PMA P030016-S001

OPHTHALMIC DEVICES PANEL

EXECUTIVE SUMMARY

December 20, 2013

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ABBREVIATIONS AND DEFINITIONS

ACD	anterior chamber depth
AE	adverse event
ANSI	American National Standards Institute
BCVA	best corrected visual acuity
BSS	balanced salt solution
CE	Conformité Européenne certification (European Union)
CI	confidence interval
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Forms
d	diameter
D	diopter(s)
DFU	directions for use
DLK	diffuse lamellar keratitis
ELP	effective lens position
FDA	Food and Drug Administration (U.S.)
HEMA	Hydroxyethyl Methacrylate
Hg	mercury (pressure reading)
I/A	irrigation/aspiration
ICL	Implantable Collamer Lens
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IOL	intraocular lens
IOP	intraocular pressure
IRB	Institutional review board

ISO	International Organization for Standardization
LASEK	Laser-Assisted Sub-Epithelial Keratectomy
LASIK	Laser In-Situ Keratomileusis
LOCS III	Lens Opacities Classification System III
LRI	limbal relaxing incision
MRSE	manifest refraction spherical equivalent
MSI-PF	model number for lens injector
MSI-TF	model number for lens injector
Nd:YAG	neodymium:yttrium-aluminum-garnet treatment laser
NRSC	Navy Refractive Surgery Center
PMA	Premarket Approval
PMI	Promedica International
PRK	photorefractive keratectomy
RD	retinal detachment
SAP	statistical analysis plan
SD	standard deviation
SIA	surgically induced astigmatism
SSI	secondary surgical intervention
TICL	Toric Implantable Collamer Lens
UCVA	uncorrected visual acuity
UV	ultraviolet

1. EXECUTIVE OVERVIEW

1.1. Introduction

The Visian Toric Implantable Collamer Lens® (Visian TICL) is a modification of the FDA-approved Visian Implantable Collamer Lens (Visian ICL). The proposed indication of the Visian TICL is for the correction or reduction of myopic astigmatism. The Visian ICL was the subject of PMA Application P030016, approved on December 22, 2005. Other than the addition of a cylinder correction on the front surface of the optic, the plate-haptic design and posterior surface geometry are unchanged from the Visian ICL. Other than alignment of the cylinder axis, the Visian TICL is implanted using the same surgical technique as the Myopic ICL.

The Visian TICL for the treatment of patients with myopia and astigmatism is commercially available in over 60 countries. The Visian TICL was first introduced in 2002 with a CE mark for distribution in the European Union. Between 2003 and 2006, the Visian TICL was approved for sale in Canada, Korea, China and India and in 2011, approved for sale in Japan. As of November 2013, over 400,000 Visian ICLs have been implanted worldwide, including over 45,000 implanted in the U.S. Approximately 110,000 Visian TICLs, the subject of P030016-S001, have been successfully implanted internationally.

In 2009, a study conducted by the National Eye Institute showed that the incidence of myopia in Americans increased from 25% in the 1970s to 42% three decades later. Myopia severity also increased with moderate nearsightedness doubling, and severe myopia rising sharply. In addition, the majority of Americans with moderate to high myopia also have astigmatism. Although a number of surgical and nonsurgical options are currently available for correction of moderate to high myopia with astigmatism, treatment for these conditions remains a challenge.

The Visian TICL is a minimally invasive intraocular refractive technology that corrects refractive errors by adding power rather than removing tissue. If necessary, the lens can be removed, and correction reversed, while maintaining the natural asphericity of the cornea.

To treat patients that have high myopia combined with astigmatism, surgeons commonly perform more than one refractive procedure in order to achieve the desired correction with the least amount of complications. This approach of using two separate procedures is known as bioptics. While bioptics has been considered effective in correcting high refractive errors with astigmatism, the availability of the Visian TICL can eliminate the need for a secondary corneal refractive treatment together with its inherent risks. Furthermore, implantation of toric phakic IOLs provide not only a reliable, but a more stable visual outcome when compared to bioptics (Choi and et al).

1.2. Visian Toric Implantable Collamer Lens

Like the Visian ICL, the Visian TICL is an intraocular implant manufactured from Collamer®, a proprietary hydroxyethyl-methacrylate (HEMA)/porcine collagen-based biocompatible polymer material. The Visian TICL contains a UV-absorbing material. The Visian TICL lens features a plate-haptic design with a central convex/concave optical zone and incorporates a forward vault to minimize contact of the Visian TICL with the central anterior capsule.

The Visian TICL features an optic diameter that varies with the dioptric power; the smallest optic diameter being 4.9 mm and the largest being 5.8 mm. The Visian TICL is capable of being folded and inserted into the posterior chamber through an incision of 3.5 mm or less. The Visian TICL is intended to be placed entirely within the posterior chamber directly behind the iris and in front of the anterior capsule of the human crystalline lens. When correctly positioned, the Visian TICL functions as a refractive element to optically correct or reduce moderate to high myopic astigmatism.

The Visian TICL is labeled using a plus cylinder axis format. The lens can be manufactured to order, with the axis in 1° steps from 0° to 180°. However, the lens is designed to be rotated up to 22.5° clockwise or counterclockwise in order to align the lens axis at the preoperative plus cylinder axis. The lens has two diamond shaped markings, one on each side of the optic. These are designed to aid with the alignment of the lens. The markings indicate the meridian from which the cylinder axis is measured and do not indicate the cylinder axis of the lens. See Figure 1.

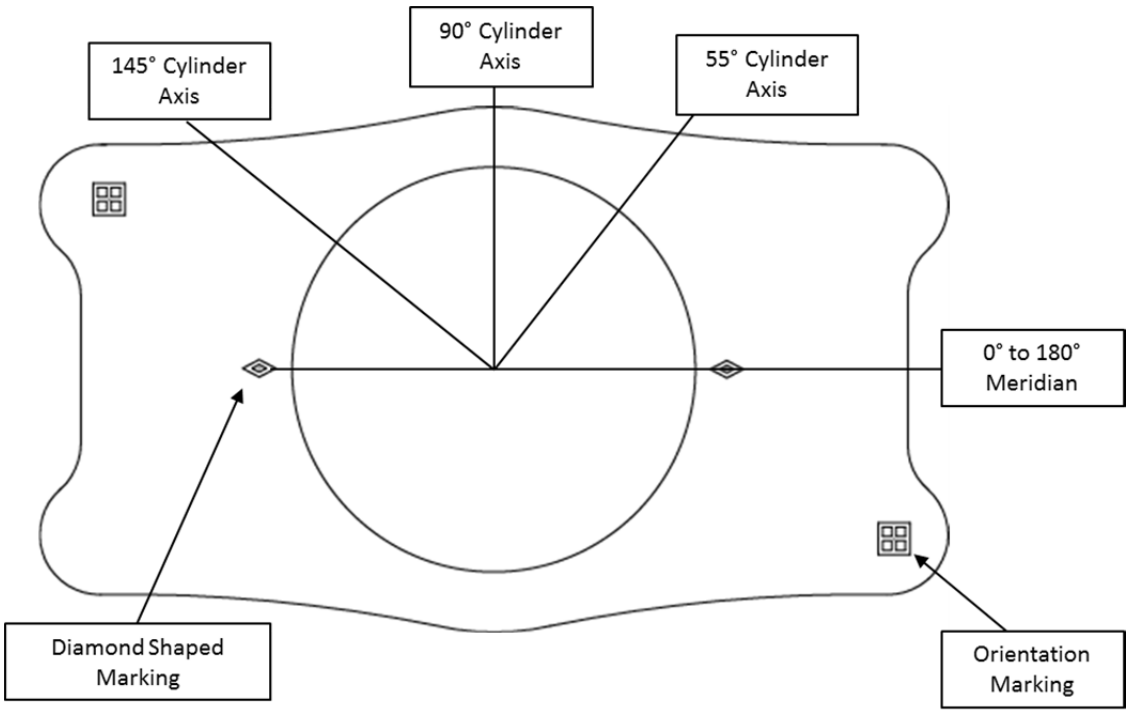

Figure 1 — Visian TICL Showing Lens Markings and Axis Alignment

The Visian TICL's proposed indications for use are as follows:

- For adults 21-45 years of age;
- For correction of myopic astigmatism in adults with spherical equivalent ranging from 3.0D to ≤-15.0D with cylinder of 1.0D to 4.0D;
- For the reduction of myopic astigmatism in adults with spherical equivalent ranging from greater than -15.0D to -20.0D with cylinder 1.0D to 4.0D;
- With an anterior chamber depth (ACD) of 3.0 mm or greater, when measured from the corneal endothelium to the anterior surface of the crystalline lens and a stable refractive history (within 0.5 Diopter for 1 year prior to implantation); and
- The Visian TICL is intended for placement in the posterior chamber (ciliary sulcus) of the phakic eye.

1.3. Visian TICL Clinical Study

The Visian TICL Clinical Investigation was conducted as a separate investigational device exemption (IDE) and submitted as a PMA supplement to the Visian ICL (Spherical Implantable Collamer Lens). The objective was to conduct a prospective, multi-investigator, multi-site clinical study to assess the effectiveness of the STAAR Surgical Company (STAAR) Implantable Toric Phakic ICL (Toric ICL) in human eyes

for the correction of moderate to high myopic astigmatism. The primary goal of the Visian TICL Clinical Investigation has been to evaluate the effectiveness of STAAR's ICL technology in the correction of moderate to high myopic astigmatism by adding to the larger safety dataset from the spherical myopia clinical study. The Toric ICL study was designed with input from the FDA to evaluate the effectiveness of the STAAR ICL in an expanded patient population with myopia and astigmatism.

The Toric ICL study was approved in April 2002 and submitted to the FDA as a PMA supplement in April 2006. In March 2007, the FDA placed the PMA supplement on integrity hold, largely based on the findings from a clinical data audit by Bioresearch Monitoring (BIMO). This resulted in an audit of 100% of STAAR's clinical data for this PMA supplement. The audit was performed by an independent third party reporting directly to the FDA and receiving instruction and guidance solely from the FDA, without direction from STAAR. At the conclusion of the audit, the auditing group provided reports on their activity and findings directly to the FDA and also provided a certification to STAAR, which provided, in part, as follows:

> *The corrected database is a true reflection of the data in the field. This corrected database can be used to analyze the study data.*

This third party audited data was used for the analysis presented in this document. A more detailed timeline of the progress of this Toric ICL study is given in Section 3.0.

1.4. Patient Population

The Visian TICL Study Cohort consisted of 210 eyes from 124 subjects. The subjects' average age was 35 years (range of 21-45), and 55.6% were female. 82.3% were Caucasian, 8.1% were Hispanic, and 4.8% were Afro-American. The mean preoperative manifest refraction spherical equivalent (MRSE) for the Visian TICL Study Cohort was highly myopic at –9.37D (ranging from -2.38 D to −19.50 D). The mean preoperative manifest refractive cylinder was +1.95D (ranging from 1.00 D to 4.00 D).

1.5. Eligibility

The patient inclusion criteria was as follows:

- patients 21 to 45 years of age;
- phakic;
- myopia (−3.0D to −20.0D sphere);
- astigmatism (1.0D to 4.0D);
- stable refraction for the last 12 months;
- Best Corrected Visual Acuity (BCVA) of at least 20/40 in the eye to be treated; and
- absence of ocular pathology.

1.6. Study Endpoints

Safety Endpoints

Although safety of the Visian ICL has been established in the Visian ICL study, the following safety data were collected during the study:

- Preservation of BCVA;
- Slit lamp examination - lens opacities;
- Intraocular pressure; and
- Incidence of complications and adverse events.

Effectiveness Endpoints

The following effectiveness data were collected during the study:

- Improvement in uncorrected visual acuity;
- Decrease in refractive myopia and cylinder;
- Predictability -- the intended correction vs. achieved correction for sphere and cylinder;
- Stability of refraction;
- Subjective patient satisfaction; and
- Rotation of the Visian TICL.

1.7. Safety

The incidence of adverse events for the study was lower than in the ISO-Defined Safety and Performance Endpoint (SPE) Rates for all adverse events with the exception of surgical intervention and retinal detachment.

Preservation of BCVA

The outcomes in the study are compared to the targets as established in the approved clinical protocol. These targets were established based the published guidance at the time of the study. The guidance was "Refractive Implants: Investigational Device Exemptions (IDEs) and Premarket Approval Applications (PMAs)."

Preservation of BCVA was excellent after implantation of the Visian TICL. There were no eyes with postoperative BCVA worse than 20/40 in the subset of eyes with preoperative BCVA of 20/20 or better compared to the Protocol Target of < 1%.

Only 0.5% of the eyes at six months or later after Visian TICL implantation lost greater than two lines of BCVA. This loss after implantation of the Toric lens is an order of magnitude below the Protocol Target of less than 5.0% of eyes with > 2 Line Loss.

Slit lamp examination - lens opacities

Utilizing the standardized Lens Opacities Classification System (LOCS III) in the Visian TICL Cohort, there were six anterior subcapsular opacities (2.9%), four of which were asymptomatic and two of which were clinically significant anterior subcapsular cataracts (1%).

Intraocular Pressure

The mean within-eye change in IOP (0.1mm Hg (14.1mm Hg preoperative and 14.2mm Hg at 12 months)) was statistically insignificant between baseline and 12-months.

Only three eyes had elevated IOP at any time point after 1 week postoperative, however, all of these eyes were below 25 mmHg at 12 months postoperative.

One eye had an IOP spike (55 mmHg) at one day postop, related to a pupillary block, which resolved with an additional Nd:YAG iridotomy. IOP at the one day follow up visit after Nd:YAG iridotomy was 12 mmHg, At the final 12 month post op visit, the BCVA was 20/25 and IOP was 14mmHg.

Incidence of complications and adverse events

As shown in Table 1 below, the incidence of adverse events is lower than in the ISO SPE Rates for all adverse events with the exception of surgical intervention and retinal detachment. The five cases of surgical intervention all had improvement or no change in BCVA, or no significant loss in BCVA (1 line in 1 case), at the last follow-up visit (these cases are discussed in detail in Section 5.5). The single case of retinal detachment had UCVA of 20/16 at the 12-month visit, and was extremely satisfied with their Visian TICL outcome.

The risk of retinal detachment in the study within one year of implantation of this device was 0.5%. The ISO SPE Rate for retinal detachment is based on the general population following cataract surgery. The eye with retinal detachment in this study had myopia of −12.0D. Patients with high myopia are known to be at up to forty fold greater risk for retinal detachment than the emmetropic population.

Table 1 — Adverse Events

Adverse Event	Cumulative % n = 210	ISO Rate %	Persistent % 12 months n = 210	ISO Rate %
Endophthalmitis	0% (0)	0.1%	0% (0)	—
Hyphema	0% (0)	2.2%	0% (0)	—
Hypopyon	0% (0)	0.3%	0% (0)	—
IOL Dislocation	0% (0)	0.1%	0% (0)	—
Cystoid Macular Edema	0% (0)	3.0%	0% (0)	0.5%
Pupillary Block	0% (0)	0.1%	0% (0)	—
Retinal Detachment	0.5% (1)	0.3%	0% (0)	—
Surgical Reintervention	2.4% (5)	0.8%	0% (0)	—
Corneal Edema (after 1 week)	0% (0)	—	0% (0)	0.3%
Iritis (after 1 week)	0% (0)	—	0% (0)	0.3%
Raised IOP Requiring Intervention	0.5% (1)	—	0% (0)	0.4%

In conclusion, there were no new safety event risks identified with the Visian TICL.

1.8. Effectiveness

The Visian TICL met all effectiveness end points. The outcomes in the study are compared to the targets as established in the approved clinical protocol. These targets were established based upon the published guidances at the time of the study. The guidances were "Refractive Implants: Guidance for Investigational Device Exemptions (IDE) and Premarket Approval (PMA) Applications, Draft", "Revision of Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers" and "Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers, October 10, 1996."

Improvement in UCVA

Comparison of postoperative UCVA to a patient's preoperative BCVA is considered the most challenging measure for assessing the effectiveness of any refractive surgical procedure. **In the TICL Study, 76.2% (147/193) of eyes had 12-month postoperative UCVA equal to or better than preoperative BCVA. Furthermore, 47% of eyes had 12-month postoperative UCVA better than preoperative BCVA.**

Uncorrected visual acuity after implantation of the Visian TICL exceeded the Protocol Targets. **UCVA 20/40 or better in eyes with a preoperative BCVA of 20/20 or better**

was achieved in 100% of eyes at 6 months and at 12 months after Visian TICL implantation compared to the Protocol Target of **85%** for all eyes. UCVA 20/20 or better for the same study subset in the total Visian TICL Study Cohort was 90.3% at 6 months postoperative; 89.3% at 12 months after Visian TICL implantation. Taking the entire Visian TICL population regardless of preoperative BCVA, 81.9% saw 20/20 or better and 95.3% saw 20/40 or better uncorrected at 12 months postoperatively.

Decrease in refractive myopia and cylinder

The mean MRSE improved from −9.34D (± 2.63) preoperatively to 0.03D (± 0.46) at the 12 month follow-up visit.

Preoperatively, the manifest refractive cylinder ranged from 1.00D to 4.00D. **The mean refractive cylinder at baseline for the entire Visian TICL Cohort was 1.95D (± 0.84D) improving to 0.52D (± 0.48D) at twelve months postoperatively**. The mean reduction in absolute cylinder was 77.8% at the 12 month visit.

Predictability

The target MRSE values as per the Protocol are 75% within ± 1.00D and 50% within ± 0.50D. The Visian TICL Study Cohort outcomes were 96.4% within 1.00D and 74.7% within 0.50D at 12-months postoperatively.

The percent of cases with cylinder within 0.50D of target was 69.6% and within 1.00D of target was 92.3%.

Stability

Refractive stability was well established for both MRSE and absolute cylinder correction. MRSE changed within 1.00D in 100.0% from the one to three month postoperative visit, 98.8% from 3 to 6 months, and 99.4% from 6 to 12 months. The change in absolute cylinder for the same three time points was 98.4%, 98.8% and 98.3%, respectively.

The cylindrical outcomes were above 95.0%.

Subjective patient satisfaction

Within the standardized subjective patient questionnaire, there were three subjective assessments: Patient Satisfaction, Willingness to have Surgery Again, and Quality of Vision.

The overwhelming majority of patients, **97.9% at 12 months**, reported being “Very Satisfied” or “Extremely Satisfied” with the results of their Visian TICL surgery. No patients reported being “unsatisfied” with the outcomes of their Visian TICL surgery at any point in time.

