1 STATISTICAL ANALYSIS PLAN / SIGNATURE PAGE

Protocol Number: 884

Protocol Title:

A Study to Investigate the Safety and Effectiveness of the Technolas® TENEO 317 Model 2 Excimer Laser for Laser-Assisted In Situ Keratomileusis (LASIK) Surgery to Treat Myopia or Myopic Astigmatism

Study Phase: Pivotal IDE Clinical Trial

Sponsor:

Bausch & Lomb Incorporated

[redacted]

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[redacted]

Approval:

[redacted]

1.1 SAP Version History / Summary of Changes

Version/Date	Summary of Changes

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2.1 Table of Tables

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Terms or Abbreviations	Definitions
ADaM	Analysis Data Model
AE	Adverse Event
ANSI	American National Standards Institute
ATC	Anatomical Therapeutic Chemical
BSCVA	Best Spectacle Corrected Visual Acuity
COVID-19	Coronavirus Disease 2019
cpd	Cycles per Degree
CR	Correction Ratio
CRF	Case Report Form
D	Diopter
ECD	Endothelial Cell Density
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRC	Intended Refractive Correction
LASIK	Laser-Assisted In Situ Keratomileusis
logMAR	Logarithm of the Minimum Angle of Resolution
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest Refraction Spherical Equivalent
OSDI	Ocular Surface Disease Index
PMA	Premarket Approval
POQ	Post-Operative Questionnaire
PROWL	Patient Reported Outcome with LASIK
PRQ	Pre-Operative Questionnaire
PT	Preferred Term
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Spherical Equivalent
SIRC	Surgically Induced Refractive Correction
SOC	System Organ Class
SPK	Superficial Punctate Keratopathy
SW	Software
UADE	Unanticipated Adverse Device Effect
UCNVA	Uncorrected Near Visual Acuity
UCDVA	Uncorrected Distance Visual Acuity

WHODrug	World Health Organization Drug Dictionary

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for clinical study Bausch & Lomb 884 conducted according to TENEO 317 Clinical Investigation Plan, Version 8.0, dated 19 November 2020.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E3 Guideline (July 1996), entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed and the subject characteristics, device effectiveness, and safety assessments that will be evaluated.

This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they will be completed and will be identified in an amended SAP (approved prior to database lock) or in the clinical study report.

Device Description

The Technolas Teneo 317 Model 2 (ver. 1.28 US software [SW]) excimer laser is a scanning excimer laser that operates at 193 nm ultraviolet wavelength to photoablate corneal tissue and employs a proprietary aspheric ablation profile rather than a conventional “Munnerlyn” ablation profile. By scanning a small diameter beam (1 mm in diameter) in a random raster pattern, the Teneo 317 Model 2 (ver. 1.28 US SW) excimer laser offers the following advantageous features:

- Flexible treatment patterns for the treatment of myopia,
- Wide ablation zones (up to 7 mm), and
- A smooth ablation-surface.

5 STUDY OBJECTIVES

The primary objective of this clinical investigation is to collect safety and effectiveness data for the Technolas Teneo 317 Model 2 excimer laser for Laser-Assisted In Situ Keratomileusis (LASIK) correction of myopia and myopic astigmatism. It is intended that the results of the study will be submitted to the U.S. Food and Drug Administration (FDA) in a 180-day premarket approval (PMA) application supplement.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design

The design of this clinical study is a prospective, open-label, multicenter, non-randomized clinical investigation, where the effects of LASIK in correcting myopia and myopic astigmatism are evaluated by comparing postoperative refraction and visual acuity to performance standards. The study treatment range (indication for use) includes up to manifest refraction spherical equivalent (MRSE) of -11.50 diopters (D).

