity, and the incidences of complications and AEs reported for the All Toric IOL population did not exceed the FDA Grid of historical controls or those reported with the parent Crystalens Accommodating IOL (Model AT45; PMA P030002). It is significant that no SSIs were related to rotational instability, which is critical for an astigmatism correcting toric IOL.

6.2 Benefits of Trulign Toric Accommodating IOL

The Trulign Toric Accommodating IOL provides the benefits of the Crystalens Accommodating IOL plus astigmatic correction. In particular, the accommodative technology of the Crystalens IOL does not produce the unwanted glare, halos, and waxy vision often associated with other presbyopic correcting (multifocal) IOLs.[33] The Trulign Toric Accommodating IOL corrects the effect of corneal astigmatism, thereby providing good UCDVA. Moreover, the Toric IOL is effective at providing good uncorrected intermediate and functional near vision.

In Study 650, the Trulign Toric Accommodating IOL demonstrated significant, effective improvement in visual outcomes across a range of cylinders. Eyes implanted with the Toric IOL achieved significantly greater percent reduction in absolute cylinder, less residual refractive cylinder, and superior UCVA. The mean percent reduction of absolute cylinder was 85.8% for All Toric IOLs. When comparing the mean percent reduction of absolute cylinder between Control and Toric 1.25 IOLs, the Toric IOLs were statistically significantly superior ($p<0.001$). The majority of subjects (79.9%) implanted with Toric IOLs demonstrated a reduction of cylinder within 0.50 D of intended correction. In addition, refractive predictability was shown by accuracy to target for MRSE. For the All Toric IOL group, MRSE within 0.50 D and 1.00 D of intended MRSE target was 73.7% and 93.2%, respectively. This refractive predictability compares quite favorably to the reported refractive predictability of standard monofocal IOLs.[34]

Rotational instability is a common concern specific to astigmatism-correcting toric IOLs. The Trulign Toric Accommodating IOL, however, demonstrated excellent rotational stability, with a mean absolute rotation < 2°. There were no reports of lens rotation > 10° for the Trulign Toric Accommodating IOL, which is consistent with recent reports of the AcrySof Toric IOL (2.9%)[24] and a marked improvement compared with first-generation toric IOLs (10%).[35] In Study 650, at Form 4, 99.2% of subjects implanted with a Toric IOL demonstrated ≤ 5° rotation between consecutive visits. Additionally, 96.9% of Toric IOLs exhibited ≤ 5° rotation between the day of surgery and Form 4, demonstrating rotational stability in the early postoperative period.

Overall, the favorable percentage reduction of cylinder, MRSE accuracy to target, and rotational stability contribute to good UCDVA. In Study 650, UCDVA was superior in both the Toric 1.25 IOL eyes ($p=0.002$) and All Toric IOL eyes ($p<0.001$), compared with Control IOL eyes. In addition, the Trulign Toric Accommodating IOL provided good UCIVA (mean Snellen, 20/20) and functional UCNVA (mean Snellen, 20/40). The mean residual add required for DCNVA in Toric IOL subjects was 1.43 D. Given near visual acuity was measured at a vergence of 2.50 D (40 cm), this add is consistent with the labeling of the Crystalens Accommodating IOL, which provides approximately 1.00 D of accommodation.

6.3 Risk-Benefit Summary

The results from Study 650 demonstrate that the Trulign Toric Accommodating IOL is a safe and effective option for cataract patients with astigmatism who, with the counsel of their surgeon, select the Crystalens Accommodating IOL. This may eliminate the need for patients to pursue spectacle or contact lens overcorrection or undergo additional surgical procedures that may result in added risk and undesirable sequelae. These findings support a favorable risk-benefit ratio for visual correction of aphakia and astigmatism with the Trulign Toric Accommodating IOL. Cataract patients with astigmatism who desire to minimize their dependence on spectacles after surgery may also prefer an accommodative IOL to avoid the disabling photic phenomena (glare and halos) that may accompany implantation of a multifocal lens. For these patients, the Trulign Toric Accommodating Posterior Chamber IOL offers an important new safe and effective alternative.