At 12 months postoperatively, 98.4% of patients reported they would be willing to undergo Visian TICL surgery again, one patient (0.6%) did not know and two patients (1.1%) responded "No." However, both patients who responded "No" reported that they were "Very Satisfied" with their Visian TICL surgery.

There was a marked improvement in patient reported quality of vision in the study. Patients were asked to rate their quality of vision as; Very Poor, Poor, Good, Very Good, or Excellent, preoperatively and at 3 and 12 months postoperatively. None of the patients reported having "Very Poor" or "Poor" vision postoperatively, as compared to 22 eyes (10.5%) preoperatively. Of the 22 eyes, 21 improved from "Poor" or "Very Poor" vision preoperatively, to "Very Good" or "Excellent" postoperatively, the one eye improved to "Good". **The percent of patients reporting "Very Good" or "Excellent" quality of vision rose from 64.3% preoperatively to 94.6% at 12 months after implantation of the Visian TICL.**

Rotation of the Visian TICL

The protocol called for observation during the slit lamp examination to record TICL axis position. Rotational stability was assessed based upon lens rotation between 2 consecutive visits. Outcomes of the analysis indicate that 97.8% of lenses rotated 5 degrees or less between 3 to 6 months (n = 136) postoperatively, and 94.3% of lenses rotated 5 degrees or less between 6 to 12 months (n = 140). In addition, as noted by the FDA - "you may retain the original data and analyses, and rely primarily upon the refractive data for information concerning axis position (if the direct axial measurement method was too gross to be very useful)," - rotational stability of the Visian TICL was also evaluated through the absolute difference in cylinder axis using manifest refraction outcomes. The majority of eyes had a change in manifest cylinder axis of ≤5°, between the 6- and 12-month visits. There were 69 eyes with a change greater than 5°, per the manifest refraction. Eyes with less than 1.00D of manifest refractive cylinder may tolerate wide variability in axis shift without visual compromise, rendering the change in axis relatively unreliable and clinically insignificant.

UCVA was used to cross reference the refractive outcomes. Eyes with post-operative UCVA of > 20/20 or eyes with post-operative UCVA the same or better than preoperative BCVA, were assumed to be stable and excluded from the analysis. Of the remaining ten eyes, four achieved an average reduction in absolute cylinder of approximately 73% (range 50% to 91%). Therefore, clinically significant lens rotation may have occurred in approximately 6/177 of eyes, a rate calculated to be less than 4%.

1.9. Risk Benefit Analysis

The results from the study demonstrate that the Visian TICL is safe and effective to treat patients with moderate to high myopia with astigmatism. The visual acuity of patients

with the Visian TICL met all established standards and surpassed patients' subjective needs. Currently, many patients with moderate to high myopic astigmatism are being corrected with the currently approved Visian ICL, with an additional surgical procedure to correct their astigmatism (i.e. bioptics). Accordingly, the Visian TICL will reduce the risk to which these patients are exposed by eliminating the need and associated risks of a secondary procedure.

Beyond the improvement in vision offered by the Visian TICL, and the reduction in the number of procedures for patients with moderate to high myopia with astigmatism, there is another key benefit offered by this refractive technology. Specifically, implanting the Visian TICL adds to the patient's optical system rather than irreversibly removing eye tissue with an excimer laser. This provides the surgeon the option to remove the Visian TICL if the patient is not satisfied with the outcome, rather than having to tolerate dissatisfaction in cases where permanent reshaping of the cornea (such as with LASIK or PRK) fails to deliver the patient's desired results.

Additional benefit of not permanently changing the shape of the cornea becomes important when a patient may need cataract surgery. For an eye where the cornea has been permanently reshaped with a laser, calculation of the correct IOL power becomes more difficult and post-operative outcomes can be less predictable; however, with the Visian ICL and TICL, this would not be the case. It is important to note that the presence of the Visian ICL does not impact the pre-operative axial length measurements used to assist in calculating the IOL power.

For patients with moderate to high myopia with astigmatism, the Visian TICL offers an important safe and effective alternative to other methods of refractive correction. The benefits outweigh the risks for the Visian TICL in treatment of moderate to high myopia with astigmatism. This conclusion is supported by both the results from this clinical study and from extensive clinical results of the Visian TICL from around the world, where surgeons and patients have embraced this technology. The adoption of the procedure has increased year after year since it was launched in international markets in 2003. Since then, approximately 110,000 Visian TICL lenses have been implanted, and approximately 25,000 will be implanted in 2013.

1.10. Conclusion

The data and information provided in PMA P030016-S001 supports the safety and effectiveness of the Visian Toric ICL. This builds upon the larger body of safety data from the parent Visian ICL presented in PMA P030016 and is supported by the clinical experience with over 400,000 Visian TICLs and Visian ICLs implanted worldwide.

The mean pre-operative MRSE of the Study Cohort was −9.34D (± 2.63) with a mean cylinder of 1.95D (± 0.84D), a very challenging group of eyes to treat with a single or

even multiple procedures. At 12 months the mean MRSE had been reduced to 0.03D (± 0.46) with mean cylinder improving to 0.52D (± 0.48D).

Adverse event rates were comparable to ISO-Defined Safety and Performance Endpoint (SPE) Rates for all adverse events, with the exception of surgical intervention and retinal detachment, for standard IOL surgery. Despite the majority of the Study Cohort having pathologic myopia that is associated with a higher risk profile and higher potential rates of adverse events.

No other refractive surgical procedure has been reported to provide such visual improvement (both best corrected and uncorrected), refractive predictability and stability in a population with this degree of highly myopia and astigmatism as in this Visian TICL Study Cohort.

The Visian TICL met or exceeded all safety and effectiveness endpoints. The Visian TICL reduces the need for a secondary procedure or additional aids to correct for astigmatism. Unlike laser-based refractive procedures, the Visian TICL does not remove ocular tissue and is removable if so desired, which further supports the favorable risk-benefit ratio for the Visian TICL. Indeed, the Visian TICL greatly improves patient vision in a safe and effective manner.

The Visian TICL is a line extension to the approved Visian ICL, which will offer a relatively low risk option to treat eyes within the proposed label range. The data supports the safe and effective use of the Visian TICL in the proposed patient population.

2. INTRODUCTION

2.1. Visian TICL Overview

The Visian Toric Implantable Collamer Lens® (TICL) is a modification of the myopia-correcting Visian Implantable Collamer Lens (ICL). The Visian TICL is designed with the cylinder power on the front surface of the optic, with other key elements, including haptic design and posterior surface geometry, remaining unchanged from the Visian ICL. Other than the alignment of axis, the Toric ICL is implanted using the same surgical technique as the Myopic ICL.

The parent Visian ICL was the subject of PMA Application P030016. This application included preclinical and clinical data and information supporting the safety and effectiveness of the Visian ICL. The Ophthalmic Devices Panel reviewed the PMA data and recommended approval on October 3, 2003. The FDA subsequently approved PMA Application P030016 for the Visian ICL on December 22, 2005.

The Visian TICL was first introduced in 2002 with a CE mark for distribution in the European Union. Between 2003 and 2006, the Visian TICL was approved for sale in

Canada, Korea, China, and India. In 2011, the Visian TICL was approved for sale in Japan. STAAR currently markets Visian ICLs for myopia and Visian TICLs for myopia with astigmatism in 60 countries. STAAR has not withdrawn the Visian ICL or the Visian TICL from any market for any reason.

As of November 2013, over 400,000 Visian ICLs have been implanted worldwide, including over 45,000 implanted in the U.S. Approximately 110,000 Visian TICLs, for which we currently seek approval by the FDA, have been successfully implanted internationally.

2.2. Background of Vision Correction

In 2009, a study conducted by the National Eye Institute showed that the incidence of myopia in Americans increased from 25% in the 1970s to 42% three decades later. Myopia severity also increased with moderate nearsightedness doubling, and severe myopia rising sharply. In addition, one-third of Americans with myopia also have astigmatism. Although a number of surgical and nonsurgical options are currently available for correction of moderate to high myopia with astigmatism, treatment for these conditions remains a challenge.

Spectacles and contact lenses have long been considered an acceptable means for the correction of refractive error. While refractive error can be minimized with spectacles or contact lenses, the moderate to highly myopic astigmatic patient may consider these methods of correction unsatisfactory based on functional or cosmetic limitations. Although spectacles offer minimal risk, the wearer may experience a narrowed visual field, and for the moderate to highly myopic patient there is a potential for significant diminishment in image size. Spectacles that correct astigmatic errors often distort peripheral vision and/or create problems with stereopsis due to the concentration of the toric correction in the optical center of the lenses.

Contact lenses offer vision correction equal to or better than spectacles but also have limitations—they cannot be worn constantly, can easily be lost, and are not suitable for many professional and recreational activities. The vast majority of contact lens wearers are also dependent on spectacles at some point during their daily activities. In addition, the FDA states that contact lens wear puts the eye at risk for several serious conditions including infections and corneal ulcers that can develop fairly quickly, and in rare conditions may cause blindness. Toric contact lenses, to address patients with astigmatism, have not gained widespread acceptance due to their inability to remain stable in the axis subsequent to blinking. Thus, while spectacles and contact lenses enjoy excellent acceptance, they have drawbacks or complications.

In recent years, refractive surgery for the correction of myopia and astigmatism has become a viable option for myopic and astigmatic patients who cannot tolerate, or wish

to reduce, dependence on contact lenses or spectacles. The most common forms of refractive surgery to correct myopic astigmatism are LASIK and PRK, both of which permanently reshape the surface of the cornea. While many patients who undergo these procedures achieve a satisfactory visual outcome, the final success of any of these techniques has been shown to be variable. Higher refractive errors have less predictable results, resulting in higher potential for under- and overcorrection, often requiring re-treatment. Such re-treatment exposes the patient to a second surgical procedure, with accompanying risks.

Complications reported with laser-based surgery include variable rates of healing, loss of BCVA, induced astigmatism, diffuse lamellar keratitis (DLK), topographical aberrations, infection, postoperative corneal haze, corneal ectasia, and regression of refractive outcome (Olson).

LASIK uses a microkeratome or a femtosecond laser to make a corneal flap, which is folded back toward the hinge, and then an excimer laser ablation is formed. This flap creation has its own complications, such as intraoperative bleeding, irregular flap, free cap, buttonhole, and improper flap dimensions.

A more recently reported complication related to all refractive surgery options that change the shape of the cornea is difficulty in determining the proper IOL power when the patient eventually requires cataract surgery. IOL formulas are based on an accurate measurement of the eye's axial length, effective lens position and corneal power. Currently available instruments to measure corneal power can be inaccurate when measuring corneas that have undergone laser refractive surgery (Wang and et al). These inaccurate measurements can lead to the selection of the wrong IOL power especially in IOLs with complex optics (i.e., toric, multifocal and accommodating IOLs).

The common thread to all of the aforementioned surgical approaches to correct refractive errors is the underlying assumption that cutting or reshaping of the cornea is better and safer than a minimally invasive intraocular procedure. Studies have shown continuous change in corneal power years after refractive laser or incisional based surgeries. These corneal changes would consequently result in fluctuations in vision when the power of the cornea varies after surgery (Anders and et al) (Kemp and et al).

Refractive lensectomy, or clear lens extraction and phakic intraocular lens (IOL) implantation are the only procedures currently performed for correcting refractive errors without reshaping the cornea. Excellent outcomes and the low risk-to-benefit ratio of modern cataract/IOL surgery has provided the impetus for the low, yet steady frequency of use of clear lensectomy/IOL implantation as an effective treatment for very high levels of myopia and hyperopia (Kraff and et al) (Siganos and et al, Clear lens extraction and intraocular lens implantation in normally sighted hyperopic eyes.). However, in younger patients (pre-presbyopia) the loss of accommodation clearly outweighs the advantages of the procedure, and there continues to be risks associated with clear lensectomy,

particularly retinal detachment (Ripandelli and et al) (Perez-Santonja and et al) (Colin and et al) which is already a significant risk factor in high myopes.

The phakic IOL is a minimally invasive intraocular refractive technology that corrects refractive errors by adding power rather than removing tissue. Phakic IOL implantation is considered an attractive approach based in large part on the acceptance of intraocular lenses for aphakic or cataract patients. That is, the widespread use of IOLs in cataract surgery has led to a high degree of confidence among ophthalmic surgeons that the lenses can be implanted in an otherwise healthy eye in a safe manner and with excellent predictability of the refractive outcome (Martin and et al). The use of phakic IOLs offers greater predictability and effectiveness compared to standard IOL technologies and is less invasive since the crystalline lens is left intact. In addition, phakic IOLs can be removed and correction reversed while maintaining the natural prolate aspheric shape of the cornea. The maintenance of corneal asphericity after phakic IOL implantation significantly reduces the rate of higher order visual aberrations compared to laser refractive surgery even in low degrees of myopia (Kamiya and et al) (Shin and et al).

To treat patients that have high myopia combined with astigmatism, surgeons commonly perform more than one refractive procedure in order to achieve the desired correction with the least amount of complications (Zaldivar and et al) (Velarde and et al) (Guell and et al) (Probst and et al) (Pop and et al) (Huang and et al). This combined refractive modality, which has been gaining popularity, is known as bioptics (Leccisotti).

Bioptics is the planned combination of phakic or aphakic IOL surgery with one of the aforementioned corneal surgery modalities (most commonly LASIK, PRK and LRI, or AK) to correct large refractive errors with astigmatism. This procedure is often preferable to laser ablation alone because of the reduced risk of visual aberrations, contrast loss, glare, and halos that are associated with extremely large myopic excimer laser ablations. In addition, the increased tissue ablation and smaller optical zones necessary with large myopic corrections decrease the predictability and stability of laser refractive surgery (Sher and et al) (Hersh and et al) (Gartry and et al) (Seiler and et al) (Goes) (Knorz and et al) (Waring and et al) (Aydin and et al).

While bioptics has been considered an efficacious means of correcting high refractive errors with astigmatism, the availability of a phakic IOL with a toric component can eliminate the need for a secondary corneal refractive treatment together with its inherent risks. Furthermore, studies have shown that implantation of toric phakic IOLs provide not only a reliable, but a more stable visual outcome when compared to bioptics (Choi and et al).

Toric phakic IOLs are becoming a popular choice in refractive error correction in markets where they are available. They simplify the treatment of patients with moderate to high myopia combined with astigmatism by reducing or eliminating the need for a second surgical procedure.

2.3. Device Description

The Visian TICL is manufactured from Collamer®, a proprietary hydroxyethyl methacrylate (HEMA)/porcine-collagen-based biocompatible UV-absorbing polymer. The Visian TICL features a plate haptic design with a central convex/concave optical zone, and incorporates a forward vault to minimize contact with the central anterior capsule of the natural crystalline lens. It can be folded and inserted through an incision or injected using the recommended STAAR Injector and Cartridge. It is supplied in a sterile hydrated form, stored in Balanced Salt Solution (BSS) in a non-pyrogenic glass vial, for single use only.

The Visian TICL features an optic diameter that varies with the dioptric power; the smallest optic diameter being 4.9 mm and the largest 5.8 mm. All descriptions of optic diameter, overall diameter or power refer to measurements in BSS unless otherwise noted. The Visian TICL is capable of being folded and inserted into the posterior chamber through an incision of 3.5 mm or less. The Visian TICL is intended to be placed entirely within the posterior chamber directly behind the iris and in front of the anterior capsule of the human crystalline lens. See Table 2.

Table 2 — Visian TICL Models

Model Number	Spherical Equivalent Dioptric Power D*	Cylinder Dioptric Power D*	Overall Diameter mm	Optic Diameter mm	Haptic Design
TMICL 12.1	−3.0 to −16.0	1.0 to 4.0	12.1	4.9 to 5.8	Flat, plate
TMICL 12.6	−3.0 to −16.0	1.0 to 4.0	12.6	4.9 to 5.8	Flat, plate
TMICL 13.2	−3.0 to −16.0	1.0 to 4.0	13.2	4.9 to 5.8	Flat, plate
TMICL 13.7	−3.0 to −16.0	1.0 to 4.0	13.7	4.9 to 5.8	Flat, plate

*in 0.5D increments

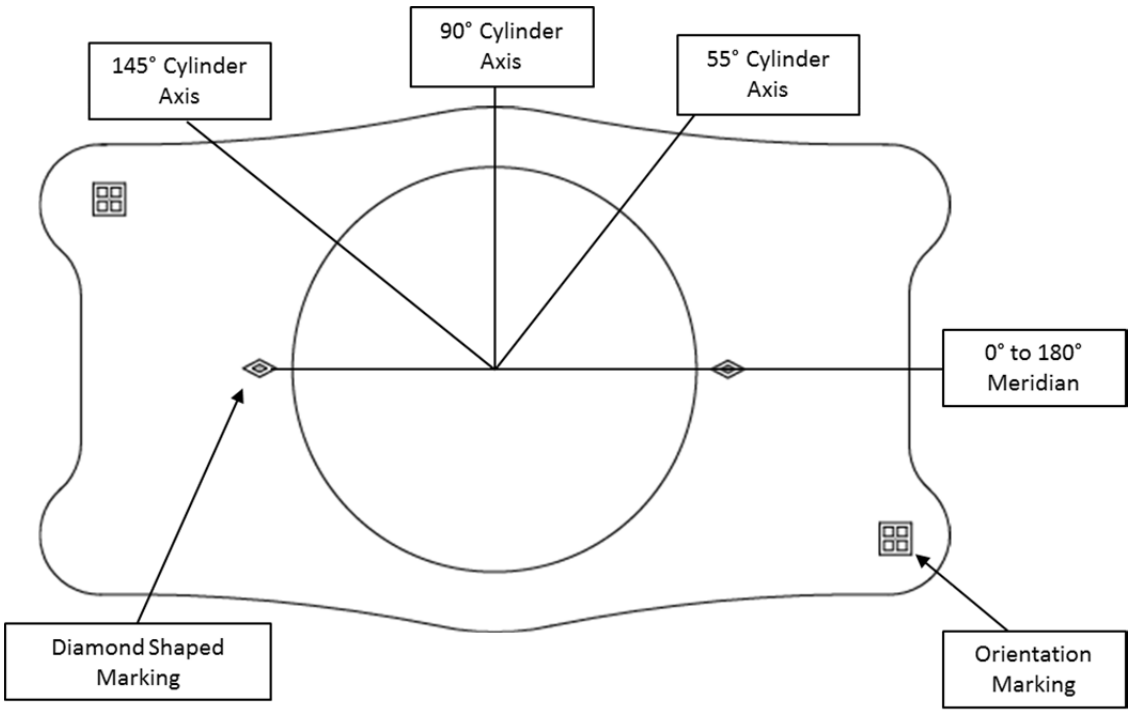

Figure 2 — Visian TICL Showing Lens Markings and Axis Alignment

The Visian TICL is labeled using a plus cylinder axis format. The lenses are labeled to the nearest degree, and as such, lenses of any axis between 0°to 180° may be held in inventory. The Visian TICL is designed to be rotated up to 22.5° clockwise or counterclockwise in order to align the lens axis at the preoperative plus cylinder axis. The lens has two diamond shaped markings, one on each side of the optic, which are designed to aid with the alignment of the lens. The markings indicate the meridian from which the cylinder axis is measured and do not indicate the cylinder axis of the lens. See Figure 2.