The study will involve an evaluation of approximately 334 treated eyes at up to 12 investigational sites, with a final sample size of at least 300 study eyes evaluable at the final visit. Every effort will be made to enroll approximately the same number of eyes at each investigational site. The additional 34 study eyes will allow for losses up to 10% due to early subject discontinuation. Both eyes of a subject may be enrolled. Subjects will be permitted to have both eyes enrolled so long as both eyes meet all inclusion/exclusion requirements. Analyses will include all enrolled eyes treated with the TENEO 317 laser. Enrollment will be limited to subject eyes with sphere of -1.0 D up to -10.00 D, cylinder between 0.0 D and -3.0 D, and with a spherical equivalent (SE) between -1.0 D and -11.50 D. Enrolled subjects can possibly attend up to 8 scheduled study visits. It is planned to enroll and treat approximately 334 subject eyes, with an expectation that approximately 300 study eyes will complete post-surgical follow-up for 9 months. All subjects, regardless of the time of individually achieving refractive stability, will be followed up until the last study visit (Visit 8) which is Month 9 postoperatively.

For completed subjects, it is planned to have ≥ 20 eyes per each dioptric bin (see **Table 1**) of spherical correction to be studied and ≥ 30 eyes per dioptric bin of cylinder correction

to be studied. Of the eyes in the -0.25 to -1.0 D astigmatism range, at least 30 eyes are planned to be in each of the -0.25 to -0.5 D and the -0.5 to -1.0 D astigmatism ranges (see **Table 1**, Bin Table).

A 180-Day PMA supplement application will be submitted to the U.S. FDA when the enrolled study cohort has completed approximately 9 months of safety and effectiveness assessments post-surgery.

Table 1. LASIK Preoperative 'Dioptric Bin' Enrollment Plan

Refractive Error Stratified by Manifest Sphere and Cylinder						
		Cylinder (in minus notation)				
	0 Cylinder (Sphere Only)	−0.25 to − 0.5 D	−0.51 to −1 D	−1.01 to −2 D	−2.01 to −3 D	Total
Sphere (in minus notation)	n	n	n	n	n	n
−1 to −2 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−2.01 to −3 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−3.01 to −4 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−4.01 to −5 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−5.01 to −6 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−6.01 to −7 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−7.01 to −8 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−8.01 to −9 D	> 0	> 0	> 0	> 0	> 0	≥ 20
−9.01 to −10 D	> 0	> 0	> 0	> 0	> 0	≥ 20
Total	≥30	≥ 30	≥ 30	≥ 30	≥ 30	≥ 300

6.1.1 Fellow Eye Treatments

Because unilateral enrollment would result in subjects with a significant degree of anisometropia, and the safety and effectiveness of the TENEO 317 Model 2 excimer laser (ver. 1.28 US SW) specific to the treatment of myopia or myopic astigmatism are supported by retrospective data, bilateral LASIK treatments will be permitted in this study. Both eyes may be enrolled for effectiveness and safety assessments if the subject is fully informed that the surgical risks apply equally to each eye. If an intraoperative complication or adverse

event (AE) occurs in the first eye, treatment must be abandoned in the second eye. Each eye treated according to this protocol for an enrolled subject will be reported separately and included in the data analysis.

6.1.2 Enhancement and Retreatment Procedures

If the treated eye remains under-corrected and/or corneal haze or vision regression decreases to an uncorrected distance visual acuity (UCDVA) of 20/30 or worse, then an enhancement or retreatment may be performed. No enhancement or retreatment may be performed before a subject exits the study. Therefore, no data analysis related to enhancement or retreatment is planned.

6.1.3 Scheduled Visits

The schedule of visits and parameters is presented in **Table 2** below. All study tasks must be performed by qualified study site personnel as indicated on the delegation of authority log under the supervision of the Principal Investigator.

Further detail for scheduled visit procedures can be found in the study protocol.