Clinical Perspective: *The toric optic is a very welcome addition for surgeons and patients who select an accommodating IOL, especially because it will significantly reduce the need for ancillary procedures to correct residual astigmatism. Data presented in this study show that the Trulign Toric Accommodating IOL provides accurate correction of corneal astigmatism and superior uncorrected distance visual acuity by virtue of its exceptional rotational stability. At the same time, the results demonstrate that the Trulign Toric Accommodating IOL maintains the unique benefits of the accommodative lens parent platform by providing excellent intermediate acuity and functional near acuity. These are real world, clinical advantages that make the Trulign Toric Accommodating IOL a desirable addition to our refractive cataract surgical armamentarium.*

7.0 OVERALL CONCLUSIONS

The data and information provided in PMA P030002/S027 support the safety and effectiveness of the Trulign Toric Accommodating IOL. The parent Crystalens design and material have a proven safety and effectiveness profile with more than 315,000 implants since the first clinical experience more than a decade ago. Under controlled clinical investigation (Study 650), the Trulign Toric Accommodating IOL met or exceeded the safety and effectiveness endpoints established for the trial. The Trulign Toric Accommodating IOL demonstrated outstanding rotational stability with favorable effectiveness and safety compared with the Control IOL and the historical control ("FDA Grid") population. The Trulign Toric Accommodating IOL provides correction of astigmatism in a single procedure that meets or exceeds that of currently approved toric IOLs. With respect to presbyopic management, the Trulign Toric Accommodating IOL provides good distance, intermediate, and functional near vision. Unlike multifocal IOLs, the accommodative technology of the Trulign Toric Accommodating IOL minimizes the loss of contrast sensitivity and the development of photic phenomena (glare and halos), further supporting a favorable risk-benefit ratio for visual correction of aphakia and astigmatism. These findings support the safe and effective use of the Trulign Toric Accommodating IOL in the proposed patient population.

8.0 REFERENCES

1. Chen W, Zuo C, Chen C, et al. Prevalence of corneal astigmatism before cataract surgery in Chinese patients. J Cataract Refract Surg 2013;39:188-92.
2. Hoffer KJ. Biometry of 7,500 cataractous eyes. Am J Ophthalmol 1980;90:360-8.
3. Khan MI, Muhtaseb M. Prevalence of corneal astigmatism in patients having routine cataract surgery at a teaching hospital in the United Kingdom. J Cataract Refract Surg 2011;37:1751-5.
4. Lekhanont K, Wuthisiri W, Chatchaipun P, Vongthongsri A. Prevalence of corneal astigmatism in cataract surgery candidates in Bangkok, Thailand. J Cataract Refract Surg 2011;37:613-5.
5. Riley AF, Grupcheva CN, Malik TY, Craig JP, McGhee CN. The Auckland Cataract Study: demographic, corneal topographic and ocular biometric parameters. Clin Experiment Ophthalmol 2001;29:381-6.
6. Ferrer-Blasco T, Montes-Mico R, Peixoto-de-Matos SC, Gonzalez-Meijome JM, Cervino A. Prevalence of corneal astigmatism before cataract surgery. J Cataract Refract Surg 2009;35:70-5.
7. Hoffmann PC, Hutz WW. Analysis of biometry and prevalence data for corneal astigmatism in 23,239 eyes. J Cataract Refract Surg 2010;36:1479-85.
8. Ruckl T, Dexl AK, Bachernegg A, et al. Femtosecond laser-assisted intrastromal arcuate keratotomy to reduce corneal astigmatism. J Cataract Refract Surg 2013.
9. Miller AD, Kris MJ, Griffiths AC. Effect of small focal errors on vision. Optom Vis Sci 1997;74:521-6.
10. Muller-Jensen K, Fischer P, Siepe U. Limbal relaxing incisions to correct astigmatism in clear corneal cataract surgery. J Refract Surg 1999;15:586-9.
11. Troutman RC, Swinger C. Relaxing incision for control of postoperative astigmatism following keratoplasty. Ophthalmic Surg 1980;11:117-20.
12. Thornton SP. Astigmatic keratotomy: a review of basic concepts with case reports. J Cataract Refract Surg 1990;16:430-5.
13. McDonnell PJ, Moreira H, Garbus J, Clapham TN, D'Arcy J, Munnerlyn CR. Photorefractive keratectomy to create toric ablations for correction of astigmatism. Arch Ophthalmol 1991;109:710-3.
14. Amesbury EC, Miller K M. Correction of astigmatism at the time of cataract surgery. Curr Opin Ophthalmol 2009;20:19-24.
15. Bayramlar HH, Daglioglu MC, Borazan M. Limbal relaxing incisions for primary mixed astigmatism and mixed astigmatism after cataract surgery. J Cataract Refract Surg 2003;29:723-8.
16. Horn JD. Status of toric intraocular lenses. Curr Opin Ophthalmol 2007;18:58-61.
17. Nichamin LD. Astigmatism control. Ophthalmol Clin North Am 2006;19:485-93.
18. Netto MV, Mohan RR, Ambrosio R, Jr., Hutcheon AE, Zieske JD, Wilson SE. Wound healing in the cornea: a review of refractive surgery complications and new prospects for therapy. Cornea 2005;24:509-22.
19. Shimizu K, Misawa A, Suzuki Y. Toric intraocular lenses: correcting astigmatism while controlling axis shift. J Cataract Refract Surg 1994;20:523-6.