The Visian TICL has orientation markings on the footplates to ensure the lens is implanted right side up. When correctly oriented, the orientation markings will be on the leading right and trailing left footplates.

2.3.1. Proposed Indications for Use

The Visian TICL is indicated for use in:

- Adults 21 to 45 years of age;
- Correction of myopic astigmatism in adults with spherical equivalent ranging from -3.0D to ≤-15.0D with cylinder of 1.0D to 4.0D;
- Reduction of myopic astigmatism in adults with spherical equivalent ranging from greater than -15.0D to -20.0D with cylinder 1.0D to 4.0D;

- Adults with an anterior chamber depth (ACD) of 3.0 mm or greater, when measured from the corneal endothelium to the anterior surface of the crystalline lens and a stable refractive history (within 0.5 Diopter for 1 year prior to implantation); and
- The Visian TICL is intended for placement in the posterior chamber (ciliary sulcus) of the phakic eye.

2.4. Summary of Nonclinical Studies

Since the parent model and subsequent models are approved under PMA P030016 and subsequent supplements, much of the preclinical information relating to the materials, design, and finished process was previously submitted and approved under PMA P030016. Overall, the Visian Toric Implantable Collamer Lenses are biocompatible and provided in a sterile state. Based on the available data, packaging is sufficient to maintain the sterility and stability of the Visian TICLs throughout the 2-year shelf-life.

These nonclinical studies further demonstrate that the Visian TICLs comply with the requirements for physical and mechanical properties.

2.4.1. Biocompatibility and Toxicological Testing

The Visian TICL is composed of identical materials as the currently approved Visian ICL. Therefore, no new biocompatibility/toxicological data was 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) were provided in the approved PMA P030016 (December 22, 2005).

2.4.2. Chemical Testing

Chemical testing was performed on the materials used in the Visian TICL. Characterization tests confirmed that the material meets the requirements of ISO 11979-5 (Ophthalmic Implants – Intraocular Lenses – Part 5: Biocompatibility) and the results were provided in the approved PMA P030016 (December 22, 2005).

2.4.3. Optical Testing

The optical tests were performed on the Visian TICL in accordance with EN ISO 11979-2 (Ophthalmic Implants – Intraocular Lenses – Part 2: Optical Properties and Test Methods) and provided in PMA P030016/S001.

2.4.4. Mechanical Testing

The mechanical tests were performed on the Visian TICL in accordance to EN ISO 11979-3 (Ophthalmic Implants – Intraocular Lenses – Part 3: Mechanical Properties and Test Methods) and the results were provided in PMA P030016 (December 22, 2005) and PMA P030016/S001.

2.4.5. Sterilization, Packaging, and Shelf Life

2.4.5.1. Sterilization

The Visian TICLs are sterilized using a validated steam sterilization process, which is used for the currently approved Visian ICL. Supporting data was provided in the approved PMA P030016 (December 22, 2005).

2.4.5.2. Packaging

The packaging components for the Visian TICLs are identical to the packaging components for the currently approved Visian ICL. [redacted] Supporting data was provided in the approved P030016 (December 22, 2005). The finished product includes the Directions For Use (DFU) and other pertinent labeling (chart stickers, patient information card, and patient registration card).

2.4.5.3. Shelf Life

The Visian TICL has the same 2-year shelf life as the parent Visian ICL. Supporting data was provided in the approved PMA P030016 (December 22, 2005).

3. VISIAN TICL CLINICAL STUDY

The Visian TICL Clinical Investigation was conducted as a separate investigational device exemption (IDE) and submitted as a PMA supplement to the Visian ICL (Spherical Implantable Collamer Lens) The primary goal of the Visian TICL clinical investigation was to evaluate the effectiveness of the Visian TICL in the correction of moderate to high myopic astigmatism. This adds to the larger safety data collected in conjunction with the spherical myopia clinical study. The only difference between the two lenses involves the toric correction on the anterior surface lens optic. Therefore, the earlier non-clinical and clinical safety data is transferable from the Visian ICL to the Visian TICL.

Since the Visian TICL poses no new or different safety risks, the Visian TICL study was designed with input from the FDA to evaluate the effectiveness of the Visian ICL in an expanded patient population with myopia and astigmatism.

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4. VISIAN TICL CLINICAL INVESTIGATIONAL PLAN

This section provides a summary of the key elements of the Visian TICL Clinical Investigational Plan.

4.1. Study Objective

The objective was to conduct a multi-investigator, multi-site clinical study to assess the effectiveness of the Visian TICL in human eyes for the correction of moderate to high myopic astigmatism. The primary objective is to evaluate efficacy, since safety of the Visian ICL technology has already been established during the Visian ICL Clinical Investigation. Seven sites participated in this clinical study, which involved the enrollment of 210 eyes of 124 subjects.

4.2. Study Design

Similar to the Visian ICL study design, the Visian TICL study patients were not compared to a control group since an appropriate comparison did not yet exist. Thus, assessment of the Visian TICL results was based on a comparison to the patient's preoperative condition and achieved versus expected visual and refractive outcomes, as well as an analysis of reported complications.

Implantation of the Visian TICL in the fellow eye may have been performed if the fellow eye met the clinical study inclusion/exclusion criteria a minimum of six weeks after the primary TICL surgery. The fellow eye could undergo implantation if:

1. the manifest refraction was stable in the primary eye (spherical equivalent within 0.50D between 2 refractions at least 2 weeks apart);
2. there was no unresolved intraoperative or postoperative adverse events, no loss of two or more lines of BCVA and no uncontrolled intraocular pressure in the primary eye; and
3. there was no corneal edema in the primary eye. If the fellow eye met the spherical myopia criteria for the Visian TICL study but had less than 1.00D of refractive astigmatism, a Visian ICL may have been implanted in the fellow eye to only correct the spherical refractive error, and if there was ≥ 1.00D of refractive astigmatism in the fellow eye then a Visian TICL could be used.

4.2.1. Sample Size

The necessary sample sizes for obtaining two-sided 95% confidence intervals extending no more than 0.25D from the observed mean are provided for a range of standard deviations. These confidence intervals were computed using a coverage probability of 0.8, and assuming the confidence intervals are based on the t-statistic. It was determined that a sample size of 40 eyes would provide sufficient power to estimate the mean deviation from target refraction with a two-sided 95% confidence interval that extended no more than 0.25D from the observed mean. Thus, the current sample size of 124 patients (210 eyes) enrolled is more than sufficient to obtain this point estimate.

4.3. Patient Population

Up to 125 phakic patients from a maximum of seven investigative sites who have provided informed consent for implantation of the Visian TICL, who are capable of comprehending the nature of the clinical study, and who are likely to comply with the examination schedule, were entered into the study, provided they conformed to the following inclusion and exclusion criteria.

4.3.1. Inclusion Criteria

The inclusion criteria were as follows:

- Patients must be phakic with moderate to high myopia (−3.0D to −20.0D sphere) measured at the spectacle plane and astigmatism in the range of 1.0D to 4.0D measured as “plus” cylinder;
- Patients must have had a stable refraction for the last 12 months as documented by previous clinical records (MRSE progressed at a rate of 0.5D or less during the year prior to the baseline examination);

- Patients must be correctable (BCVA) to at least 20/40 in the eye to be treated, and absent of ocular pathology (except that myopic degeneration is allowed);
- Patients must be at least 21 years of age and at most 45 years of age at the time of surgery;
- Patients must be contact lens tolerant, willing to limit fellow eye treatment only to approved refractive procedures and/or be agreeable to waiting for approval from the FDA for the use of the Visian TICL in their fellow eye;
- Patients must sign a written informed consent form;
- Patients must be able and willing to return for scheduled follow-up examinations after surgery; and
- Patients who do not meet any of the exclusion criteria referenced in this protocol.

4.3.2. Exclusion Criteria

The exclusion criteria were as follows:

- A history of/or clinical signs of, iritis, uveitis, synechiae, pigment dispersion syndrome, retinal disease (other than manifestation of myopic degeneration), chronic intraocular inflammation, macular degeneration, irregular astigmatism, keratoconus or cystoid macular edema in either eye;
- Diabetes;
- Glaucoma in either eye;
- A history of previous intraocular surgery (including refractive surgery) in the eye to be treated;
- Amblyopia or blindness in the fellow eye;
- A serious (i.e., life-threatening) non-ophthalmic condition, which may preclude study completion;
- A progressive sight-threatening disease (patients with retinal findings associated with pathological myopia are allowed);
- A diagnosis of ocular hypertension;
- Fuch's dystrophy or other corneal pathology;
- Keratoconus, cataract in either eye, or systemic collagen sensitivity;
- An unstable refraction in the past 12 months (myopia and/or astigmatism);
- Patients who do not fall in the range of pre-treatment myopia and/or astigmatism as outlined in the inclusion criteria; or

- Patients who are involved in another clinical study or who may have been involved in a different clinical study within 30 days prior to this clinical study or will be involved in a different clinical study within 30 days of beginning this study.

4.4. Study Materials and Methods

4.4.1. Examination Schedule

The patients were followed for a 12-month period at the time intervals listed in Table 3 below.

Table 3 — Exam Schedule Form Intervals

Form	Examination	Suggested Interval
Form 0	preoperative/operative	0 to 60 days before surgery
Form 1	1 day postoperative	15 to 30 hours postoperative
Form 2	1 week postoperative	7 to 14 days postoperative
Form 3	1 month postoperative	3 to 6 weeks postoperative
Form 4	3 months postoperative	10 to 14 weeks postoperative
Form 5	6 months postoperative	5 to 7 months postoperative
Form 6	12 months postoperative	11 to 14 months postoperative (study endpoint)

4.5. Surgical Procedure

4.5.1. Lens Calculation and Selection

The Visian TICL power is determined using the Visian TICL Calculator software. The following parameters must be entered to calculate the lens: manifest refractive sphere; cylinder and axis; back vertex distance; keratometry; anterior chamber depth; and white to white. Following the calculation, the software displays the expected outcomes for a range of Visian TICL powers, and from this information the surgeon selects the lens which best meets the treatment plan for the eye. The Visian TICL can be rotated in-eye by 22.5 degrees to align the cylinder axis of the lens to the cylinder axis of the pre-operative manifest refraction. The software generates an Implantation Orientation Diagram, by comparing the cylinder axis of the lens selected to the cylinder axis of the pre-operative manifest refraction. This diagram shows the surgeon the extent to which the lens needs to be rotated and the direction of the required rotation (either clockwise or counterclockwise).

In the study, the recommended method for sizing was based on white-to-white measurement. Vault was assessed at all time-points (with the exception of the 1 week

post-operative visit) by slit-lamp evaluation and recorded as a percentage of corneal thickness (CT). Analysis of vault from 186 eyes at the 12 month visit demonstrated that the mean vault was 102.8% CT with a standard deviation of 51.2%. The percentage of lenses with vault in the ranges of 50% to 150% CT and 25% to 200% CT were 82.3% and 92.5%, respectively.

4.5.2. Preoperative

Within the two weeks prior to surgery, the patients received two iridotomies performed 90° apart, preferably using an Nd;YAG laser; iridectomies may have been done intra-operatively (at the time of surgery).

4.5.3. Operative Technique

Preoperative pupil dilation could be done according to the surgeon's preference using the same regime as would typically be used for cataract surgery. It was recommended that a minimum dilation of 8mm be confirmed before proceeding to the operative theater. A pupil size of less than 8mm required excessive distortion of the Visian TICL to place it behind the iris and was thus considered too small for safety. If the pupil would not dilate to 8mm, surgery was aborted.

Surgery to implant the Visian TICL was recommended to be performed under either topical or local anesthesia. At the time of surgery, subjects were draped and the ocular area prepared in the same manner as would be done for cataract surgery. Once draped, but before placing the lid speculum or making any incisions in the eye, loading of the Visian TICL into the injection cartridge was completed.

The Visian TICL was implanted into the eye using a STAAR injector. The lens was loaded into an injector cartridge. Orientation markings on two of the four footplates should appear on the leading right and trailing left footplate, signifying the lens was the correct side up.

The cartridge was lubricated with BSS and viscoelastic, and the lens was loaded into the cartridge using forceps. The cartridge was then inserted and locked into position in the lens injector. Once the lens was properly loaded, the Visian TICL cartridge was kept hydrated in a sterile basin with BSS or saline, and surgery was ready to proceed.

Two paracentesis incisions were made 60° to 90° away from the main incision, which was made at the horizontal temporal position. The lens was implanted through a 2.8mm to 3.2mm clear corneal tunnel incision that was constructed parallel to the iris plane.

Prior to implantation, 2% methylcellulose viscoelastic (OcuCoat) was introduced into the anterior chamber by placing the cannula just inside the incision. The tip of the cartridge was then inserted through the incision and the lens injected in a slow controlled manner.

The surgeon needed to check lens orientation when approximately 2/3 of the lens had exited the cartridge tip.

The lens was then allowed to unfold entirely, on top of the iris, within the anterior chamber with the surgeon verifying that the orientation marks were located on the leading right and trailing left foot plates. If the lens needed to be rotated to align the lens axis with the pre-operative axis of astigmatism, up to 22.5° from the horizontal axis, this was done prior to placing the footplates behind the iris. Once aligned, the footplates were gently tucked one by one behind the iris, first the distal then the proximal footplates.

Any viscoelastic remaining in the eye was then removed using manual irrigation with BSS followed by Miochol (acetylcholine chloride) to constrict the pupil. At this point, the surgeon needed to once again check the axis alignment to ensure the lens had not been moved during the irrigation/aspiration process.

At this same point, the iridotomies were rechecked for patency. Wound integrity was then checked to ensure it was water tight, and surgery was complete.

The intraocular pressure (IOP) was checked at approximately 2 to 3 hours postoperative. If the IOP was below 21 mm Hg, the patient was sent home. In cases where the IOP was at or above 21mm Hg, pressure reduction was attempted. The patient was not discharged until IOP below 25mm Hg was verified at 3 to 4 hours postoperatively.

4.5.4. Postoperative Care

The recommended postoperative medical regimen was as follows:

- Ofloxacin solution 0.3% one drop four times daily beginning on the day before surgery and continuing through the first postoperative week; and
- Tobramycin and dexamethasone suspension for a total of sixteen days — one drop four times a day for the first four days following surgery, one drop three times a day for the next four days, one drop twice a day for the next four days and one drop once a day for the final four days.

4.6. Primary Endpoints

4.6.1. Safety Endpoints

The objective of the Visian TICL study was to evaluate effectiveness of the Visian TICL. Although safety of the Visian ICL has been established in the Visian ICL study, the following safety data were collected during the Visian TICL study:

- Preservation of BCVA;
- Slit lamp examination results;

- Intraocular pressure; and
- Incidence of complications and adverse events.

4.6.2. Effectiveness Endpoints

The following parameters were used for effectiveness of the Visian TICL surgery:

- Improvement in uncorrected visual acuity;
- Decrease in refractive myopia and cylinder;
- Predictability (intended correction vs. achieved correction for sphere and cylinder);
- Stability of refraction;
- Subjective patient satisfaction; and
- Rotation of the Visian TICL.

4.7. Clinical Evaluation and Data Collection

4.7.1. Statistical Methods

The objective of this clinical study was to evaluate effectiveness outcomes associated with the implantation of the Visian TICL for the correction of myopic astigmatism, since the safety of this lens design had already been established in the Visian ICL study. All effectiveness data was to be reported in accordance with the study examination visit schedule to document changes from baseline at each reporting interval.

In reference to effectiveness, the Student's paired t-test was used to calculate the mean paired difference between preoperative and postoperative refractive cylinder to demonstrate a statistically significant decrease in astigmatism.

4.8. Clinical Study Information

4.8.1. Accountability

Both eyes of Visian TICL patients were included in the Visian TICL Study Cohort, which was consistent with the Visian ICL PMA study cohort, where 526 eyes of 294 patients were included for both the safety and efficacy evaluation (fellow eyes were included in the cohort and no primary-eye-only analysis was performed). The accountability summaries are provided in Table 4.

Table 4 — Accountability Analyses

Total Enrollment n = 210	1 D	1 W	1 M	3 M	6 M	12 M
Available for Analysis	210 (100%)	195 (92.9%)	184 (87.6%)	157 (74.8%)	167 (79.5%)	146 (69.5%)
Missing Subjects						
Discontinued[1]	0 (0%)	0 (0%)	2 (1.0%)	3 (1.4%)	3 (1.4%)	3 (1.4%)
Missing at scheduled visit but seen later	0 (0%)	10 (4.8%)	16 (7.6%)	34 (16.2%)	15 (7.1%)	48 (22.9%)
Not seen but accounted for	0 (0%)	3 (1.4%)	6 (2.9%)	13 (6.2%)	16 (7.6%)	0 (0%)
Lost to follow-up[2]	0 (0%)	2 (1.0%)	2 (1.0%)	3 (1.4%)	9 (4.3%)	13 (6.2%)
Active	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Accountability	100%	92.9%	88.5%	75.8%	80.7%	70.5%
Accountability including out-of-window visits[3]	100%	97.6%	96.2%	92.3%	87.9%	93.7%

[1] Cumulative total number of eyes discontinued is 3.

[2] Cumulative total number of eyes lost to follow-up is 13.

[3] Calculated (available for analysis+missing at scheduled visit but seen later)/(enrolled-discontinued).