Table 2. Schedule of Visits and Parameters

Test	Visit 1 Pre-Op (Day-60 to Day -1)	Visit 2 Operative Visit (Day 0)	Visit 3 Day 1	Visit 4 Week 1 (Day 5-9)	Visit 5 Month 1 (Week 3-5)	Visit 6 Month 3 (Week 10-14)	Visit 7 Month 6 (Week 21-26)	Visit 8 Month 9 (Week 35-43)
Informed Consent/HIPAA	X							
Eligibility	X	X						
PROWL Questionnaire	X					X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Complications		X	X	X	X	X	X	X
Subject Demographics	X							
Medical/Ocular History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Schirmer's Test	X						X	
LASIK Surgery, Intraoperative Events		X						
Manifest Refraction	X			X	X	X	X	X
Keratometry	X							
Endothelial Cell Density (ECD)	X						X	
Corneal Topography	X				X	X	X	X
Pupil Size	X					X	X	X
UCNVA	X		X	X	X	X	X	X
UCDVA	X		X	X	X	X	X	X
Distance BSCVA	X			X	X	X	X	X
Contrast Sensitivity	X						X	
Slit Lamp Examination	X		X	X	X	X	X	X
Pachymetry	X							
Cycloplegic Refraction	X							
Intraocular Pressure	X				X	X	X	X
Dilated Fundoscopic Examination	X					X	X	X

6.2 Selection of Study Population

The subject must satisfy all eligibility criteria prior to enrollment. The subject is considered enrolled in the study at the time they sign the informed consent form, with the study eye selected by the Investigator at the first study visit (Preoperative). It is understood that the number of subject eyes enrolled at the first study visit may be slightly more or less than the target number of 334 treated eyes.

Subjects failing to meet eligibility criteria prior to scheduling of surgery are considered screen failures.

6.2.1 Inclusion Criteria

1. Are 22 years of age or older.
2. Have read, understood, and signed an informed consent form (ICF).
3. Have demonstrated stable refraction (i.e., a change of ≤ 0.5 D in sphere and cylinder) for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history.
4. Have myopic refractive error with or without astigmatism; sphere between -1.0 D and -10.00 D, cylinder between 0.0 D and -3.0 D; with a manifest refraction spherical equivalent (MRSE) between -1.0 D and -11.50 D.
5. Have UCDVA of 20/40 or worse.
6. Have manifest best spectacle corrected distance visual acuity (BSCVA) of 20/25 (logarithm of the minimum angle of resolution [logMAR] 0.1) or better in an operative eye.
7. Have less than or equal to 0.50 D SE difference between cycloplegic and manifest refractions at Visit 1 (Preoperative).
8. Have normal corneal topography as determined by the Investigator.
9. Have discontinued use of contact lenses for at least 2 weeks (for hard or toric lenses) or 3 days (for soft contact lenses) prior to the preoperative examination, and through the day of surgery.
10. All contact lens wearers must demonstrate a stable refraction (within ± 0.5 D), as determined by MRSE, on two consecutive examinations at least 1 week apart, in an eye to be treated and the axis of cylinder should not differ by more than 15 degrees.
11. Have the ability to lie flat without difficulty.
12. Are willing and able to comply with the schedule for all post-surgery follow-up visits.

6.2.2 Exclusion Criteria

1. Subjects for whom the combination of their baseline corneal thickness and the planned operative parameters for the LASIK procedure would result in treatment depth less than 250 microns from corneal endothelium.
2. Eyes for which the baseline manifest subjective refraction exhibits a difference greater than 0.50 D in sphere power, or a difference greater than 0.50 D in cylinder power, or a difference in cylinder axis of more than 15 degrees compared to the baseline cycloplegic subjective refraction. For manifest cylinder of less than 0.50 D, the difference in cylinder axis will not be taken into consideration.
3. Subjects for whom the preoperative assessment of the cornea indicates that one or both eyes are not suitable candidates for treatment based upon the Investigator's medical judgment.
4. Have evidence of retinal vascular disease.
5. Have a history of or have active corneal disease or infection (e.g., recurrent corneal erosion syndrome, herpes simplex or herpes zoster keratitis, etc.) in an eye.
6. Have a known sensitivity to any study medication.
7. Have central corneal scars affecting visual acuity or unstable keratometry with irregular mires in an eye considered for eligibility.
8. Have keratoconus, subclinical or forme fruste keratoconus, corneal dystrophy, or other corneal irregularity (e.g., irregular astigmatism).
9. Have visually significant or progressive cataract in an eye considered for eligibility.
10. Had previous intraocular or corneal surgery in an eye considered for eligibility that might confound the outcome of the study or increase the risk to the subject.
11. Use chronic medications by any administration route that may increase risk to the subject or may confound the outcome of the study, including those known to affect wound healing (e.g., corticosteroids, antimetabolites, etc.).
12. Are known to have acute or chronic disease or illness (e.g., dry eye, cataract, glaucoma, immuno-compromised, rheumatoid arthritis, clinically significant atopic disease, acne rosacea, etc.) that would increase operative risk or may confound the results of the study.
13. Are taking medications contraindicated for LASIK such as isotretinoin (Accutane) or amiodarone hydrochloride (Cordarone).
14. Are known to be pregnant, lactating, or who plan to become pregnant during the course of the study.
15. Have known sensitivity to medications used for standard LASIK.