20. STAAR Surgical. Collamer, toric, and silicone IOL models - intraocular lens cataract solutions. Available at: http://www.staar.com/html/iol.html#aa4203tf. Accessed January 29, 2013.
21. Alcon Surgical. AcrySof IQ ReSTOR IOL product specifications. Available at: http://www.alconsurgical.com/Product-Specifications.aspx. Accessed January 29, 2013.
22. U.S. Food and Drug Administration. Premarket approval: Staar Elastic Ultraviolet-Absorbing Silicone Posterior Chamber Intraocular Lens with Toric Optic, Models AA-4203T and AA-4203TF - P880091/S14. Summary of Safety and Effectiveness Data (SSED). November 4, 1998.
23. Till JS, Yoder PR, Jr., Wilcox TK, Spielman JL. Toric intraocular lens implantation: 100 consecutive cases. J Cataract Refract Surg 2002;28:295-301.
24. U.S. Food and Drug Administration. Premarket approval: ACRYSOF Toric Posterior Chamber Intraocular Lens - P930014/S015. Summary of Safety and Effectiveness Data (SSED). September 14, 2005.
25. Holland E, Lane S, Horn JD, Ernest P, Arleo R, Miller KM. The AcrySof Toric intraocular lens in subjects with cataracts and corneal astigmatism: a randomized, subject-masked, parallel-group, 1-year study. Ophthalmology 2010;117:2104-11.
26. ICH E3 Guidance to Industry on Structure and Content of Clinical Study Reports: Questions and Answers (R1). January, 2013. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM336889.pdf. Accessed February 12, 2013.
27. Wolffsohn JS, Buckhurst PJ. Objective analysis of toric intraocular lens rotation and centration. J Cataract Refract Surg 2010;36:778-82.
28. Trindade F, Pascucci SE. Keratorefractive approaches to achieving pseudoaccommodation. Ophthalmol Clin N Am 2006;19:35-44, vi.
29. Verzella F, Calossi A. Multifocal effect of against-the-rule myopic astigmatism in pseudophakic eyes. Refract Corneal Surg 1993;9:58-61.
30. Nanavaty MA, Vasavada AR, Patel AS, Raj SM, Desai TH. Analysis of patients with good uncorrected distance and near vision after monofocal intraocular lens implantation. J Cataract Refract Surg 2006;32:1091-7.
31. Jardim D, Soloway B, Starr C. Asymmetric vault of an accommodating intraocular lens. J Cataract Refract Surg 2006;32:347-50.
32. Yuen L, Trattler W, Boxer Wachler BS. Two cases of Z syndrome with the Crystalens after uneventful cataract surgery. J Cataract Refract Surg 2008;34:1986-9.
33. Pepose JS, Qazi MA, Davies J, et al. Visual performance of patients with bilateral vs combination Crystalens, ReZoom, and ReSTOR intraocular lens implants. Am J Ophthalmol 2007;144:347-57.
34. Gale RP, Saldana M, Johnston RL, Zuberbuhler B, McKibbin M. Benchmark standards for refractive outcomes after NHS cataract surgery. Eye (Lond) 2009;23:149-52.
35. Chang DF. Early rotational stability of the longer Staar toric intraocular lens: fifty consecutive cases. J Cataract Refract Surg 2003;29:935-40.
36. Marchini G, Mora P, Pedrotti E, Manzotti F, Aldigeri R, Gandolfi SA. Functional assessment of two different accommodative intraocular lenses compared with a monofocal intraocular lens. Ophthalmology 2007;114:2038-43.
37. Marchini G, Pedrotti E, Sartori P, Tosi R. Ultrasound biomicroscopic changes during accommodation in eyes with accommodating intraocular lenses: pilot study and