Overall accountability for this study consisted of follow-up for 194 eyes examined for the one-year postoperative visit, including 48 eyes seen outside the defined visit window of 11 to 14 months. There were 146 eyes seen timely at the 1 year visit. Thirteen eyes from twelve study subjects were lost to follow-up over the course of the Visian TICL clinical study. In 7 of the 13 cases lost to follow-up, the site was unable to locate or contact the patients. In four of the cases, the patient moved and was not available for examination. In two cases from the Navy site, the patients were deployed to Iraq and were unavailable for examination prior to study closure.

There were three eyes of three subjects discontinued from the Visian TICL Study Cohort. In all of these cases, the Visian TICL was removed with no subsequent IOL/ICL implantation.

4.8.2. Demographics

Clinical study subject demographics for the 210 eyes from 124 subjects enrolled in the Visian TICL Study Cohort to date are summarized in Table 5. The mean preoperative manifest refraction spherical equivalent (MRSE) for the Visian TICL Study Cohort was highly myopic at –9.37D (range of−2.38D to −19.50D). The mean preoperative manifest refractive cylinder was 1.95D (range of 1.00D to 4.00D). See Table 5.

Table 5 — Demographics

		Number	Percentage
Gender	Male	55	44.4%
	Female	69	55.6%
Race	Caucasian	102	82.3%
	Black	6	4.8%
	Hispanic	10	8.1%
	Other	6	4.8%
Eye	Right	108	51.4%
	Left	102	48.6%

	Mean	Standard Deviation	Minimum	Maximum
Age	35	6.8	21	45
Preoperative Spherical Equivalent	−9.37 D	2.67 D	−19.50 D	−2.38 D
Preoperative Cylinder	1.95 D	0.84 D	1.00 D	4.00 D

4.8.3. Distribution of Preoperative Manifest Refraction by Preoperative Cylinder

Table 6 provides a distribution of the preoperative manifest refraction by the preoperative cylinder for the Visian TICL population.

Table 6 — Distribution of Preoperative Manifest Refraction by Preoperative Cylinder

Preoperative Spherical Equivalent	Preoperative Cylinder n=210						
	1.00 to 1.50D	1.51 to 2.00D	2.01 to 2.50D	2.51 to 3.00D	3.01 to 3.50D	3.51 to 4.00D	Total
≤ −3.00 to −8.00D	31 (14.8%)	20 (9.5%)	7 (3.3%)	11 (5.2%)	0 (0.0%)	4 (1.9%)	73 (34.8%)
−8.01 to −12.00D	46 (21.9%)	15 (7.1%)	18 (8.6%)	5 (2.4%)	12 (5.7%)	7 (3.3%)	103 (49.1%)
−12.01 to −15.00D	10 (4.8%)	8 (3.8%)	6 (2.9%)	2 (1.0%)	2 (1.0%)	0 (0.0%)	28 (13.3%)
−15.01 to −20.00D	3 (1.4%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	6 (2.9%)
Total	**90 (42.9%)**	**44 (21.0%)**	**32 (15 2%)**	**19 (9.0%)**	**14 (6.7%)**	**11 (5.2%)**	**210**

4.8.4. Preexisting Preoperative Ocular Conditions

Six eyes (3.0%) of the 210 cohort eyes were reported to have a preexisting ocular condition in the Visian TICL Study Cohort (Table 7). Two had extensive lattice degeneration, one requiring retinopexy (1.0%), and two additional eyes (1.0%) had

retinopexy for retinal holes, one had ptosis (0.5%) and one had amblyopia (0.5%). None of the cases had any complications or reported any new lens opacities. The amblyopia case had 20/40 BCVA preoperatively but was reported to have 20/60 at the 6-month and one year visits with no reason given. This patient was subsequently seen five months after the one year visit and was within one line of preoperative BCVA. The remainder of the cases had either an improvement (4 out of 5 cases) or the same BCVA (1 out of 5 cases) at last visit.

Table 7 — Preoperative Conditions and Previous Ocular Surgery

Preoperative Condition	n (%) n=210
Amblyopia	1 (0.5%)
Ptosis	1 (0.5%)
Extensive Lattice Degeneration (1 requiring Retinopexy)	2 (1.0%)
Retinopexy for Retinal Holes	2 (1.0%)
Total	**6 (3.0%)**

4.8.5. Study Conduct

This section details issues raised with the conduct of the study that were not reported as protocol violations.

4.8.5.1. Data integrity hold

In August 2007, the FDA placed the PMA supplement on data integrity hold. This was largely based upon the findings of a clinical data audit by Bioresearch Monitoring (BIMO) in March 2007. STAAR complied with the terms of the hold, and in July 2009 the FDA released the PMA supplement to resume substantive review. The terms of the data integrity hold included a condition that an independent third party audit 100% of STAAR's clinical data for this PMA supplement. From November 2007 through March 2009, Promedica International (PMI) acted in this capacity. PMI reported directly to FDA and received instruction and guidance solely from FDA, without direction from STAAR. During the course of the audit, PMI reviewed the patient charts at all seven clinical sites, comparing each chart's data to the related data on the case report forms (CRF) and then comparing the CRF data to the data in the clinical database. Based on PMI's findings and recommendations, STAAR made certain changes to the clinical database. All changes to the database were reviewed and approved by PMI during the audit. At the conclusion of the audit, PMI provided reports on their activity and findings directly to FDA and also provided a certification to STAAR that provided, in part, as follows;

> *"…the corrected database is a true reflection of the data in the field. This corrected database can be used to analyze the study data."*

STAAR believes this reconfirmed the scientific validity and accuracy of the clinical data set used to analyze this clinical study.

4.8.6. Protocol deviations

Protocol deviations were categorized in accordance with International Conference on Harmonisation (ICH) E3 Guidance on the Structure and Content of Clinical Study Reports (R1). As defined by the guidance, 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.

Table 8 categorizes the protocol deviations into the two sub categories.

Table 8 — Protocol Deviation Categories

Type of Deviation	Total
Major	
Lens power outside protocol approved range	32
Lens length not selected according to protocol	18
Non-compliance with surgical procedure	4
Minor	
Unapproved randomization	41
Eyes outside of the inclusion criteria	3
Inconsistency between protocol and CRF	13
Non-compliance with pre-surgical procedure	8
Out-of-window visits	123
Missed visits	33
Missing information	272
Manufactured axis not according to protocol	126
Snellen instead of ETDRS	33
Total Occurrences	**706**

4.8.6.1. Lens power outside of protocol approved range

There were 32 lenses implanted with powers outside the range in the protocol. Six eyes were implanted with sphere power above -20.00D, twenty four eyes were implanted with cylinder power below +1.50D and two eyes were implanted with sphere above -20.00D and cylinder below +1.50D.

All 32 lenses were correct in both spherical and cylindrical power for the TICLs implanted outside the protocol-defined range. The outcomes would not have impacted scientific validity, or more importantly, compromised subject safety.

4.8.6.2. Lens length selected not according to protocol

The methodology used for determining the recommended TICL length was white to white (WTW) measurement and anterior chamber depth (ACD). There were 18 lenses implanted where the TICL length selected was not in accordance with this methodology.

Eleven of the 18 lenses consisted of surgeon-requested lengths that differed from the length recommended in the TICL DFU. Some of the cases were fellow eyes where the surgeon determined the need for variance based on experience from the primary eye. One site utilized sulcus-to-sulcus measurements obtained by ultrasound rather than WTW.

Five lenses were incorrectly sized due to an error in measurement of ACD, where one site included corneal thickness which resulted in the selection of a longer lens.

Two of these 5 were implanted with a 13.5 mm lens, which were outside the range designated in the DFU. In addition, two other 13.5 mm were implanted based on correct sizing, although this was again outside the range of the DFU.

4.8.6.3. TICL implants outside of eligibility constraints

Three eyes were implanted with the Visian TICL that were not eligible according to protocol. Two of these eyes were fellow eyes of two subjects that were implanted after the subjects reached the age of 46. The protocol inclusion criteria cutoff was 45 years of age, however, the primary eyes of these subjects were implanted in accordance to the protocol inclusion criteria. The third eye was a fellow eye that had 0.75D of preoperative astigmatism, in which the protocol required a minimum of 1.00 D of preoperative astigmatism. All three eyes were not included in the analysis.

4.8.6.4. Non-compliance with surgical procedure

Four eyes had deviations from the protocol during the operative visit of the study. These eyes were included in the analysis as the deviations were not determined to impact scientific validity of the study or subject safety.

- Three eyes were implanted with the use of a viscoelastic not recommended in the protocol. None of these eyes had any surgical complications.
- One eye was implanted with a Visian TICL and rotated 90° (protocol required rotation of no more than 22.5°). The surgery was uneventful and at one year postoperatively the refraction was plano in sphere and cylinder power with BCVA and UCVA of 20/20.

4.8.6.5. Changes to manufacturing process

[redacted]

[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

If a lens of the correct sphere and cylinder power and within ±22.5° cylinder range was available to satisfy the patient's requirements, the lens was selected from inventory. If no suitable lens was available, a lens was manufactured.

Despite this change in axis targeting approach during the study, lenses implanted in the study showed an average angle of alignment and range of alignments equivalent to the alignment that would have been required if all lens had been manufactured to the four axes. (Shown in Table 10 below.)

Table 10 — Average Angle of Alignment and Range of Alignments

Degrees of Required TICL Rotation	Number of Eyes	Percent	Average Rotation
0°	12	6%	0.0°
1° to 5°	79	38%	3.0°
6° to 10°	53	25%	7.9°
11° to 15°	31	15%	12.5°
16° to 22°	34	16%	18.6°
>23° *	1	0%	90.0°
Total	**210**	**100%**	**8.4°**

*90° rotation was noted as protocol deviation

Rotational stability of the Visian TICL lens at 12 months postoperatively, relative to the extent needed to align in-eye during the procedure, showed there was no correlation between rotational stability and fixation angle (extent of in-eye rotation of the lens during implantation) from 0° to 22°.

As shown in Figure 3's scatterplot, there was a weak correlation between the variables compared. The Pearson r for absolute angle of rotation and fixation angle was low in degree of association with a statistically significant p-value of 0.0247 at the last available visit. This indicates that it is unlikely to have occurred by chance. However given the low degree of association, while the difference is significant the relevance is questionable. The shared variance was approximately only 2.5%.

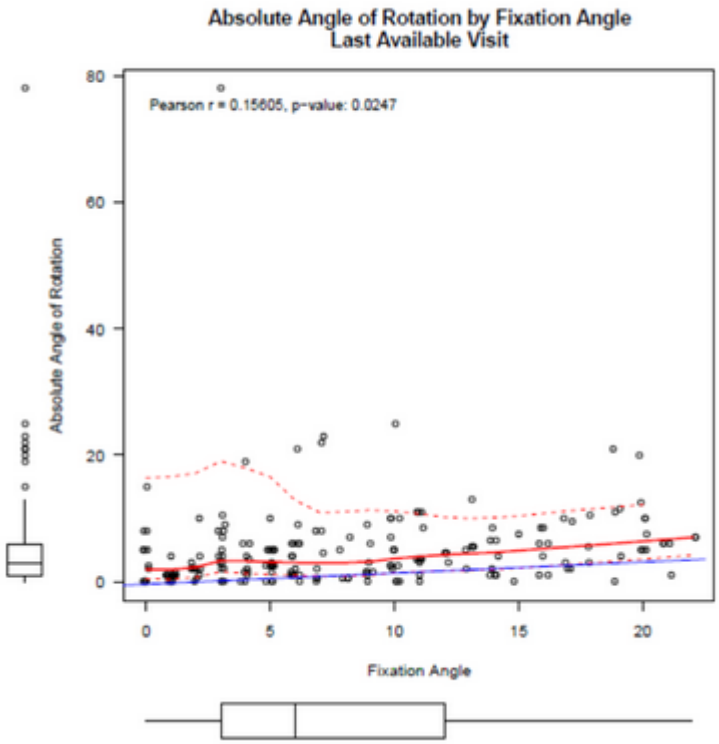

Figure 3 — Absolute Angle of Rotation by Fixation Angle (Last Available Visit).

Further, if this analysis is performed in eyes with absolute angle of rotation greater than 10°, the slope of the blue line (a least squares fit) is reversed indicating a higher rotation in lenses with a lower fixation angle. However, this difference is not significant.

Therefore, in terms of the manufacturing processes, this change had no impact on lens labeling, lens selection, or lens implantation, and accordingly no impact on the scientific validity of the study or on the safety and effectiveness of the Visian TICL.

4.8.6.6. Unapproved randomization into study

The Navy Refractive Surgery Center (NRSC) in San Diego submitted, and received approval from the local IRB for a randomized clinical trial, with patients randomized to either implantation of the Visian TICL or to photorefractive keratectomy (PRK) with mitomycin C. The NRSE intended that the patients randomized to treatment with the Visian TICL would be part of the IDE Study Cohort. Consistent with this, the Visian TICL arm of the NRSC study was conducted in accordance with the protocol approved under IDE G010252.

Therefore, with respect to the patients that are included in the clinical study data, the only difference at the NRSC was that the Visian TICL study subjects were randomized into

the TICL arm of the study. The NRSC subjects enrolled into the PRK arm were not considered part of the IDE clinical trial.

While this approach was not planned, the independent third party auditors at Promedica International (PMI) commented that while subjects were randomized to the Visian TICL or to PRK, the Visian TICL treatment arm used the same case report forms as those approved under IDE G010252 and the study was performed consistent with the protocol approved under G010252. An excerpt from the audit report is provided below:

> *"In conclusion, as evidenced through the third party independent audit conducted by Promedica, the study subjects randomized to receive the STAAR Toric Implantable Contact Lens (TICL) followed the investigational plan as approved by the FDA under IDE G010252, however, the study protocol and subject informed consent were modified under the Navy CRADA document approved by Navy IRB. The revision modified the FDA approved non-randomized, open-label study to a randomized study in which the subjects were randomly assigned to receive either the TICL implant or PRK (photorefractive keratectomy) with Mitomycin C. The subject case report form utilized for the subjects randomized to receive the STAAR Toric Implantable Contact Lens was the same subject case report form as approved by the FDA under IDE G010252. No data collection processes were altered throughout the course of the study for the implanted subjects."*

The study subjects were not exposed to additional risk as a result of the additional study arm, therefore, data collected in the Visian TICL arm is scientifically valid for analysis in the Visian TICL study effectiveness assessments.

4.8.6.7. Inconsistency between approved clinical protocol and case report forms

In some cases, the case report forms (CRFs) did not request the following information that was required in the clinical study protocol:

- an eligibility exclusion related to patients involvement in another clinical study;
- timing of YAG iridotomies;
- preoperative and postoperative drug regimen at all visits;
- wound size and closure method; and
- operative and postoperative lens centration.

The omission of this information did not significantly affect any of the study endpoints, and therefore does not impact the overall scientific validity of the clinical study.

4.8.6.8. Non-compliance with pre-surgical procedure

Eight eyes were discovered to have deviations from the protocol during the preoperative portion of the study. Six of these eyes had YAG iridotomies performed outside the protocol window due to a scheduling conflict. There are no clinically significant effects of iridotomies being performed earlier than the protocol defined time period.

Two additional eyes did not meet the requirement for a stable refraction for 12 months prior to surgery.

Since these deviations did not impact the scientific validity of the data collected, and had no effect on subject safety, all eight of these eyes were included in the study analysis.

4.8.6.9. Out-of-window visits

A total of 123 visits fell outside the visit windows defined in the study protocol; these eyes are in the category of "missing at scheduled visit but seen later" according to ISO 11979 7.

The inclusion of the out of window visits in the analysis was based upon the assumption that no time based therapeutic benefits exist that are related to safety or effectiveness solely based on visit timing.

Forty-seven (47) of the 123 out-of-window visits were active duty military personnel enrolled and treated at the Navy Refractive Surgery Center in San Diego. Availability of these patients under their duty schedules restricted the timing of the study visits, resulting in the deviations summarized in Table 11.

Table 11 — Out of Window Visits

Missing at scheduled visit but seen later	1 D	1 W	1 M	3 M	6 M	12 M
Navy Refractive Center	0	1	1	16	4	25
Other Sites	0	9	15	18	11	23
Total	**0**	**10**	**16**	**34**	**15**	**48**

4.8.6.10. Missed visits

There were a total of 33 missed visits (as opposed to visits conducted out of window), distributed across the postoperative visits.

4.8.6.11. Missing Information

In a number of cases, the clinical sites did not provide all information as required by the study protocol and CRF. The main category of missing data consisted of failure to record lens orientation observed at the slit lamp. However, since this data was not used in the analysis of rotational stability (as discussed in Section 6.6) the missing information does not affect the scientific integrity of the study.

Other sources of missing data included subjective questionnaires that were not completed as required, in whole or in part, as well as isolated cases of unreported information, including IOP, manifest refraction, BCVA, UCVA and LOCS scores. Again, the lack of this data does not compromise the scientific validity of the overall data.

4.8.6.12. Snellen chart used rather than ETDRS

The IDE protocol originally identified use of Snellen charts for measurement of visual acuity. However prior to initiation of the study, FDA requested that sites use an ETDRS to measure VA and that the ETDRS acuity be converted to Snellen equivalent. During the August 2013 BIMO audit, FDA auditors reviewed a sample of study files and found that in 33 cases, visual acuity was recorded in Snellen rather than Snellen equivalent format. This deviation does not have an impact on the scientific integrity, effectiveness, or safety of subjects within the study.

5. SAFETY

This section contains a summary of the data from the clinical study that supports safety parameters, and builds upon the body of safety data established by the previous Visian ICL study which are also confirmed by extensive commercial experience from approximately 110,000 Visian TICL implantations in over 60 international markets.

This section discusses the primary endpoints listed below:

- Preservation of BCVA;
- Slit lamp examination--lens opacities;
- Intraocular pressure (IOP); and
- Incidence of complications and adverse events.

In addition, the safety parameters below are addressed:

- Pigment, Flare and Cell incidence; and
- Patient subjective symptoms.

5.1. Preservation of BCVA

BCVA was analyzed for both the overall cohort and for a subset of those with preoperative BCVA of 20/20 or better. In addition, BCVA was analyzed in terms of lines gained or lost.

The proportion of eyes with BCVA of 20/16 and with 20/20 or better increased across all postoperative follow-up exams compared to the preoperative level. The proportion of eyes with BCVA of 20/16 or better increased from 41.0% preoperatively to 81.8% and

77.3% at 6 months and 12 months respectively. Furthermore, the proportion of eyes with 20/20 or better BCVA rose from 82.4% preoperatively to 96.1% (6 months) and 96.9% (12 months). All eyes (100%) had 20/40 or better BCVA at the preoperative visit; 99.4% at 6 months and 99% at 12 months postoperatively. BCVA at key study visits in the Visian TICL Study Cohort is summarized in Table 12.