16. Have the presence of systemic disease likely to affect wound healing, e.g., autoimmune disease, systemic connective tissue disease, diabetes, or severe atopic disease.
17. Are participating in any other ophthalmic clinical trial within 30 days of screening or during this clinical trial.
18. Have an ocular muscle disorder including a strabismus or nystagmus, or other disorder affecting fixation.
19. Have a history of or evidence of glaucoma or are a glaucoma suspect.
20. Have eyes with mesopic pupil size > 7.0 mm.
21. Have a Schirmer's preoperative test without anesthesia < 4 mm/5 minutes.

6.3 TENEO 317 Model 2 Excimer LASIK Laser Device (Treatment Device)

Eligible subjects will undergo a LASIK surgical procedure with the TENEO 317 Model 2 (ver. 1.28 US SW) excimer laser device on one or both eyes.

6.4 Effectiveness and Safety Variables

The following endpoints will be evaluated.

6.4.1 Effectiveness Variables

Data for the following primary effectiveness endpoints will be evaluated statistically at the achievement time for refractive stability. Since the time of achievement for refractive stability cannot be predicted *a priori*, the effectiveness endpoints will be evaluated at 1-month, at 3 months, and at 6 months. In the absence of refractive stability occurring by 6 months post-surgery, the primary effectiveness endpoints will also be evaluated at 9 months post-surgery.

6.4.1.1 Primary Effectiveness Endpoints

The primary effectiveness endpoints are:

- The percentage of eyes that achieve predictability of MRSE within ± 0.50 D;
- The percentage of eyes that achieve predictability of MRSE within ± 1.00 D; and
- The percentage of eyes targeted for emmetropia that achieve a UCDVA of 20/40 or better.

6.4.1.2 Secondary Effectiveness Endpoints

There are no secondary effectiveness endpoints.

6.5 Statistical Methods

6.5.1 Disposition of Subjects

Eye accountability will be presented by postoperative visit separately for all treated eyes, eyes treated for spherical myopia, and eyes treated for astigmatic myopia. The numbers and percentages of subjects who were available for analysis, discontinued from the study, ongoing, lost to follow-up, or missed the visit will be displayed. Percent accountability, defined as eyes available for analysis divided by (enrolled minus discontinued minus active eyes) will also be presented by visit.

The reasons for premature study discontinuation will not be summarized but will be listed. In addition, subject data listings will be provided that include exclusions from study populations and any inclusion and exclusion criteria violations.

6.5.2 Protocol Deviations

Protocol deviations will not be summarized but will be presented in a data listing.

As required under §21 CFR 56.108(a)(3) & (4), an Investigator should notify the Sponsor and reviewing Institutional Review Board (IRB) of any deviation from the investigational plan intended to protect the life or physical well-being of a subject in an emergency. The date of and reason for protocol deviations will be documented in all cases. Significant or major protocol deviations affecting the safety, rights, and welfare of the subject or the integrity of the study must be reported by the Investigator to the IRB immediately. Reporting of all other protocol deviations must adhere to the requirements of the governing IRB.

Protocol assessments will continue until the end of the study, unless the protocol deviations put the subject at risk or the subject's condition requires that he/she should be discontinued from the study.

Protocol deviations related to Coronavirus Disease 2019 (COVID-19) pandemic impact on assessments described in the protocol will be presented in a separate data listing.