hypothesis for the mechanism of accommodation. J Cataract Refract Surg 2004;30:2476-82.

38. Stachs O, Schneider H, Beck R, Guthoff R. Pharmacological-induced haptic changes and the accommodative performance in patients with the AT-45 accommodative IOL. J Refract Surg 2006;22:145-50.
39. Trattler W. Quantitative measurement of accommodation in eyes with a wavefront aberrometer. Presented at the annual meeting of the International Society of Refractive Surgery, San Francisco, California, October 2009.
40. Waltz KL. The Crystalens changes its radius of curvature Cataract Refractive Surg Today 2005;June:66-8
41. Cumming JS, Colvard DM, Dell SJ, et al. Clinical evaluation of the Crystalens AT-45 accommodating intraocular lens. J Cataract Refract Surg 2006;32:812-25.
42. U.S. Food and Drug Administration. Premarket approval: Tecnis Multifocal Posterior Chamber Intraocular Lens, Models ZM900 (silicone) and ZMA00 (acrylic) - P080010. Summary of Safety and Effectiveness Data (SSED). January 16, 2009.
43. Alio JL, Tavolato M, De la Hoz F, Claramonte P, Rodriguez-Prats JL, Galal A. Near vision restoration with refractive lens exchange and pseudoaccommodating and multifocal refractive and diffractive intraocular lenses: comparative clinical study. J Cataract Refract Surg 2004;30:2494-503.
44. Macsai MS, Padnick-Silver L, Fontes BM. Visual outcomes after accommodating intraocular lens implantation. J Cataract Refract Surg 2006;32:628-33.
45. Hantera MM, Hamed AM, Fekry Y, Shoheib EA. Initial experience with an accommodating intraocular lens: controlled prospective study. J Cataract Refract Surg 2010;36:1167-72.
46. Patel S, Alio JL, Feinbaum C. Comparison of Acri.Smart multifocal IOL, Crystalens AT-45 accommodative IOL, and Technovision presbyLASIK for correcting presbyopia. J Refract Surg 2008;24:294-9.
47. Beiko GH. Comparison of visual results with accommodating intraocular lenses versus mini-monovision with a monofocal intraocular lens. J Cataract Refract Surg 2013;39:48-55.
48. Szigeti A, Kranitz K, Takacs AI, Mihaltz K, Knorz MC, Nagy ZZ. Comparison of long-term visual outcome and IOL position with a single-optic accommodating IOL after 5.5- or 6.0-mm femtosecond laser capsulotomy. J Refract Surg 2012;28:609-13.
49. Carter HL. Correcting capsular contraction after crystalens implantation. Cataract Refractive Surg Today. Oct 2007:31-2.
50. Crystalens Physician Labeling (directions for use). Bausch & Lomb Incorporated.
51. Young T. The Bakerian lecture: on the mechanism of the eye. Philosophical Transactions of the Royal Society of London 1801;91:23-88.
52. Davison JA. Capsule contraction syndrome. J Cataract Refract Surg 1993;19:582-9.
53. Deokule SP, Mukherjee SS, Chew CK. Neodymium:YAG laser anterior capsulotomy for capsular contraction syndrome. Ophthalmic Surg Lasers Imaging 2006;37:99-105.