Table 12 — Best Corrected Visual Acuity

BCVA	Preoperative n (%) n = 210	3 M n (%) n = 190	6 M n (%) n = 180	12 M n (%) n = 194
20/16 or better	86 (41.0%)	151 (79.5%)	148 (81.8%)	150 (77.3%)
20/20 or better	173 (82.4%)	185 (97.4%)	174 (96.1%)	188 (96.9%)
20/40 or better	210 (100%)	190 (100%)	180 (99.4%)	192 (99.0%)
Worse than 20/40	0 (0%)	0 (0%)	1 (0.6%)	2 (1%)
Not Reported	0	1	1	0
Total	**210**	**191**	**182**	**194**

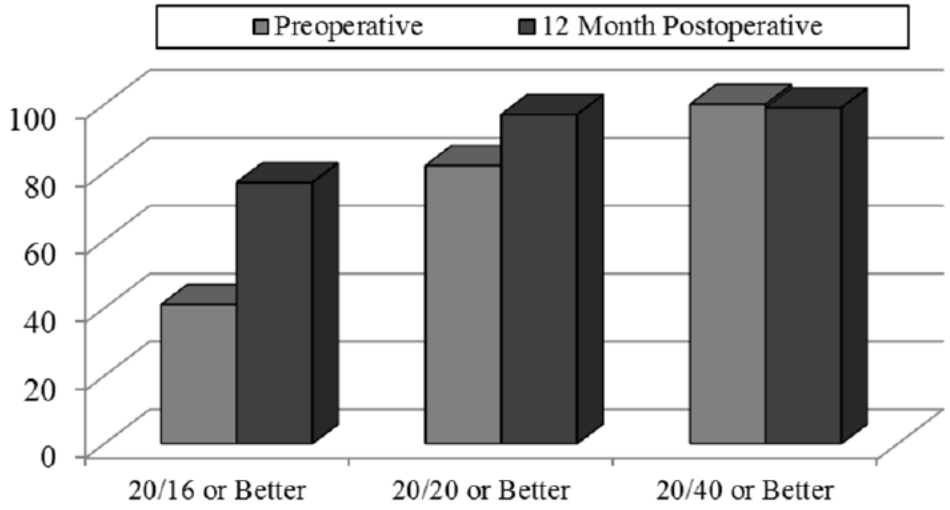

Figure 4 — BCVA Preoperative and at 12 months postoperative examination in consistent cohort of cases with both visits

The proportion of eyes with BCVA of 20/16 or better improved across all postoperative follow-up exams compared to the preoperative level. The proportion of eyes with BCVA of 20/16 or better improved from 49.7% preoperatively to 91% and 89.9% at 6 months and 12 months respectively. All eyes were 20/20 or better at 12 months following implantation, which surpasses the Protocol Target of less than 1% of eyes at 20/40. Table 13 summarizes BCVA levels at key study visits for the subset of eyes with preoperative 20/20 or better.

Table 13 — Best Corrected Visual Acuity for Eyes with Preoperative BCVA 20/20 or Better

BCVA	Preoperative n/N (%)	3 M n/N (%)	6 M n/N (%)	12 M n/N (%)
20/16 or better	86/173 (49.7%)	139/160 (86.9%)	141/155 (91.0%)	143/159 (89.9%)
20/20 or better	173/173 (100%)	159/160 (99.4%)	155/155 (100%)	159/159 (100%)
20/40 or better	173/173 (100%)	160/160 (100%)	155/155 (100%)	159/159 (100%)
Worse than 20/40	0/173 (0%)	0/160 (0%)	0/155 (0%)	0/159 (0%)
Not Reported	0	1	0	0
Total	**173**	**161**	**155**	**159**

The change in BCVA from baseline is given in Table 14. These results for the Visian TICL Study Cohort were better than the suggested target value, which states that less than 5% of cases should have ≥ 2-line loss in BCVA, as outlined in the Protocol. There was a significant improvement in BCVA, with 76.8% of eyes gaining at least one line, and an overall mean change of 0.89 lines at 12 months. This improvement in BCVA may be explained by image magnification, due to the Visian TICL being placed closer to the nodal point. Only three eyes (1.5%) experienced loss of two or more lines of BCVA at 12 months (Table 14 and Figure 5). One case was due to a 2+ anterior subcapsular cataract. The second case involved subject with preoperative BCVA of 20/12.5 All reported visits except the 12 month visit had a BCVA of 20/16 or better, however, at the 12 month visit the subject had 20/20 BCVA. All other testing and clinical assessments were deemed to be unremarkable with no pathological cause to the change in BCVA. The cause of the change in BCVA was undetermined. However, it is important to note that the subject consistently reported "very satisfied" with their procedure. The third case involved a subject who presented with pre-existing amblyopia and BCVA of 20/40 pre-operatively. At the 12 month visit, the subject had BCVA of 20/60, with unremarkable slit lamp findings that may have contributed to the change in BCVA, either in the anterior or posterior segment. It is important to note, 5 months after the 12 month post-operative visit, BCVA improved to 20/50.

Table 14 — Change in BCVA from Baseline

	3 M n (%) n = 190	6 M n (%) n = 181	12 M n (%) n = 194
Decrease > 2 Lines	0(0%)	0 (0%)	1 (0.5%)
Decrease 2 Lines	1 (0.5%)	1 (0.6%)	2 (1.0%)
Decrease 1 Line	3 (1.6%)	5 (2.8%)	9 (4.6%)
No Change	42 (22.1%)	39 (21.5%)	33 (17.0%)
Increase 1 Line	99 (52.1%)	101 (55.8%)	113 (58.2%)
Increase 2 Lines	35 (18.4%)	31 (17.1%)	32 (16.5%)
Increase > 2 Lines	10 (5.3%)	4 (2.2%)	4 (2.1%)
Mean Line Change	1.02	0.93	0.89
% Increase	144 (75.8%)	136 (75.1%)	149 (76.8%)
% Decrease	4/190 (2.1%)	6/181 (3.3%)	12/194 (6.2%)
Not Reported	1	1	0
Total	**191**	**182**	**194**

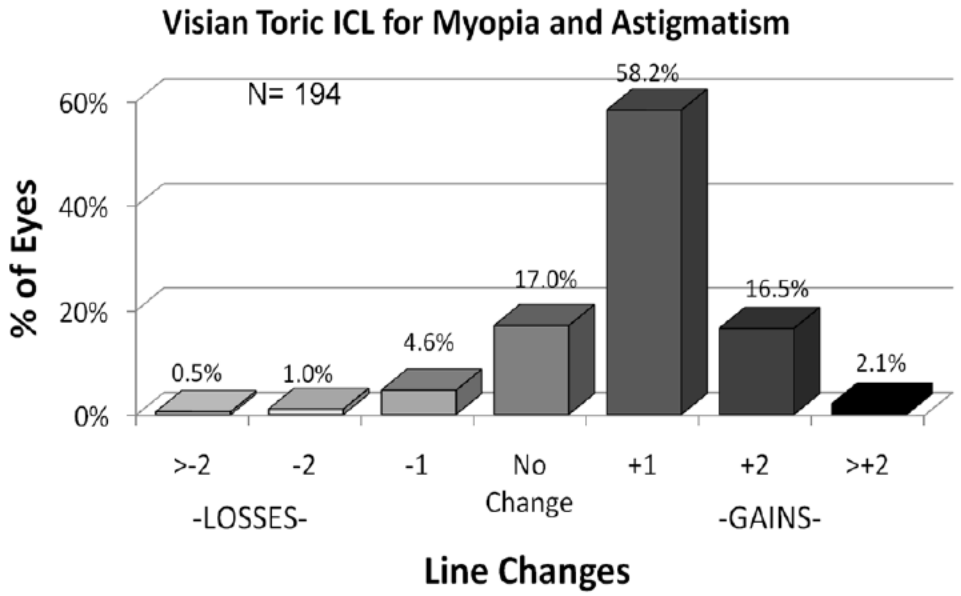

Figure 5 — Change in BCVA Preoperative vs. 12-Month Visit

5.2. Slit Lamp Examination - Lens Opacities

The standardized Lens Opacities Classification System (LOCS III) photographic images were utilized across all clinical sites in the Visian TICL clinical investigation for the

assessment of the incidence, type, and severity of lens opacities. Anterior subcapsular appearance was assessed using photographs for posterior subcapsular appearance, and the slit lamp examination localized the opacity anteriorly.

There were no cases of trace or greater reported for nuclear color, nuclear opalescence, cortical, or posterior subcapsular changes preoperatively or at any postoperative visit.

Six eyes (2.9%) reported anterior subcapsular opacities of trace or more postoperatively. Four cases were asymptomatic with 20/16 or better BCVA, 20/25 or better UCVA, and glare scores of absent/mild at the last reported visit (see Table 15). Two cases had a clinically significant cataract; one subject had BCVA of 20/50 at the 12 month visit compared to 20/25 preoperatively, associated with a 2+ anterior subcapsular opacity. The other case with anterior subcapsular opacity did not have a change in BCVA, but the patient had a decrease in glare score by one category. This change was considered insufficient evidence to diagnose a clinically significant cataract. However, after 22 months from the initial Visian TICL surgery, the Visian TICL was removed and cataract extraction was performed. Therefore, this case was included even though it did not fulfill the criteria during the 12 month course of the study.

Table 15 — Distribution of LOCS III Scores Over Time; Anterior Subcapsular

Severity	Preoperative n/N (%) n=210	1 W n (%) n=204	1 M n (%) n =199	3 M n (%) n =199	6 M n (%) n =199	12 M n (%) n =199
Clear (0 to 0.5)	210 (100%)	204 (100%)	198 (99.5%)	189 (99.5%)	180 (99.4%)	189 (97.4%)
Trace (0.6 to 1.0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	3 (1.5%)
Mild (1.1 to 2.0)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	0 (0%)	1 (0.5%)
Moderate (2.1 to 3.0)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
Marked (> 3)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	0	1	1	1	1	0
Total	**210**	**205**	**200**	**191**	**182**	**194**

A peer-reviewed paper studying the incidence of anterior subcapsular opacities and cataracts 5 years after surgery was reported using the Visian ICL database (Sanders). Five hundred twenty-six eyes were followed for an average of 4.7 years; 89% (468 eyes), 73% (384 eyes), and 59% (311 eyes) were seen at 3, 4, and 5 years or later, respectively. Kaplan-Meier cumulative probability estimates demonstrated that approximately 6% to 7% of eyes develop anterior subcapsular opacities at 7+ years following ICL implantation but only 1% to 2% progress to clinically significant cataract during the same period, especially very high myopes and older patients. Visual outcome following cataract extraction was good.

5.3. Intraocular Pressure (IOP)

Table 16 summarizes the IOP over time for all eyes in the Visian TICL Study Cohort. Only one eye had an intraocular pressure reading > 25mm Hg after 1 week during the postoperative follow-up for the Visian TICL clinical study. One eye (0.5%) had between 21 to 25mm Hg at 1 year postoperatively. 26mm Hg was the highest IOP measured at any postoperative follow-up visit at 1 week or later. No eyes required treatment with pressure-lowering drops after the first month.

Table 16 — Intraocular Pressure with Time

IOP	Preoperative n (%)	1 W n (%)	1 M n (%)	3 M n (%)	6 M n (%)	12 M n (%)
10mmHg or Less	23 (11.0%)	17 (8.3%)	23 (11.6%)	26 (13.8%)	18 (9.9%)	19 (9.8%)
11 to 15mm Hg	124 (59.0%)	118 (57.6%)	126 (63.3%)	113 (60.1%)	118 (64.8%)	112 (57.7%)
16 to 20mm Hg	60 (28.6%)	66 (32.2%)	48 (24.1%)	48 (25.5%)	42 (23.1%)	62 (32.0%)
21 to 25mm Hg	3 (1.4%)	3 (1.5%)	2 (1.0%)	1 (0.5%)	3 (1.6%)	1 (0.5%)
26 to 30mm Hg	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)
More than 30mm Hg	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	0	0	1	3	0	0
Total	**210**	**205**	**200**	**191**	**182**	**194**

Change in IOP between the preoperative baseline and postoperative follow-up visits for the Visian TICL Study Cohort is provided in Table 17. Only two eyes (0.5%) experienced an increase in IOP > 10mm Hg at 1 month postoperative or later during the Visian TICL study. One of these eyes had a preoperative IOP of 8mm Hg, which increased to 17mm Hg at 12 months postoperatively. The second eye had an IOP of 10mm Hg preoperatively and 22mm Hg at 12 months postoperatively.

The mean within-eye change in IOP at 6 months was −0.4mm Hg (14.2mm Hg preoperative and 13.8mm Hg at 6 months, n=182, p=0.12 with paired t-test) and was 0.1mm Hg at 12 months (14.1mm Hg preoperative and 14.2mm Hg at 12 months, n=194, p=0.72 with paired t-test), thus there was no statistically significant difference between baseline IOP and 6- or 12-month IOP.

Table 17 — Change in Intraocular Pressure from Baseline

IOP	1 W n (%)	1 M n (%)	3 M n (%)	6 M n (%)	12 M n (%)
Increase > 10	1 (0.5%)	0 (0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Increase 6 to 10	17 (8.3%)	5 (2.5%)	4 (2.1%)	7 (3.8%)	6 (3.1%)
No Change (± 5mmHg)	178 (86.8%)	186 (93.5%)	171 (91.0%)	166 (91.2%)	179 (92.3%)
Decrease 6 to 10	9 (4.4%)	8 (4.0%)	11 (5.9%)	8 (4.4%)	8 (4.1%)
Decrease > 10	0 (0%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)
Not Reported	0	1	3	0	0
Total	**205**	**200**	**191**	**182**	**194**

Only one (0.5%) eye had an IOP reading > 25 mmHg any time point after 1 week postoperative. One eye (0.5%) had between 21 to 25 mmHg at 1 year postoperatively. Two eyes (0.9%) experienced an increase in IOP > 10mmHg at 1 month postoperative or later during the study.

5.4. Incidence of Adverse Events

5.4.1. Comparison to the ISO-Defined Safety and Performance Endpoint Rates

Table 18 summarizes the incidence of adverse events reported with the Visian TICL Cohort, comparing them to the ISO-Defined Safety and Performance Endpoint (SPE) Rates. As documented below, the incidence of adverse events is lower than the ISO SPE Rates for all adverse events with the exception of surgical intervention and retinal detachment. As described previously, the five cases of surgical intervention all had improvement or no change in BCVA, or no significant loss in BCVA (1 line in 1 case) at the last follow-up visit. The single case of retinal detachment had UCVA of 20/16 at the 12-month visit, and was extremely satisfied with Visian TICL outcome. **The rates of surgical reintervention and retinal detachment were less than those in the previously approved Visian spherical ICL study cohort, (2.4% vs. 3.1%) and (0.5% vs. 0.6%) respectively**.

Secondary surgical interventions were reported in 6 eyes (2.9%) in the Visian TICL Study cohort. Five of these cases, or 2.4% of Visian TICL-related surgeries (which is comparable to the 3.1%), reported incidence in the Visian spherical ICL study. The secondary surgical interventions in the Visian TICL Study cohort are described in detail below (Section 5.5).

Table 18 — Adverse Events

Adverse Event	Cumulative		Persistent at 12 Months	
	TICL % (n)	ISO Rate %	TICL % (n)	ISO Rate %
Endophthalmitis	0% (0)	0.1%	0% (0)	—
Hyphema	0% (0)	2.2%	0% (0)	—
Hypopyon	0% (0)	0.3%	0% (0)	—
IOL Dislocation	0% (0)	0.1%	0% (0)	—
Cystoid Macular Edema	0% (0)	3.0%	0% (0)	0.5%
Pupillary Block	0% (0)	0.1%	0% (0)	—
Retinal Detachment[1]	0.5% (1)	0.3%	0% (0)	—
Surgical Reintervention	2.4% (5)	0.8%	0% (0)	—
Corneal Edema (after 1 week)	0% (0)	—	0% (0)	0.3%
Iritis (after 1 week)	0% (0)	—	0% (0)	0.3%
Raised IOP Requiring Intervention	0.5% (1)	—	0% (0)	0.4%

[1] Comparison should be made to literature for retinal detachment rates for high myopia. Retinal detachment rates increase with increasing myopia. The risk of retinal detachment within one year of implantation of this device is 0.5%. The ISO SPE Rate for retinal detachment is based on the general population following cataract surgery. Retinal detachment rate after cataract surgery in axial lengths ≥ 26.0mm (≥ −6.0D) is 2.4% (Williams and al). Risk of retinal detachment in high myopia alone (> −12.0D) without surgery has been estimated to be 40 times the risk of RD in emmetropia (Colin and et al). The eye with retinal detachment in this study had myopia of −12.0D and the average rate in the Visian TICL study was −9.4D. Rate of retinal detachment in the approved Visian ICL is 0.6% which is comparable to the 0.5% rate for this study.

5.5. Serious Adverse Events

The following serious Adverse Events were reported in the Visian TICL study, comprising five secondary surgeries (three of which resulted in eyes being discontinued from the study) and one retinal detachment.

The first secondary surgery (lens explanted, eye discontinued from study) was from a patient who complained of a line in his vision from the preoperative laser iridotomies. This symptom was noted one day prior to the date of surgery. Two months after the initial surgery, the patient decided to have the Visian TICL removed with no further surgical procedure performed. This removal was a response to the patient's discontent in vision quality due to the line in the vision caused by the YAG and had no relationship to the Visian TICL. The patient decided to have the Visian TICL removed in spite of being informed that his visual symptom may not improve.

The second secondary surgery (lens explanted, eye discontinued from study) was of a patient who decided to have the Visian TICL removed. The right eye was reported with an anterior subcapsular LOCS III score of 0.5 (lower than grade for trace) at 1 week

postoperative. No complications were reported at this visit. The patient was an optometrist who worked in the office of the surgeon, was completely asymptomatic from the anterior subcapsular opacity but was concerned about the possible future progression of the opacity and had the Visian TICL removed at 1 week postoperatively.

The third secondary surgery (lens explanted, eye discontinued from study) was due to excessive vaulting of the Visian TICL, attributable to implantation of too long of a lens, which was noted at one day postoperative. The eye also had an IOP spike at one day postoperatively, considered a pupillary block, and required an additional YAG iridotomy. This large vault to the TICL caused the pupil to enlarge, producing an anisocoria that was cosmetically unacceptable to the patient. The TICL was removed one month postoperatively. At one month after the removal, the BCVA was within one line of baseline (20/25), the IOP was 14mmHg, and no lens opacity or subsequent complications were reported.