6.5.3 Data Sets Analyzed

6.5.3.1 Study Population

All subjects will be analyzed as enrolled in the following study populations.

- All Treated Eyes: All eyes enrolled and treated with the TENEO 317 model 2 excimer-laser,
- All Eyes Treated for Spherical Myopia,
- All Eyes Treated for Astigmatic Myopia,
- All Treated Eyes with Low to Moderate (> -7 D MRSE) Preoperative Myopia, and
- All Treated Eyes with High (<= -7 D MRSE) Preoperative Myopia
- Consistent Cohort (cohort of eyes that have every postoperative visit from 1 month up to the stability visit).

6.5.3.2 COVID-19 Pandemic Population

The COVID-19 pandemic population includes subjects who were discontinued or were lost to follow-up due to COVID-19 complications or pandemic concerns, or subjects that had significant COVID-19 related protocol deviations. The subjects in the COVID-19 pandemic population will be presented in an accountability table.

6.5.4 Demographic and Other Baseline Characteristics

6.5.4.1 Demographic Variables

The demographic variables collected in this study include age, sex, childbearing potential (if female), race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as Multi-racial.

Age (years) will be summarized using continuous descriptive statistics. Age will also be categorized as follows: <65 years and ≥65 years.

The number and percentage of subjects will be presented for age category, sex, childbearing potential (for female subjects), study eye, race, and ethnicity. The demographic variables will be summarized for all treated eyes. A data listing by subject will be provided that includes all demographic variables.

6.5.4.2 Baseline Refractive Parameters

The preoperative bin distribution of enrolled eyes by sphere and cylinder is based on the preoperative manifest refraction, specifically sphere and cylinder. All eyes will be treated for myopia with a target refraction of emmetropia. All eyes enrolled and treated will have at least -1.0 D of spherical myopia or more and at least 0.0 D or more of cylinder in the study. Table 1, above, provides the expected bin distribution stratified by preoperative sphere and cylinder. Tables will be provided of preoperative bin distributions for all treated eyes, eyes treated for spherical myopia, and eyes treated for astigmatic myopia. A data listing of preoperative sphere and cylinder by subject also will be provided. Sphere and cylinder values will be converted to minus notation for presentation and subsequent analysis in the efficacy section as follows:

If the Original Cylinder <= 0, then no conversion is necessary.

If the Original Cylinder > 0 then

New Sphere = Original Sphere + Original Cylinder

New Cylinder = - Original Cylinder

New Axis = Original Axis - 90, if Original Axis > 90

Original Axis + 90, if Original Axis ≤ 90

6.5.4.3 Preoperative Procedure Variables

Preoperative clinical procedure data collected at the Preoperative Visit, including the Schirmer's test, manifest refraction, keratometry, corneal topography, pupil size, uncorrected near visual acuity (UCNVA), UCDVA, distance BSCVA, slit lamp examination, pachymetry, cycloplegic refraction, endothelial cell density, contrast sensitivity, and dilated fundoscopic examination for ophthalmic assessments, and intraocular pressure (IOP) will not be summarized but will be listed.

6.5.4.4 Operative Procedure Variables

Parameters of the LASIK surgery, including treatment type, targeted refractive outcome, optical zone (mm), LASIK ablation (microns), central ablation depth (microns), maximum

ablation depth (microns), method of flap creation, anticipated flap thickness (microns), anticipated flap diameter (mm), treatment interruption, and problems during surgery, will not be summarized but will be listed.

6.5.4.5 Ocular Medical History

Ocular medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0. Ocular medical history will not be summarized but will be listed.

6.5.5 Concomitant Medications

Concomitant medications are medications listed for a subject as having been taken (1) prior to LASIK surgery and continuing for any time following the surgery or (2) at any time following LASIK surgery. Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) terminology, Version B3 Global March 2019. However, medications will not be summarized in tables.

In addition, the Investigator may use any medication that is judged necessary, appropriate, and beneficial to the subject. Documentation of all such medications used by the subject during this study for the treatment of operative eyes (with the exception of the surgeon's standard regimen for pre-, intra-, and post-operative medications) will be made on the appropriate sections of the electronic case report forms (eCRFs).