9.0 APPENDIX: GLOBAL CLINICAL EXPERIENCE

9.1 Effectiveness

The Trulign Toric Accommodating IOL provides the combined benefits of the Crystalens Accommodating IOL and astigmatic correction. The Crystalens was approved as an accommodating IOL in 2003 and noted to provide approximately 1.00 D of accommodative amplitude by a mechanism that was not fully elucidated at the time. According to the first proposed mechanism (anterior translation), the optic of the Crystalens is pushed forward by the vitreous as the ciliary muscle "bulks up" and increases pressure in the vitreous cavity. A number of studies have found the Crystalens does indeed move forward during accommodation.[36-38] According to the second proposed mechanism (accommodative arching), in addition to anterior vitreous pressure, the capsular bag contracts during accommodation, and these capsular contraction forces bend the optic. Wavefront analyses of eyes implanted with the Crystalens Accommodating IOL have shown transient changes in higher-order aberrations during accommodation, which could only occur if the optic changed shape or tilted.[39,40] Therefore, more recent evidence suggests that "accommodative arching" may better explain the mechanism of action.

Regardless of the precise mechanism, clinical data based on subjective accommodation support the claim of approximately 1.00 D of accommodative amplitude. This is evidenced by the following: UCIVA and UCNVA; DCIVA and DCNVA; and the minimal amount of add required to reach BCNVA as demonstrated in the Crystalens clinical trial.[41] These data include uncorrected and distance-corrected intermediate and near visual acuities that are clearly superior to those that may be obtained with a standard monofocal IOL (e.g., as observed in the Tecnis Multifocal clinical trial monofocal control group).[42]

A number of other peer-reviewed studies have confirmed the effectiveness of the Crystalens Accommodating IOL based on clinical measures of subjective accommodation.[33,36,37,43-48]

- Alio et al[43] examined 12 patients who underwent refractive lens exchange surgery with bilateral implantation of Crystalens Accommodating IOLs. Comparing 12-month postoperative measurements to preoperative measurements, they found significant improvements in UCNVA ($p=0.14$), BCNVA ($p<0.001$), and DCNVA ($p=0.04$), and a significant reduction in minimal add to achieve BCNVA ($p<0.001$). Mean binocular DCNVA at 40 cm was 20/25 for Crystalens eyes
- Macsai et al[44] examined 112 patients who were bilaterally implanted with either a Crystalens Accommodating IOL (N = 56) or a standard monofocal IOL (N = 56). The Crystalens IOL group achieved significantly better uncorrected monocular (20/25 vs 20/50; $p<0.01$) and binocular (20/20 vs 20/50) near visual acuities compared with the monofocal IOL group. In addition, the Crystalens IOL eyes demonstrated significantly more accommodation, as measured by dynamic retinoscopy (2.42 D vs 0.91 D; $p<0.01$), monocular defocus to blur (1.74 D vs 0.75 D; $p<0.01$), and monocular near point of accommodation (4.78 D vs 1.23 D; $p<0.01$), compared with the monofocal IOL eyes
- Pepose et al[33] compared various combinations of Crystalens Accommodating IOLs and multifocal IOLs in cataract patients. Visual acuity and contrast sensitivity data were collected 4 to 6 months postoperatively. Crystalens IOLs demonstrated better BCDVA and DCIVA,

while the multifocal IOLs demonstrated better DCNVA. Mean monocular and binocular DCNVA at 40 cm were 20/41 and 20/31, respectively, for the Crystalens IOLs. Moreover, Crystalens IOLs demonstrated better contrast sensitivity than the multifocal IOLs