The fourth secondary surgery (lens replacement) involved an eye that experienced excessive vault associated with irido-corneal touch at one day postoperative. This adverse reaction was attributed to the TICL being too long for the eye. One month after initial surgery the TICL was replaced with a shorter lens. Four months after TICL replacement the patient had an uncorrected visual acuity of 20/25, and 12 months from the original surgery, a BCVA of 20/20 (a one-line improvement) with no postoperative complications or lens opacities.

The fifth secondary surgery (lens repositioning) occurred when the Visian TICL was found to be misaligned and was repositioned three days after initial surgery. At 12 months postoperatively, the patient achieved an improvement of one line of BCVA to 20/16, a UCVA of 20/20 with no postoperative complications or lens opacities, and no residual refractive cylinder.

One retinal detachment (0.6%) was reported during the course of this clinical study, in a patient with very high myopia (−12.0 +3.25 × 82). This patient experienced a superior temporal retinal detachment not involving the macula, which was thought by the surgeon to be a chronic condition. Note that the risk of retinal detachment in high myopia alone (> −12.0D) without surgery has been estimated to be 40 times the risk of retinal detachment in emmetropia (Colin and et al). The detachment was treated with a laser retinopexy six months after initial TICL surgery. At the 12-month visit, this eye had a UCVA of 20/16 and a BCVA of 20/12.5. MRSE was within 0.50D and the patient reported being extremely satisfied with the TICL surgery outcome.

5.5.1. Global Adverse Events for Visian ICL/TICL

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5.6. Clinical Assessment of Pigment Deposits, Clinical Flare and Cell

Pigment deposits were observed at various time intervals but were not associated with any other inflammatory signs and did not affect BCVA. Change in lines of BCVA from preoperative to one year postoperatively was not significantly different between cases with pigment deposits and those without (0.92 line gain vs. 0.87 line gain respectively, p=0.65).

Routine clinical assessment of aqueous flare and cellular reaction was performed at every study visit across all investigative centers in the Visian TICL clinical investigation following standard clinical diagnostic techniques.

No flare or cellular reaction over 1+ was seen in any patient at 1 week or later postoperatively. Furthermore, 1+ flare/cellular reaction was reported in only 1 eye at 1 month (no eyes at 3, 6, 12 months after Visian TICL implantation). This case demonstrated no flare or cellular reaction at the 3 month and 6 month postoperative visits.

No fibrin in the anterior chamber was reported in any case. No patients required treatment with anti-inflammatory medication after the 1 month postoperative visit. The lack of significant long term inflammatory response following Visian ICL implantation was documented in the U.S. in the PMA trial of the spherical ICL. A paper summarizing the data from the PMA trial, as well as three studies reporting laser flare cell meter measurements also demonstrating no significant inflammatory response after the first postoperative week has been reported in the peer-reviewed literature (ICL in Treatment Myopia (ITM) Study Group Postoperative Inflammation after Implantation of the Implantable Contact Lens).

5.7. Patient Subjective Symptoms

A subjective patient questionnaire was administered to all subjects in the Visian TICL Study Cohort, preoperatively and after TICL implantation. Patients reported subjective assessments of ocular symptoms preoperatively and at the 3- and 12-month visits.

In summary, there was no marked increase in the incidence of subjective patient symptoms (glare, halos, double vision, impaired night vision and night driving difficulty) for the entire Visian TICL Study. Details of each of the subjective symptoms are shown below.

Glare was reported as “absent/mild” in 80.0% at 12 months compared to 86.2% prior to Visian TICL implantation. Preoperatively, 2.9% of eyes were reported with “marked/severe” glare compared to 5.4% at 12 months postoperative. See Table 20.

Table 20 — Glare

Severity	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Absent/Mild	181 (86.2%)	146 (83.0%)	148 (80.0%)
Moderate	23 (11.0%)	24 (13.6%)	27 (14.6%)
Marked/Severe	6 (2.9%)	6 (3.4%)	10 (5.4%)
Not Reported	0	15	9
Total	**210**	**191**	**194**

Halos were reported as "absent/mild" in 80% of eyes at 12 months compared to 86.7% prior to Visian TICL implantation. "Marked/severe" halos were reported by four eyes (1.9%) at baseline compared to 13 eyes (7.0%) at the 12-month follow-up visit. See Table 21.

Table 21 — Halos

Severity	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Absent/Mild	182 (86.7%)	137 (77.8%)	148 (80.0%)
Moderate	24 (11.4%)	30 (17.0%)	24 (13.0%)
Marked/Severe	4 (1.9%)	9 (5.1%)	13 (7.0%)
Not Reported	0	15	9
Total	**210**	**191**	**194**

Double vision was reported as "absent/mild" by 98.4% of eyes at 12 months, compared to 98.6% prior to Visian TICL implantation. See Table 22.

Table 22 — Double Vision

Severity	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Absent/Mild	207 (98.6%)	173 (98.3%)	182 (98.4%)
Moderate	3 (1.4%)	0 (0%)	3 (1.6%)
Marked/Severe	0 (0%)	3 (1.7%)	0 (0%)
Not Reported	0	15	9
Total	**210**	**191**	**194**

Impaired night vision was reported as "absent/mild" in 83.2% of eyes at the 12-month follow-up exam compared to 82.3% prior to Visian TICL implantation. "Marked/severe" difficulty was reported in eight eyes (3.8%) at baseline, and in six eyes (3.3%) at 12 months after Visian TICL surgery. See Table 23.

Table 23 — Night Vision Impairment

Severity	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Absent/Mild	172 (82.3%)	150 (85.2%)	153 (83.2%)
Moderate	29 (13.9%)	18 (10.2%)	25 (13.6%)
Marked/Severe	8 (3.8%)	8 (4.5%)	6 (3.3%)
Not Reported	1	15	10
Total	**210**	**191**	**194**

Night driving difficulty was reported as "absent/mild" in 82.0% of cases at the 12-month follow-up exam, compared to 82.7% prior to Visian TICL implantation. "Marked/severe" night driving difficulty was reported in four cases (1.9%) at baseline, and by nine cases (4.9%) at 12 months after Visian TICL surgery. See Table 24.

Table 24 — Night Driving Difficulty

Severity	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Absent/Mild	172 (82.7%)	144 (83.2%)	150 (82.0%)
Moderate	32 (15.4%)	20 (11.6%)	24 (13.1%)
Marked/Severe	4 (1.9%)	9 (5.2%)	9 (4.9%)
Not Reported patient does not drive	2	18	11
Total	**210**	**191**	**194**

5.8. Safety Summary

The U.S. FDA clinical trial data from the approved myopia study with spherical ICLs is the primary source of data supporting the safety of the Visian TICL. As highlighted in Table 25, safety outcomes reported during the Visian TICL Clinical Investigation provide additional support for the safety of the Visian TICL for the correction of moderate to high myopic astigmatism. As shown in Table 25, all primary safety outcomes with the Visian TICL were better or comparable to those previously reported with the FDA-approved Spherical Visian ICL.

Table 25 provides a summary of both the primary safety outcomes for the Visian TICL and the Spherical Visian ICL PMA Cohort (PMA P030016). Preservation of BCVA, the primary safety endpoint for refractive surgery, was excellent after implantation of the Visian TICL, exceeding the targets suggested by the FDA in both the Refractive Implants

and Refractive Lasers Guidance Documents; this supports the reported results with the spherical Visian ICL.

- The overall incidence of postoperative BCVA worse than 20/40 in the subset of eyes in the Visian TICL Study Cohort with preoperative best corrected vision of 20/20 or better was 0%, compared to the Protocol Target of < 1%; (also 0% with Spherical ICL).
- At six months or later after Visian TICL implantation, only 1.5% of eyes lost two or more lines of BCVA (1.0% lost 2 lines and 0.5% lost > 2 lines). This low loss after implantation of the Toric lens falls well below the Protocol Targets < 5% of eyes with a ≥ 2 Line Loss) and complements the earlier Spherical Visian ICL outcomes (1.1% lost 2 lines and 0.8% lost > 2 lines).

No eye showed an increase in refractive cylinder of > 2D 1 year after Visian TICL surgery (0.4% Spherical ICL). Five eyes (2.4%) underwent a secondary TICL related surgery in the Visian TICL Study Cohort. In the Spherical Visian ICL PMA Cohort, 3% of eyes underwent a secondary ICL surgery. As noted, there were no cataract extractions with Visian TICL implantations during the 1-year study duration.

Using the Lens Opacities Classification System (LOCS III) in the Visian TICL Cohort, there were six anterior subcapsular opacities ≥ trace degrees (2.9%), four of which were asymptomatic (2.7% with the Spherical Visian ICL). There were two clinically significant anterior subcapsular cataracts (1%); no nuclear cataracts with the Visian TICL were reported; as compared to 0.4% and 1% respectively with the Spherical Visian ICL.

One eye (0.5%) experienced a postoperative IOP of 25mmHg and/or an increase of >10mm Hg compared to baseline at the last visit with the Visian TICL (compared to 0.2% with the Spherical ICL).

The incidence of adverse events was minimal during the Visian TICL clinical study with no cases of endophthalmitis, no corneal ulcers, no ocular hypertension and no corneal haze/edema after the first week of follow-up. One case (0.5%) of retinal detachment was reported. These results compared favorably to the Spherical Visian ICL outcome, where adverse event incidence was as follows: no endophthalmitis or corneal ulcers, ocular hypertension (0.4%), and no corneal haze/edema after the first week of follow-up. There were three cases of retinal detachment with the spherical Visian ICL (0.6%).

In conclusion, safety outcomes for the Visian TICL are consistent with the approved parent Visian ICL

Table 25 — Summary of Safety Variables

Variable Change	TICL n=210	Spherical ICL n=526	Protocol Targets
BCVA worse than 20/40 at 1 to 12 months postoperative if 20/20 or better preoperative[1]	0 (0%)	0 (0%)	≤ 1%
Loss of 2 Lines BCVA 6 months or later postoperative	2 (1.0%)	6 (1.1%)	<5%
Loss of > 2 Lines BCVA 6 months or later postoperative	1 (0.5%)	4 (0.8%)	<5%
Increase > 2D Cylinder 12 months postoperative[2]	0 (0%)	2 (0.4%)	
ICL Repositioning	1 (0.5%)	4 (0.8%)	
ICL Replacement, then Removal	0 (0%)	1 (0.2%)	
ICL Replacement	1 (0.5%)	8 (1.5%)	
ICL Removal no IOL or ICL replacement	3 (1.4%)	0 (0%)	
ICL Removal/Cataract Extraction/IOL	0 (0%)	3 (0.6%)	
Total Any Secondary ICL Surgery	5 (2.4%)	16 (3.0%)	
LOCS Trace or More			
Anterior Subcapsular including clinically significant cataracts	6 (2.9%)	14 (2.7%)	
Clinically Significant Cataract[3]			
Anterior Subcapsular	2 (1.0%)	2 (0.4%)	
Nuclear	0 (0%)	5 (1.0%)	
IOP > 25mm Hg or IOP > 10mm Hg Increase from Preoperative[4] at last visit	1 (0.5%)	1 (0.2%)	
Endophthalmitis	0 (0%)	0 (0%)	
Corneal Ulcer	0 (0%)	0 (0%)	
Ocular Hypertension	0 (0%)	2 (0.4%)	
Corneal Melting	0 (0%)	0 (0%)	
Corneal Haze/Edema after 1 week postoperative	0 (0%)	0 (0%)	
Retinal Detachment	1 (0.5%)	3 (0.6%)	

[1] For Spherical Myopia column, time interval is from 1 to 36 months postoperative.

[2] For Spherical Myopia column, time interval is for 3 years postoperative.

[3] Any LOCS Anterior Subcapsular/Posterior score ≥ 1.0 at any postoperative visit with either increase in glare or ≥ 2 line loss BCVA or Nuclear ≥ 2.0 or symptomatic.

[4] Includes IOP from unscheduled visits 3 months or later postoperative.

6. EFFECTIVENESS

This section contains a summary of the data from the clinical study that support the effectiveness parameters listed below, which are also confirmed by extensive commercial experience from approximately 110,000 Visian TICL implantations in over 60 international markets:

- Improvement in UCVA;
- Decrease in refractive myopia and cylinder;
- Predictability – the attempted vs. achieved sphere and cylinder corrections;
- Stability;
- Subjective patient satisfaction; and
- Rotation of the Visian TICL.

6.1. Improvement in UCVA

Table 26 presents uncorrected visual acuity (UCVA) outcomes in the Visian TICL Study Cohort over time. While 100% of eyes in this cohort had a UCVA worse than 20/80 preoperatively (97.1% worse than 20/200), 95.3% had 20/40 or better UCVA at the 12 month follow-up visit. Uncorrected acuity of 20/20 or better was 81.9% at the twelve month follow-up visit. Furthermore, 12 months after implantation of the Visian TICL, 53.9% achieved UCVA of 20/16 or better; 20.7% 20/12.5 or better. All eyes (100%) were 20/200 or better at every postoperative visit.

Table 26 — Uncorrected Visual Acuity (All Eyes)

	Preop n (%)	1 M n (%)	3 M n (%)	6 M n (%)	12 M n (%)
20/12.5 or better	0 (0%)	34 (17.1%)	37 (19.4%)	41 (22.5%)	40 (20.7%)
20/16 or better	0 (0%)	106 (53.3%)	112 (58.6%)	119 (65.4%)	104 (53.9%)
20/20 or better	0 (0%)	156 (78.4%)	157 (82.2%)	154 (84.6%)	158 (81.9%)
20/25 or better	0 (0%)	181 (91.0%)	178 (93.2%)	171 (94.0%)	175 (90.7%)
20/32 or better	0 (0%)	187 (94.0%)	186 (97.4%)	176 (96.7%)	180 (93.3%)
20/40 or better	0 (0%)	191 (96.0%)	186 (97.4%)	178 (97.8%)	184 (95.3%)
20/80 or better	0 (0%)	197 (99.0%)	188 (98.4%)	182 (100%)	191 (99.0%)
20/200 or better	6 (2.9%)	199 (100%)	191 (100%)	182 (100%)	193 (100%)
Worse than 20/200	204 (97.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	0	1	0	0	1
Total	**210**	**200**	**191**	**182**	**194**

Comparison of postoperative UCVA to a patient's preoperative BCVA is considered the most challenging measure for assessing effectiveness of any refractive surgical procedure. In the TICL Study, the data concludes that 76.2% (147/193) of eyes had 12-month postoperative UCVA equal to or better than preoperative BCVA. Furthermore, 47% of eyes had 12-month postoperative UCVA better than preoperative BCVA, essentially seeing better without correction postoperatively than they did with correction preoperatively.

Table 27 provides a comparison of postoperative UCVA at 12 months to preoperative BCVA values.

Table 27 — Comparison of Postoperative UCVA at 12 Months to Preoperative BCVA[1]

Visual Acuity	Preoperative BCVA n (%)	12 Month UCVA n (%)
20/12.5 or better	7 (3.6%)	40 (20.7%)
20/16 or better	79 (40.9%)	104 (53.9%)
20/20 or better	159 (82.4%)	158 (81.9%)
20/25 or better	181 (93.8%)	175 (90.7%)
20/40 or better	193 (100%)	184 (95.3%)
20/80 or better	193 (100%)	191 (99.0%)
20/200 or better	193 (100%)	193 (100%)
Total	**193**	**193**

[1] Pairwise cohort of cases

Table 28 presents the UCVA over time in those cases with preoperative 20/20 or better BCVA. At the 12 month follow-up visit, 89.3% of these cases had UCVA of 20/20 or better and 96.9% of cases had UCVA of 20/25 or better. Furthermore, at the same time period, 63.5% of eyes were 20/16 or better UCVA; 25.2% of eyes were 20/12.5 or better with the Visian TICL. There were 173 eyes with BCVA of 20/20 or better preoperatively and, of these, 159 had 12 month follow-ups, and all of these 159 eyes had UCVA of 20/40 or better.

Table 28 — Uncorrected Visual Acuity for Eyes with Preoperative BCVA 20/20 or Better

	Preoperative (%)	1 M n (%)	3 M n (%)	6 M n (%)	12 M n (%)
20/12.5 or better	0 (0%)	32 (19.3%)	36 (22.4%)	41 (26.5%)	40 (25.2%)
20/16 or better	0 (0%)	103 (62.0%)	106 (65.8%)	117 (75.5%)	101 (63.5%)
20/20 or better	0 (0%)	139 (83.7%)	140 (87.0%)	140 (90.3%)	142 (89.3%)
20/25 or better	0 (0%)	158 (95.2%)	158 (98.1%)	152 (98.1%)	154 (96.9%)
20/40 or better	0 (0%)	164 (98.8%)	161 (100%)	155 (100%)	159 (100%)
20/200 or better	4 (2.3%)	166 (100%)	161 (100%)	155 (100%)	159 (100%)
Worse than 20/200	169 (97.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not Reported	0	0	0	0	0
Total	**173**	**166**	**161**	**155**	**159**

6.2. Decrease in Refractive Myopia and Cylinder

Table 29 highlights the manifest refraction spherical equivalent (MRSE) values at the preoperative visit compared to the 12 month visit for a pairwise cohort of eyes from the Visian TICL Cohort. The mean MRSE improved from −9.34D (± 2.63) preoperatively to 0.03D (± 0.46) at the 12 month follow-up visit. Preoperatively, no eyes had a MRSE within 2.00D of emmetropia rising to 98% of eyes within 1.00D at the 12 month visit. In this pairwise cohort of eyes, 100.0% of eyes had a preoperative MRSE of > −2.00D; 83% of eyes with a MRSE > −7.00D preoperatively. In contrast, at the 12 month follow-up exam, only 1 eye (0.5%) had > −2.00D of myopia.