A data listing by subject that includes all concomitant medications will be provided. The concomitant medication listing will not contain information on non-drug therapies.

6.5.6 Analysis of Effectiveness Endpoints

6.5.6.1 Descriptive Statistics and Data Preparation

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, data listings, and figures using landscape orientation. All study data will be listed by subject, eye, and visit (as applicable) based on all treated subjects unless otherwise specified.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima

and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

When summarized by visit, nominal visits as indicated on the case report forms will be used. Visit windows will not be considered in the presentation of data by visit.

All statistical tests will be one-sided with a significance level of 0.025 ($\alpha = 0.025$) unless otherwise specified.

Confidence intervals (CIs) around single estimated proportions will be two-sided at 95% confidence.

All p values will be rounded to 4 decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

Unless otherwise specified, summaries will be presented by visit, where appropriate. Data listings will be sorted by subject number, eye, visit/time point, and parameter as applicable.

Baseline is defined as the last measurement prior to LASIK surgery. Change from baseline will be calculated as post-baseline visit minus baseline visit.

Eyes will be treated as independent sampling units ignoring any correlation between the two eyes of each subject, as is customary for LASIK clinical trials.

6.5.6.1.1 Output Data

Data will be transferred to the responsible Biostatistics representative, or their designee, and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM) standard. Both SDTM- and ADaM-formatted data will be used to create the subject data listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM Version 1.7 model and will be implemented using the SDTM Implementation Guide Version 3.3 and the most recent version of SDTM Controlled Terminology at the time of study start. ADaM data will follow the ADaM Version 2.1 model

and will be implemented using the ADaM Implementation Guide Version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21 . Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

The define.xml descriptive document will be created for SDTM and ADaM using the Define-XML Version 2.0 model.

6.5.6.2 Primary Effectiveness Endpoints

The primary effectiveness endpoints at the time of refractive stability are the following:

- The percentage of eyes that achieve predictability (calculated as postoperative refraction minus targeted refraction. If targeted refraction is emmetropic, then it is equal to postoperative refraction) of MRSE within ± 0.50 D
- The percentage of eyes that achieve predictability of MRSE within ± 1.00 D
- The percentage of eyes targeted for emmetropia that achieve a UCDVA of 20/40 (logMAR of 0.3) or better

The primary effectiveness endpoints will be analyzed for all treated eyes with missing data imputed using multiple imputation (MI) Fully Conditional Specification (FCS) methodology. Similarly, the categorical summaries of logMAR UCDVA will be presented for treated eyes that were targeted for emmetropia which had low to moderate preoperative myopia and, separately, for eyes which had high preoperative myopia.

For the primary effectiveness endpoints, data imputation employing MI method will be performed on missing MRSE, or logMAR UCDVA values at the time of refractive stability, as recorded in the eCRF, using the SAS® procedure PROC MI by applying the following SAS® code for treated eye:

```
PROC MI DATA=INDATA SEED=1562379 NIMPUTE=20 OUT=OUTDATA1;
 BY PARAM EYE;
 FCS;
 VAR VISIT4 to VISIT8 ;
RUN;
```

where

- *INDATA* is the name of the input dataset
- *OUTDATA1* is the name of the output dataset containing twenty 'complete' datasets
- *PARAM =* MRSE and UCDVA
- *VISIT4 to VISIT8* holds post-operative values at Week 1, Month 1, Month 3, Month 6, and Month 9, respectively for each of the analysis variables

The primary analysis time point will be the time of achievement of refractive stability for all eyes. Achievement of refractive stability will be assessed in this study as required by the American National Standards Institute (ANSI) Z80.11-2012 (R2017) standard [1]. By the ANSI standard, initial attainment of refractive stability is accepted at the latter of two postoperative refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval if all recommended criteria for refractive stability are met. Achievement of refractive stability for the study cohort requires a minimum of 95% of treated eyes should have a change of < 1.00 D of MRSE between two refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval.