- Hantera et al[45] published the outcomes of their first 25 eyes implanted with Crystalens Accommodating IOLs and found good monocular UCDVA (mean, 20/25) and DCNVA at 35 cm (62% achieved J3 or better)
- Marchini et al[37] measured near vision of 20 eyes (of 14 patients) implanted with Crystalens Accommodating IOLs following cataract surgery. All eyes achieved DCNVA at 30 cm of J5 (20/40) or better, and all eyes needed an add power less than 1.25 D to achieve J1 (20/20) near visual acuity at 30 cm
- Marchini et al[36] measured 29 eyes implanted with Crystalens Accommodating IOLs and 21 eyes implanted with standard monofocal IOLs. The Crystalens group demonstrated significantly better monocular DCNVA ($p<0.001$) and less add power to achieve BCNVA. Mean monocular DCNVA at 40 cm was J4 (20/32) for the Crystalens IOL group
- Patel et al[46] examined different methods for treating presbyopia, including the Crystalens Accommodating IOL. They reported significantly better monocular UCNVA in patients implanted with the Crystalens IOL (0.51 [20/39]) compared with those implanted with a standard monofocal IOL (0.30 [20/67]; $p<0.05$)
- Szigeti et al[48] investigated the effects of 2 capsulorhexis diameters (5.5 and 6.0 mm) created with a femtosecond laser on the performance of the Crystalens Accommodating AO IOL (Model AT50AO). They found no differences in near vision performance between the 2 groups. The mean DCNVA at 35 cm was 0.60 (20/33) for all 17 eyes implanted with the Crystalens AO IOL, and 13 of 17 eyes (76%) achieved DCNVA of J3 or better
- Beiko[47] examined binocular visual acuity in patients bilaterally implanted with the Crystalens Accommodating IOL or a monofocal IOL. The monofocal IOL group was targeted for mini-monovision in which one eye had a target refraction of –0.25 D while the other eye had a target refraction of –0.75 D. The Crystalens IOL group had a target refraction of +0.25 D in both eyes. Despite being disadvantaged by 1.00 D (i.e., difference between +0.25 D and –0.75 D), the Crystalens IOL group achieved near visual acuity that was 1.5 lines better than the monofocal mini-monovision IOL group

These outcomes confirm that Crystalens is providing approximately 1.00 D of accommodation.

9.2 Safety

The risks associated with the Crystalens Accommodating IOL are consistent with cataract surgery with implantation of an IOL. The concerns associated with other presbyopic correcting (multifocal) IOLs, such as light scatter and loss of light, which can result in photic phenomena (glare and halos), loss of contrast sensitivity and, potentially, lens explantation, have not been associated with the Crystalens IOL.[33]

One set of complications associated with the Crystalens Accommodating IOL, anterior and asymmetric vault, bears mention. The Crystalens Accommodating IOL is designed to be implanted in a posterior vaulted configuration, with the optic residing posteriorly in the capsular bag parallel to the plane of the posterior capsule and the 2 plate haptics angulated anteriorly relative to the optic, with the polyimide loops in the capsular fornices. Anterior vault can occur when the lens optic vaults anteriorly, past the neutral plane, and becomes lodged in an anterior

position, independent of ciliary muscle relaxation or contraction (i.e., whether the patient is focused at distance or at near). This phenomenon occurs when both of the lens haptics vault posteriorly relative to the optic at the haptic hinges, resulting in anterior displacement of the lens. Asymmetric vault, also known as Z-syndrome, can occur when one lens haptic vaults anteriorly and the other lens haptic vaults posteriorly relative to the optic at the haptic hinges, resulting in tilting of the lens optic. Both anterior vault and asymmetric vault, however, are easily diagnosed by slit lamp examination during postoperative examinations. The lens optic is shown to be displaced anteriorly, away from its normal position along the posterior capsule (anterior vault), or displaced anteriorly combined with tilt along the long axis of the lens (asymmetric vault). No adverse medical outcomes, such as raised IOP, hyphema, persistent iritis, pupillary block, or retinal detachment, have been attributed to any reported cases of either anterior or asymmetric vault. The clinical sequelae are refractive error and the interventions to address such refractive error (i.e., spectacles, SSIs).