Table 29 — Manifest Refraction Spherical Equivalent; Preoperative vs. 12 Months Postoperative[1]

Spherical Equivalent	Preoperative n (%)	12 Months n (%)
≥ +2.01D	0 (0%)	0 (0%)
+1.01 to +2.00D	0 (0%)	0 (0%)
+1.00 to +0.01D	0 (0%)	82 (42.3%)
0.00 to −1.00D	0 (0%)	108 (55.7%)
−1.01 to −2.00D	0 (0%)	3 (1.5%)
−2.01 to −3.00D	1 (0.5%)	1 (0.5%)
−3.01 to −4.00D	2 (1.0%)	0 (0%)
−4.01 to −5.00D	5 (2.6%)	0 (0%)
−5.01 to −6.00D	3 (1.5%)	0 (0%)
−6.01 to −7.00D	22 (11.3%)	0 (0%)
−7.01 to −10.00D	93 (47.9%)	0 (0%)
−10.01 to −15.00D	62 (32.0%)	0 (0%)
−15.01 to −20.00D	6 (3.1%)	0 (0%)
Mean	−9.34	0.03
SD	2.63	0.46
Range	−19.5 to −2.375	−2.25 to 1
Total	**194**	**194**

[1] This represents the pairwise cohort of cases

Table 30 presents the manifest refractive cylinder over time for eyes in the Visian TICL Study Cohort. Preoperatively, the manifest refraction cylinder ranged from 1.00D to

4.00D. The mean refractive cylinder at baseline for the entire Visian TICL Cohort was 1.95D (± 0.84D) improving to 0.45D (± 0.45D) six months after TICL surgery; 0.52D (± 0.48D) at twelve months postoperatively.

Postoperatively, 91.2% of eyes had ≤ 1.00D of refractive cylinder 12 months after TICL surgery while only 20.5% of eyes had ≤ 1.00D preoperatively. While no eyes had refractive cylinder less than 1.00D, 65.5% were within 0.50D, and 40.2% of eyes were within 0.25D at 12 month visit.

Approximately 99.5% of eyes had refractive cylinder within 2.00D at the 12 month visit, compared to only 64.4% pre-operatively.

Table 30 — Manifest Refraction Cylinder with Time

Cylinder	Preop n (%)	1 M n (%)	3 M n (%)	6 M n (%)	12 M n (%)
0.25 or less	0 (0%)	84 (42.4%)	77 (40.5%)	87 (48.1%)	78 (40.2%)
0.50 or less	0 (0%)	128 (64.6%)	123 (64.7%)	128 (70.7%)	127 (65.5%)
1.00 or less	43 (20.5%)	180 (90.9%)	174 (91.6%)	167 (92.3%)	177 (91.2%)
1.50 or less	90 (42.9%)	193 (97.5%)	184 (96.8%)	176 (97.2%)	187 (96.4%)
2.00 or less	134 (63.8%)	197 (99.5%)	186 (97.9%)	181 (100%)	193 (99.5%)
3.00 or less	185 (88.1%)	198 (100%)	190 (100%)	181 (100%)	194 (100%)
4.00 or less	210 (100%)	198 (100%)	190 (100%)	181 (100%)	194 (100%)
Mean Diopter	1.95	0.50	0.52	0.45	0.52
STD Diopter	0.84	0.49	0.49	0.45	0.48
Range Diopter	1.00 to 4.00	0.00 to 3.00	0.00 to 3.00	0.00 to 2.00	0.00 to 3.00
Not Reported	0	2	1	1	0
Total	**210**	**200**	**191**	**182**	**194**

The change in the magnitude of refractive cylinder from preoperative to the 12 month visit for the Visian TICL Study Cohort is summarized in Table 31. **A decrease of 0.75D or more in manifest refractive cylinder was observed in 83.0% of eyes and a decrease of 1.00D or more was observed in 72.2%**. A 2.00D or more decrease in cylinder was seen in 30.4% of eyes and a decrease of more than 2.00D was observed in 22.2% of eyes at the 12 month follow-up visit.

The preoperative refractive cylinder in the 194 cases seen preoperatively and at 12 months postoperatively was 1.95D while the 12 months postoperative refractive cylinder was 0.52D. Paired t-test demonstrates a highly significant ($p < 0.001$) 1.43D mean decrease in cylinder from preoperatively to 12 months postoperatively.

Based upon a simple comparison of preoperative and postoperative refractive cylinders, the Visian TICL markedly decreased astigmatism postoperatively.

Table 31 — Change in Magnitude of Refractive Cylinder

	12 M n (%)
Decrease > 2.00D	43 (22.2%)
Decrease ≥ 2.00D	59 (30.4%)
Decrease ≥ 1.75D	71 (36.6%)
Decrease ≥ 1.50D	89 (45.9%)
Decrease ≥ 1.25D	110 (56.7%)
Decrease ≥ 1.00D	140 (72.2%)
Decrease ≥ 0.75D	161 (83.0%)
± 0.50D	32 (16.5%)
Increase ≥ 0.75D	1 (0.5%)
Not Reported	0
Total	**194**

Table 32, reports percent reduction of absolute cylinder, which is defined as the difference between the postoperative magnitude of Manifest Refractive cylinder and preoperative magnitude of Manifest Refractive cylinder, divided by the difference between the "intended" magnitude of the postoperative Manifest Refractive cylinder and the preoperative Manifest Refractive cylinder given as a percentage. The data indicates that the cylinder value was reduced at 12 months postoperatively..

Considering all 194 cases seen, the mean percent reduction in absolute cylinder was 77.8%. In general, the percent reduction averaged less for the lower amounts of preoperative cylinder (75.1% for ≤ 1.00D, and 71.4% for > 1.00D to ≤ 2.00D), and more in the higher preoperative cylinder range (87.1% for > 2.00D to ≤ 3.00D and 87.6% for > 3.00D to ≤ 4.00D.

Table 32 — Reduction of Absolute Cylinder Spectacle Plane at the 12 month Visit

Preoperative Cylinder	n (%)	Percent Reduction of Absolute (Non-Vector) Cylinder		
		Mean	Range	[% CI]
All	194	77.8	−62.7 to 151.9	[73.9 to 81.6]
> 0.5D to ≤ 1.0D	39 (20.1%)	75.1	−26.4 to 125.2	[65.4 to 84.8]
> 1.0D to ≤ 2.0D	86 (44.3%)	71.4	−62.7 to 137.3	[64.9 to 77.9]
> 2.0D to ≤ 3.0D	45(23.2%)	87.1	44.8 to 151.9	[82.2 to 91.9]
> 3.0D to ≤ 4.0D	24 (12.4%)	87.6	29.0 to 125.6	[80.3 to 95]

6.2.1. Effectiveness Stratified by Visian TICL Cylinder Power in the Corneal Plane

Figure 6 presented below demonstrates the relationship between change in refractive cylinder, preoperative to 12 months postoperative (Y-axis) and cylinder power of the Visian TICL (X-axis). All points above 0 on the Y-axis represent a decrease in cylinder with the TICL. There was no degradation in the effectiveness of the TICL cylinder correction at the higher powers, and all cases demonstrated a decrease in refractive cylinder preoperative to postoperative with TICL cylinder powers in the corneal plane above approximately 1.25D. The best fit linear regression line is also presented in Figure 6.

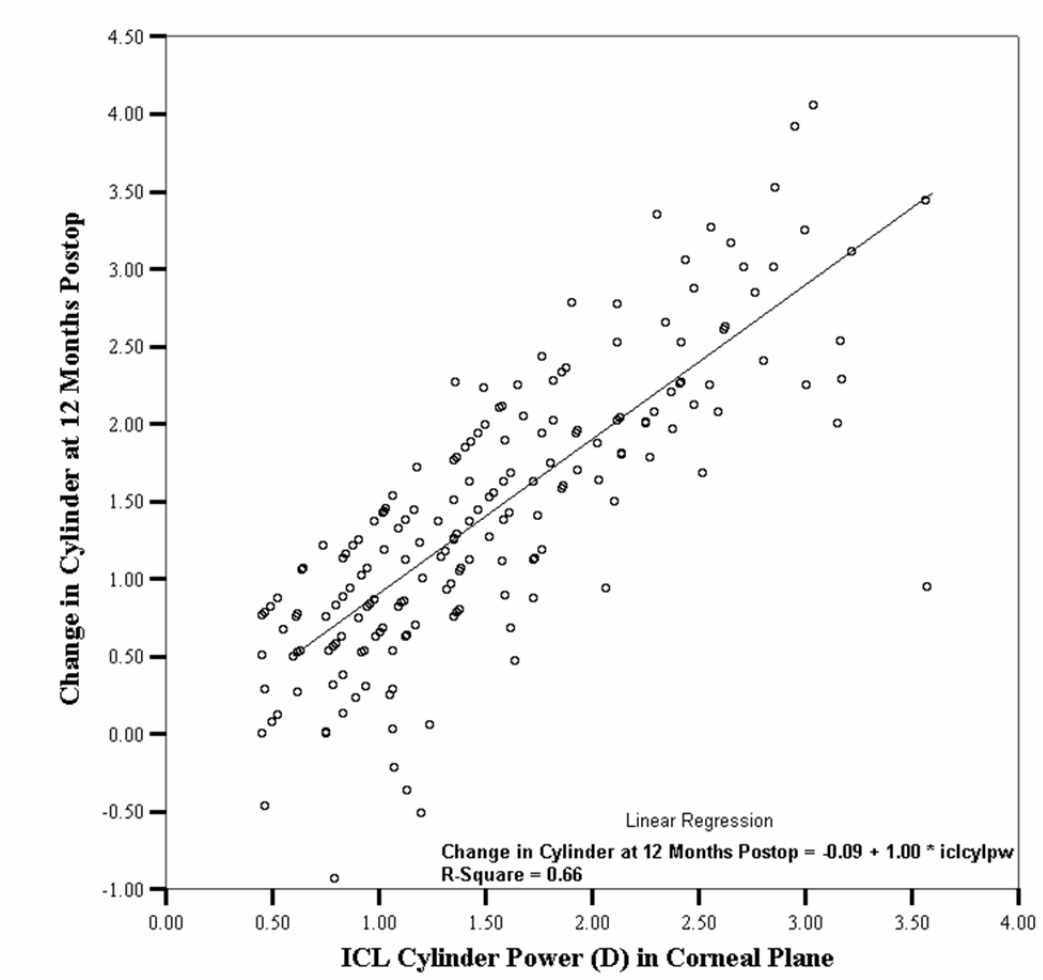

Figure 6 — Change in Refractive Cylinder (Preoperative vs. 12 Months) by TICL Power

6.3. Predictability – Attempted vs. Achieved Sphere and Cylinder Corrections

"Attempted Correction" was defined as the residual manifest refraction spherical equivalent (MRSE) predicted to be obtained given the preoperative refractive parameters for the patient and the power of the Visian TICL implanted. "Achieved Correction" was the actual MRSE obtained by the patient.

Excellent accuracy to target was achieved with the Visian TICL and maintained over the duration of the study follow-up. Predictability within 0.50D was 74.1% at 1 week after implantation of the Visian TICL with 74.7% of eyes accurately predicted within 0.50D at the 12 month follow-up visit. Similarly, within 1.00D at the 6-month and 12-month

follow-up visits after implantation of the Visian TICL was 96.1% and 96.4% of eyes, respectively See Table 33.

Table 33 — MRSE Attempted vs. Achieved Target by Preoperative MRSE (All Eyes)

Lens Group	Exam Interval	N	± 0.50D	± 1.00D	± 2.00D
Study Cohort	Week	201	74.1%	96.5%	100%
	1 Month	198	78.3%	95.5%	100%
	3 Months	190	74.7%	97.4%	100%
	6 Months	181	67.4%	96.1%	99.4%
	12 Months	194	74.7%	96.4%	100%
≤ −7D Sub-Cohort	12 Months	33	84.8%	100%	100%
> −7 to −10D Sub-Cohort	12 Months	93	81.7%	98.9%	100%
> −10D to −15D Sub-Cohort	12 Months	62	67.7%	95.2%	100%
> −15D Sub-Cohort	12 Months	6	50.0%	83.3%	100%

The predictability of the Visian TICL outcomes exceeds the Protocol Targets. **The protocol MRSE target values are 75% within ± 1.00D and 50% within ± 0.50D compared to the Visian TICL Study Cohort outcome of 96.4% within 1.00D at the 12-month postoperative visit and 74.7% within 0.50D**. Analysis of predictability stratified by preoperative MRSE shows that eyes in each dioptric sub-cohort meets the Protocol Target.

Table 34 demonstrates how accurately the desired postoperative cylinder was achieved at the spectacle plane at the 12 month visit. The mean preoperative cylinder was 1.95D, while the mean 12 month postoperative cylinder was 0.52D. The percent of cases with cylinder within 0.50D was 69.6%, and within 1.00D was 92.3%.

Table 34 — Accuracy of Cylinder to Target Spectacle Plane

Cylinder	Preop n=210	12 M n=194
Manifest Refraction Mean ± SD	1.95 ± 0.84	0.52 ± 0.48
Attempted Change Mean ± SD		1.77 ± 0.80
Achieved Change Mean ± SD		1.43 ± 0.89
% Achieved within ± 0.50D of Attempted [%CI]		135 (69.6%) [64.2 to 75]
% Achieved within ± 1.00D of Attempted [%CI]		179 (92.3%) [89.1 to 95.4]

6.4. Stability

Table 35 presents the stability of the manifest refraction spherical equivalent (MRSE) between pairs of sequential postoperative follow-up visits in all eyes in the Visian TICL Study Cohort.

Table 35 — Stability of Manifest Refraction: All Eyes with Consecutive Visits

Change in Spherical Equivalent Between	1 and 3 Months n (%)	3 and 6 Months n (%)	6 and 12 Months n (%)
0.25D or Less	136 (73.9%)	129 (75.0%)	139 (78.5%)
0.50D or Less	169 (91.8%)	159 (92.4%)	167 (94.4%)
1.00D or Less	184 (100%)	170 (98.8%)	176 (99.4%)
Mean Change	0.010	−0.009	0.081
SD	0.311	0.330	0.360
95% CI of the Mean	[−0.04 to 0.05]	[−0.06 to 0.04]	[0.03 to 0.13]
Mean Change/Month	0.005	−0.003	0.013

The manifest refraction was stable between each visit, with a maximum mean change of less than 0.09D between any sequential visits.

In Table 36, the absolute cylinder appears to be stable from the earliest reported interval. Between 98.3% and 98.8% of cases changed by 1.00D or less, and between 83.7% and 89.0% of cases changed by 0.500D or less at all reported intervals. The mean difference was between −0.03D and 0.04D at each reporting interval. The 95% confidence intervals

encompass 0 at all time periods and the mean change in cylinder per year was between −0.13D and 0.09D at all time periods.

Table 36 — Stability of Absolute Cylinder Corneal Plane

Magnitude of Change in Absolute Cylinder	1 and 3 Months		3 and 6 Months		6 and 12 Months	
	n/N (%)	[% CI]	n/N (%)	[% CI]	n/N (%)	[% CI]
≤ 1.0D	181/184 (98.4%)	[96.8 to 99.9]	170/172 (98.8%)	[97.5 to 100]	174/177 (98.3%)	[96.7 to 99.9]
≤ 0.5D	154/184 (83.7%)	[79.2 to 88.2]	153/172 (89.0%)	[85 to 92.9]	151/177 (85.3%)	[80.9 to 89.7]
Mean Difference (D)	0.00		−0.03		0.04	
SD (D)	0.34		0.30		0.31	
95% CI (D)	[−0.05 to 0.05]		[−0.08 to 0.01]		[0 to 0.09]	
Mean Change per year (D)	0.01		−0.13		0.09	

6.5. Subjective Patient Satisfaction

Within the standardized subjective patient questionnaire, there were three subjective assessments: Patient Satisfaction, Willingness to have the Surgery Again, and Quality of Vision. The results are described below.

Table 37 presents the patients' subjective satisfaction with Visian TICL surgery for the correction of moderate to high myopic astigmatism. The overwhelming majority of subjects implanted with the Visian TICL in the Study Cohort reported being "Very Satisfied" or "Extremely Satisfied" with the results of their Visian TICL surgery. After Visian TICL implantation, 94.9% were "Extremely" or "Very" satisfied at 3 months; with this percentage increasing to 97.9% at 12 months. Note that no patients reported being "Unsatisfied" with the outcomes of their Visian TICL surgery at any point in time.

Table 37 — Patient Satisfaction with Surgery

	3 Months n (%)	12 Months n (%)
Extremely Satisfied	127 (72.2%)	144 (78.3%)
Very Satisfied	40/ (22.7%)	36 (19.6%)
Fairly Satisfied	7 (4.0%)	4 (2.2%)
Moderately Satisfied	2 (1.1%)	0 (0%)
Unsatisfied	0 (0%)	0 (0%)
Not Reported	15	10
Total	**191**	**194**

Table 38 summarizes the study subject responses to the question regarding the willingness to undergo Visian TICL surgery again. At 12 months postoperative, 98.4% of patients reported they would be willing to undergo TICL surgery again, 1 patient (0.6%) did not know and 2 patients (1.1%) responded "no". However, both patients who responded negatively reported that they were very satisfied with their TICL surgery.

Table 38 — Patients Willing to have Visian TICL Surgery Again

	3 Months n (%)	12 Months n (%)
Yes	170 (96.6%)	181 (98.4%)
No	5 (2.8%)	2 (1.1%)
Undecided	1 (0.6%)	1 (0.5%)
Not Reported	15	10
Total	**191**	**194**

There was a marked improvement in quality of vision in the study. Patients were asked to rate their quality of vision as; "Very Poor, Poor, Good, Very Good, or Excellent", preoperatively and at 3 and 12 months. Postoperatively, none of the patients reported having "Very Poor" or "Poor" vision, as compared to 10.5% preoperatively. The percent of patients reporting "Very Good"/ "Excellent" quality of vision increased from 64.3% preoperatively to 94.6% at 12 months after implantation of the Visian TICL. Of the 22 eyes reporting "Poor" or "Very Poor" vision, 21 improved to "Very Good/Excellent", while the other one improved to "Good" (see Table 39).