Anterior and asymmetric vault are a rare complication. Based on global complaints received between November 2003 and September 2012 for any Crystalens Accommodating IOL implanted ([redacted]), the incidence of anterior and asymmetric vault was 0.067%.

- The total number of incidences reported for anterior vault was 59, and the overall incidence rate is 0.018% or < 2 cases per 10,000 surgeries. The total number of incidences reported for asymmetric vault was 153, and the overall incidence rate is 0.049% or < 5 cases per 10,000 surgeries
- The reported incidence rates of anterior and asymmetric vault are below the anticipated rates of 0.060% per the Bausch + Lomb Risk Analysis Report for Crystalens Models AT50AO/AT52AO, produced in accordance with ISO 14971:2009 Medical Devices Application of Risk Management to Medical Devices, and lower than the ISO/FDA Grid rate of 0.800% for SSI

A review of the reported cases of anterior and asymmetric vault determined that patient-related factors, such as noncompliance with postoperative prescribed medications, preexisting conditions with zonular laxity, or capsular contraction syndrome caused by a rare aggressive healing response were identified in 32% of all reported events. Procedure-related factors, such as incisional wound leak, failure to remove all lens material during surgery, inadequate or irregular capsulorhexis, zonular damage, or failure to provide cycloplegic medication, were identified in 34% of all reported events. The remaining 34% had no reported patient or procedural risk factors. Identification of probable causes led to the opportunity to minimize the risk through enhancements in IOL design, training[49], instructions for use, and treatment. These product design and labeling enhancements[50] have been reviewed and approved under supplements to PMA P030002.

Of note, since the introduction of the Crystalens Accommodating IOL in 2003, incidence rates for both anterior and asymmetric vault have continued to decrease (**Table 39**).

Table 39 Reduction in Reported Vaulting Incidence

Perspective	Period	Vaulting Incidence, %		
		Anterior	Asymmetric	Total[a]
Initial experience	Nov 2003 – Sep 2005	0.094	0.240	0.334
Historical	Nov 2003 – Dec 2009	0.021	0.050	0.072
Current	Jan 2010 – Sep 2012	0.013	0.045	0.058

[a] Total vault = anterior vault + asymmetric vault.
Source: Global complaints received between November 2003 and September 2012 for any Crystalens Accommodating IOL implanted.

The etiology of anterior and asymmetric vault is fairly straightforward given the physiology of the pseudophakic eye and design of the Crystalens Accommodating IOL. Following cataract surgery, capsule contraction occurs with all IOLs. Excessive or asymmetric capsular contracting forces acting upon a dynamic (accommodating) IOL can cause anterior or posterior vault at the haptic hinge.[51] Common predisposing factors associated with anterior and asymmetric vault include residual lens material, inadequate postoperative anti-inflammatory medication, asymmetric capsulorhexis, and zonular or capsular defects.[52,53] This is consistent with data showing that two-thirds of Crystalens-associated anterior and asymmetric vault cases are due to foreseeable factors related to the patient or procedure.

Successful strategies have been developed and disseminated for the prevention and treatment of anterior and asymmetric vault. Management with postoperative medications (cycloplegics and anti-inflammatories) and Nd:YAG laser-selective capsulotomy has resulted in favorable outcomes.[31,32] Furthermore, the substantial reduction in frequency of anterior and asymmetric vault observed over time can be attributed to enhanced lens design, established prevention strategies provided in the Crystalens DFU, and greater surgeon experience with these techniques. These improved strategies have also been incorporated into the Trulign Toric Accommodating IOL design, labeling, and training.