Table 39 — Patient-Rated Subjective Quality of Vision

Quality of Vision	Preoperative n (%)	3 Months n (%)	12 Months n (%)
Very Good/Excellent	135 (64.3%)	154 (87.5%)	174 (94.6%)
Good	53 (25.2%)	22 (12.5%)	10 (5.4%)
Poor/Very Poor	22 (10.5%)	0 (0%)	0 (0%)
Not Reported	0	15	10
Total	**210**	**191**	**194**

6.5.1. Relationship between TICL Cylinder Power and Quality of Vision / Patient Satisfaction

To evaluate if there is a difference in Quality of Vision and Patient Satisfaction Ratings at 12 months postoperatively between the patients receiving high cylinder power TICL and

lower powers, an analysis was performed on the relationship between TICL cylinder power and the Subjective Patient Information. Table 40 and Table 41 divide TICL cylinder powers into groups with ≤ 2.00D and those with > 2.00D (as measured in the corneal plane) and compare Quality of Vision and Patient Satisfaction Ratings, respectively. Table 40 demonstrates that both high and low cylinder cases reported "Very Good/Excellent" quality of vision in 93.3% to 95% of cases, and no cases reported "Poor/Very Poor" quality of vision. Preoperatively 10.5% of the study cohort rated their Quality of Vision as Poor. There was no significant association between Quality of Vision and TICL cylinder power (p=0.7 with Fisher's Exact Test). Table 41 demonstrates that both high and low cylinder cases had between 95.6% and 98.5% of cases that were "Very or Extremely Satisfied" with surgery and none that were "Unsatisfied". There was no significant association between Patient Satisfaction Ratings and TICL cylinder power (p=0.28 with Wilcoxon Mann Whitney Test).

Table 40 — Patient Rating Quality of Vision at 12 Months Stratified by TICL Cylinder Power

TICL Cylinder Power (Corneal Plane) n/N (%)			
Cylinder Power	**Excellent /Very Good**	**Good**	**Poor/Very Poor**
≤ 2.0D	132/139 (95.0%)	7 /139 (5.0%)	0 /139 (0%)
>2.0 D to ≤2.5D	25/26 (96.2%)	1/26 (3.8%)	0/26 (0%)
>2.5 D to ≤3.0D	13/14 (92.9%)	1/14 (7.1%)	0/14 (0%)
> 3.0D	4/5 (80.0%)	1/5 (20.0%)	0/5 (0%)
Total	**174/184 (94.6%)**	**10/184 (5.4%)**	**0/184 (0%)**

Table 41 — Patient Satisfaction with Surgery at 12 Months Stratified by TICL Cylinder Power.

TICL Cylinder Power (Corneal Plane) n/N (%)					
Cylinder Power	**Extremely Satisfied**	**Very Satisfied**	**Fairly Satisfied**	**Moderately Satisfied**	**Unsatisfied**
≤ 2.0D	110/139 (79.1%)	27/139 (19.4%)	2/139 (1.4%)	0/139 (0%)	0/139 (0%)
>2.0 D to ≤2.5D	21/26 (80.8%)	5/26 (19.2%)	0/26 (0%)	0/26 (0%)	0/26 (0%)
>2.5 D to ≤3.0D	11/14 (78.6%)	2/14 (14.3%)	1/14 (7.1%)	0/14 (0%)	0/14 (0%)
> 3.0D	2/5 (40.0%)	2/5 (40.0%)	1/5 (20.0%)	0/5 (0%)	0/5 (0%)
Total	**144/184 (78.3%)**	**36/184 (19.6%)**	**4/184 (2.2%)**	**0/184 (0%)**	**0/184 (0%)**

The association between quality of vision and TICL cylinder power was assessed using the Fisher's Exact Test, and the association between patient satisfaction and TICL cylinder power was assessed using the Wilcoxon Mann Whitney Test. The data used for each test was aggregated into two groups, each side of a given cylinder: 2.00D, 2.50D, and 3.00D. See Table 42.

Table 42 — Association between Cylinder Power and Subjective Quality of Vision/ Patient Satisfaction

Cylinder Power	Quality of Vision Fisher's Exact Test	Patient Satisfaction Wilcoxon Mann Whitney Test
≤ 2.0D vs >2.0D	p=0.70	p=0.28
≤2.5 D vs >2.5D	p=0.28	p=0.10
≤ 3.0D vs >3.0D	p=0.24	p=0.02 *

* Statistically significant.

Results demonstrate excellent Quality of Vision and Patient Satisfaction in the high and low cylinder groups, and only in the small number of cases with > 3.00D of TICL cylinder power was there a statistically significant difference between high and low powers demonstrated. This difference is most likely due to the limited sample size (n= 5) above 3.00D.

6.6. Rotation of Visian TICL

The protocol requested investigators to examine the subject at the slit lamp to estimate the orientation of the long axis of the Visian TICL based upon the alignment markings. If the lens was oriented horizontally it would be recorded as at either 3:00 or 9:00 (clock hour position). A 30° clockwise rotation would be recorded as being at 4:00 or 10:00. A 15° counterclockwise rotation would be recorded as being at either 2:30 or 8:30.

Rotational stability was assessed based upon lens rotation between 2 consecutive visits. Outcomes of the analysis indicate that lenses rotating 5 degrees or less between 3 to 6 months (n = 136) and 6 to 12 months (n = 140) post operatively were 97.8% and 94.3%, respectively. In addition, as noted by the FDA, "you may retain the original data and analyses, and rely primarily upon the refractive data for information concerning axis position (if the direct axial measurement method was too gross to be very useful)," rotational stability of the TICL was also evaluated through the absolute difference in cylinder axis using manifest refraction outcomes. Table 43 summarizes accountability and rationale of the sub-population from the study that were assessed for rotational stability based on manifest refraction data, as described above.

Table 43 — Subject Accountability for Rotational Stability Analysis

Stratification	n
Total Cohort	210
Discontinued eyes	(3)
Lost to Follow up	(13)
Eyes seen at 12 month visit	194
Eyes missed at 6 month visit (but were seen at 12)	(16)
Eye that was seen at 6 months but did not have MR done	(1)
Eyes available to analyze changes in MR between 6 and 12 months	177
Eyes with less than or equal to 5° change in MR axis between 6 and 12 months	(108)
Eyes to be analyzed for instability between 6 and 12 months	69

In total there were 69 eyes where the change in manifest cylinder axis between the 6 month and 12 month visit was refracted at greater than 5°. The UCVA of these eyes was then used as a cross reference. Eyes with post-operative UCVA of 20/20 or better, and eyes with post-operative UCVA the same or better than preoperative BCVA, were assumed to be stable and excluded from the analysis.

Table 44 shows the change in manifest cylinder axis for the 10 eyes that did not meet either of the UVCA thresholds detailed above, that may have undergone some rotation in eye.

Table 44 — Change in Manifest Axis between 6- and 12-Month Visits

Change in Manifest Cylinder Axis	Manifest Cylinder at 12 month visit		
	< 1.0 Diopter	≥ 1.0 Diopter	Total
6° to 10°	0	1	1
11° to 15°	2	1	3
16° to 30°	2	1	3
> 30°	1	2	3
Total > 5°	**5**	**5**	**10**

However, four of the 5 eyes with <1.0D of manifest cylinder achieved an average reduction in absolute cylinder of 73% (range 50% to 91%), which is more indicative of measurement error of the manifest cylinder axis change rather than true rotation of the lens. This is because lens rotation in the order of 15° to 30° would lead to a significant decrease in the effective power of the lens in eye, which is inconsistent with the absolute

cylinder reductions observed. This analysis leads to the conclusion that lens rotation may have occurred in 6/177 of eyes, a rate of less than 4%.

6.7. Effectiveness Summary

As illustrated in Table 45, the effectiveness outcomes reported during the Visian TICL Clinical Investigation support the overall effectiveness of Visian TICL implantation for the correction of moderate to high myopic astigmatism. The data shows that the Visian TICL exceeds the targets in the protocol and also exceeds the results achieved in the clinical study for the approved Visian ICL.

Table 45 — Summary of Effectiveness Variables

	Visian TICL		Spherical ICL 12 Months Postoperative	Protocol Targets
	6 Months Postoperative	12 Months Postoperative		
UCVA				
20/20 or better	154/182 (84.6%)	158/193 (81.9%)	50.4%[1]	
20/40 or better	178/182 (97.8%)	184/193 (95.3%)	91%[1]	
UCVA (if preoperative BCVA 20/20 or better)				
20/20 or better	140/155 (90.3%)	142/159 (89.3%)	60.7%[1]	
20/40 or better	155/155 (100%)	159/159 (100%)	93.7%[1]	85%
Predictability; Attempted vs. Achieved				
± 0.50D	126/181 (69.6%)	149/194 (76.8%)	67.5%	50%
± 1.00D	175/181 (96.7%)	189/194 (97.4%)	88.2%	75%
± 2.00D	180/181 (99.4%)	194/194 (100%)	98.1%	
Patient Satisfaction[2]				
Unsatisfied	0/176 (0%)	0/184 (0%)	0.6%	
Very/Extremely Satisfied	167/176 (94.9%)	180/184 (97.8%)	92.1%	

[1] Excludes patients with greater than 15D of myopia which were under corrected.

[2] Except for Patient Satisfaction, which is reported from 3 months postoperative (no reference)

Uncorrected visual acuity was excellent after implantation of the Visian TICL, exceeding the targetsin the protocol. UCVA of 20/40 or better in eyes with a preoperative BCVA of 20/20 or better was achieved in 100.0% of eyes at 12 months after Visian TICL implantation compared to the Protocol Target of 85% for all eyes. UCVA 20/20 or better for the same study subset in the total Visian TICL Study Cohort was 89.3% at 12 months after TICL implantation. Taking the entire Visian TICL population regardless of

preoperative BCVA, 81.9% saw 20/20 or better and 95.3% saw 20/40 or better uncorrected at 12 months postoperatively.

Predictability outcomes for the Visian TICL Study Cohort were also better than the Protocol Targets. The proportion of eyes falling within 1.00D of the attempted correction was 97.4% at 12 months in the Visian TICL Study Cohort (Protocol Target; 75% all eyes). The percentage of eyes within 0.50D in the Visian TICL Study Cohort was 76.8% at 12 months (Protocol Target; 50% all eyes).

Subjective patient satisfaction with the Visian TICL surgery was high with 94.9% of patients "Very/Extremely Satisfied" at 3 months (0% unsatisfied); 97.8% at 12 months (0% unsatisfied).

6.7.1. Comparison of the Visian TICL and the Visian ICL Effectiveness Outcomes

As highlighted in Table 45, the efficacy clinical outcomes for the Visian TICL (toric) were better than the approved Visian ICL for all of the key effectiveness parameters.

The proportion of eyes with 20/20 or better UCVA was 81.9% (Visian TICL cohort) compared to 50.4% with the Visian ICL cohort. Similarly, the proportion of eyes with 20/40 or better UCVA at 12 months postoperatively was 95.3% (Visian TICL cohort) compared to 91.0% (Visian ICL cohort).

When evaluating uncorrected visual acuity in the subset of eyes with a preoperative BCVA of 20/20 or better, the Visian TICL exceeded the previously approved Visian ICL. At 12 months, 89.3% of eyes in this subset of toric cases achieved 20/20 or better UCVA; compared to 60.7% in the spherical myopia subset. UCVA of 20/40 or better 12 months after ICL surgery was 100.0% in the Visian TICL subset in contrast to 93.7% in the Visian ICL subset.

Predictability to target refraction was better with the Visian TICL with 76.8% (compared to 67.5%with the Visian ICL) within 0.50D, 97.4% with the Visian TICL (compared to 88.2% with Visian ICL) within 1.00D and 100.0% in the Visian TICL cohort (compared to 98.1% in the Visian ICL cohort) within 2.00D at 12 months postoperatively.

Patient satisfaction was extremely high in both Cohorts with 12 month results of 97.8% "Very/Extremely Satisfied" in the Visian TICL Cohort and 92.1% in the Visian ICL Cohort.

6.8. Risk-Benefit Assessment

Many of the patients implanted with the approved Visian ICL have preexisting astigmatism of 1.00D or greater. To correct their residual astigmatism, these patients would have needed spectacles, contact lenses, or an additional surgical procedure, such as

limbal relaxing incisions or astigmatic ablation with an excimer laser (LASIK/PRK). The Visian TICL was developed to provide a safe and effective option for the treatment of patients with myopia and astigmatism. As demonstrated in this study, the Visian TICL meets all endpoints.

6.8.1. Risks of the Visian TICL

The risks associated with the Visian TICL are comparable to the implantation of an intraocular lens.

Regarding preservation of BCVA, 96.9% of eyes were 20/20 or better at 12 months. For the eyes that achieved 20/20 BCVA pre-operatively, 100.0% were 20/20 or better at 12 months which exceeds the Protocol Target of 99% at 20/40 at 12 months.

The occurrence of cumulative adverse events in the Visian TICL study met the ISO SPE Rate with the exception of surgical re-intervention and retinal detachment. There was a single case of retinal detachment in the study, which occurred in a highly myopic eye (-12.00D). Risk of retinal detachment in high myopia (> −12.00D) without surgery has been estimated to be 40 times the risk of retinal detachment in emmetropia (Colin and et al). The rate of retinal detachment in the approved Visian ICL, which included a study with a highly myopic patient cohort, was 0.6% ─ comparable to the 0.5% rate for the Visian TICL study.

There were five Visian TICL surgical re-interventions, of which only one was directly related to the astigmatic component of the lens, which involved lens repositioning/realignment. Two eyes required the correction of excessive lens vault. The remaining two eyes required surgical re-intervention due to the surgical procedure, not the lens; one eye involved visual disturbance caused by the peripheral iridotomies, and the other eye involved a minor anterior capsular opacification (below trace) caused by surgical trauma.

With the exception of the above, there were no adverse events during the Visian TICL clinical study: No cases of endophthalmitis, no corneal ulcers, no ocular hypertension and no corneal haze/edema after the first week of follow-up through the end of the study.

The low level of reported adverse events in the study is supported by the low rates of reported adverse events contained in the global adverse events database for the Visian ICL and Visian TICL.

Based upon global experience, the majority of cases where the Visian TICL is implanted, it is the sole procedure performed to address the refractive error. Currently, in the U.S., moderate to highly myopic patients will undergo the primary surgery to implant the Visian ICL (which has the same risk profile as the Visian TICL), then also undergo an additional procedure such as LASIK, PRK or LRI to correct astigmatism. This two-step,

two-procedure approach exposes patients to all the risks associated with an additional procedure, which are eliminated by the Visian TICL.

The safety of the Visian TICL was demonstrated by preservation of BCVA and the overall incidences of complications and adverse events reported for the Visian TICL. It is noteworthy that all the critical safety endpoints were met and deviations were readily explained.

6.8.2. Benefits of the Visian TICL

The Visian TICL provides the benefits of the Visian ICL for the correction of moderate to severe myopia, with the addition of astigmatic correction. In the study, the Visian TICL demonstrated significant improvement in UCVA across a wide range of spherical and cylindrical correction.

Comparison of postoperative UCVA to a patient's preoperative BCVA is considered the most challenging measure for assessing the effectiveness of any refractive surgical procedure. In the Visian TICL Study, 76.2% (147/193) of eyes had 12-month postoperative UCVA equal to or better than preoperative BCVA.

The mean MRSE improved from −9.34D (± 2.63) preoperatively to 0.03D (± 0.46) at the 12 month follow-up visit. Preoperative manifest refraction cylinder ranged from 1.00D to 4.00D. The mean refractive cylinder at baseline for the entire Visian TICL Cohort was 1.95D (± 0.84D) improving to 0.52D (± 0.48D) at 12 months postoperatively.

Accuracy of cylinder correction to target was consistent throughout the entire study period. The mean preoperative cylinder was 1.95D. At 12 months, 40.2% of eyes had residual cylinder of 0.25D or less, 65.5% of eyes had residual cylinder of 0.50D or less, and 91.2% of eyes showed residual cylinder of 1.00D or less. The mean reduction in absolute cylinder was 77.8%, ranging from 75.1% for ≤ 1.00D of preoperative cylinder to 87.6% for > 3.00D to ≤ 4.00D of preoperative cylinder. This data confirms the effectiveness of the Visian TICL across the cylinder range studied.

In terms of subjective patient satisfaction, at 12 months 97.8% of subjects reported "extremely" or "very satisfied" with the Visian TICL, 2.2% reported they were "fairly satisfied" and none of the subjects report they were "dissatisfied." Patients reported a marked improvement in quality of vision, with 94.6% of patients reporting "Very Good"/"Excellent" quality of vision at 12 months after implantation of the Visian TICL, as compared with 64.3% preoperatively. Of the 22 (10.5%) eyes reporting "Poor" or "Very Poor" preoperative quality of vision, 21 improved to "Very Good/Excellent" and the other to "Good".

6.8.3. Risk-Benefit Summary

The results from the study demonstrate that the Visian TICL is a safe and effective option to treat patients with moderate to high myopia with astigmatism. The visual acuity of patients with the Visian TICL met all established standards and surpassed patients' subjective needs. Currently, many patients with moderate to high myopic astigmatism are being corrected using more than one surgical procedure. Accordingly, the Visian TICL will reduce the risk to which these patients are exposed by eliminating the need and associated risks of a secondary procedure.

Beyond the improvement in vision offered by the Visian TICL, and the reduction in the number of procedures for patients with moderate to high myopia with astigmatism, there is another key benefit offered by this refractive technology. Specifically, implanting the Visian TICL adds to the patient's optical system rather than irreversibly removing eye tissue with an excimer laser. This provides a surgeon the option to remove the Visian TICL if the patient is not satisfied with their outcome, rather than the patient having to tolerate the dissatisfaction in cases where permanent reshaping of the cornea (such as with LASIK or PRK) fails to deliver the patient's desired results. This benefit is also important in later life when a patient needs cataract surgery. For an eye where the cornea has been permanently reshaped with a laser, calculation of the correct IOL power becomes more difficult and post-operative outcomes can be less predictable; with the Visian TICL, there is no such issue. Furthermore, the presence of the lens in the eye does not impact the pre-operative biometry measurement used to calculate IOL power. For patients with moderate to high myopia with astigmatism, the Visian TICL offers an important safe and effective alternative.

Therefore, the benefits clearly outweigh the risks for the Visian TICL for the treatment of moderate to high myopia with astigmatism. This conclusion is supported by both the results from this clinical study and from the extensive clinical results for the Visian TICL from around the world where surgeons and patients have embraced this alternative technology and procedure. The adoption of the technology has increased year after year since it was launched in international markets in 2003. Since then, approximately 110,000 Visian TICL lenses have been implanted, and approximately 25,000 will be implanted in 2013.

6.9. Overall Conclusions

The data and information provided in PMA P030016-S001 supports the safety and effectiveness of the Visian Toric ICL. This builds upon the larger body of safety data from the parent Visian ICL presented in PMA P03316 and is supported by the worldwide clinical experience with over 400,000 Visian TICLs and Visian ICLs implanted.

The Visian TICL is a much needed line extension to the approved Visian ICL and will offer a relatively low risk option to treat eyes within the proposed label range. The data supports the safe and effective use of the Visian TICL in the proposed patient population.

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