For each eye, the targeted manifest sphere and cylinder will be determined preoperatively. Postoperatively, manifest refraction will be assessed at all scheduled visits beginning with the Week 1 Visit.

For each observation, targeted MRSE and MRSE at the time of refractive stability will be computed in diopters as follows. Since MRSE is collected on the Case Report Form (CRF), this will not be rederived in ADaM datasets.

$$MRSE = Sphere + \frac{Cylinder}{2}$$

For each observation, the absolute difference (|ΔMRSE|) between the targeted MRSE and observed MRSE at the stability visit will be computed as follows.

$$|\Delta MRSE| = |MRSE\ at\ Stability\ Visit - Targeted\ MRSE|$$

Each observation will be classified as shown in the following example:

Condition	Classification
$\lvert\Delta MRSE\rvert \leq 0.50$ D	MRSE within ± 0.50 D
$\lvert\Delta MRSE\rvert > 0.50$ D	MRSE not within ± 0.50 D

Predictability of MRSE within 0.50 D will be summarized categorically (MRSE within ± 0.50 D, MRSE not within ± 0.50 D) for the treated eyes population at the stability visit in a table.

Eyes will be classified similarly with respect to MRSE within 1.00 D of targeted MRSE.

Additionally, the UCDVA total number of letters correct at the time of refractive stability will be converted into logMAR as follows:

$\text{logMAR} = 1.7 - 0.02 \times \text{letters correct, rounded to the first decimal place.}$

The logMAR values will be converted to Snellen scores as follows:

Log MAR	Snellen Score
1.7	20 / 1000
1.6	20 / 800
1.5	20 / 630
1.4	20 / 500
1.3	20 / 400
1.2	20 / 320
1.1	20 / 250
1	20 / 200
0.9	20 / 160
0.8	20 / 125
0.7	20 / 100
0.6	20 / 80
0.5	20 / 63
0.4	20 / 50
0.3	20 / 40
0.2	20 / 32
0.1	20 / 25
0	20 / 20
-0.1	20 / 16
-0.2	20 / 12.5
-0.3	20 / 10

Once ΔMRSE and logMAR UCDVA are derived for all observations and the observations are categorized into response variables according to various MRSE and UCDVA thresholds

(e.g., MRSE within ± 1.00 D), the imputed datasets are used to obtain the percentage of eyes that achieve MRSE predictability or UCDVA of 20/40 or better as follows:

```
PROC FREQ DATA=OUTDATA1;
    TABLES CRITERIA / BINOMIAL;
    BY _IMPUTATION_;
    ODS OUTPUT BINOMIAL=PROP;
RUN;
DATA OUTDATA2;
    MERGE PROP (WHERE=(Label1="Proportion")
     RENAME=(nValue1=PROP))
     PROP (WHERE=(Label1="ASE")
     RENAME=(nValue1=PROP_SE));
    BY _IMPUTATION_;
RUN;
PROC MIANALYZE DATA=OUTDATA2;
    MODELEFFECTS PROP;
    STDERR PROP_SE;
    BY VISIT;
    ODS OUTPUT PARAMETERESTIMATES=ESTIMATES;
RUN;
```

where

- *OUTDATA1* is the output dataset from PROC MI
- *CRITERIA* is a responder variable (either achieving MRSE predictability or UCDVA of 20/40 or better)
- *OUTDATA2* is the output dataset containing the estimated proportion of responders and the standard error
- *ESTIMATES* is the results dataset

6.5.6.2.1 Primary effectiveness endpoint hypothesis testing

All hypotheses will be tested at the one-sided 2.5% (α=0.025) level of statistical significance.

6.5.6.2.1.1 Percentage of eyes that achieve predictability of MRSE within ± 0.50 D at the time of refractive stability

The null hypothesis (H_0) is that the proportion of eyes that achieve predictability within ± 0.50 D (π) is less than or equal to 0.80 (80%) at the time of refractive stability. The alternative hypothesis (H_1) is that the proportion is greater than 0.80 (80%).

$$H_0: \pi \leq 0.80$$

$$H_1: \pi > 0.80$$

The above hypothesis will be tested using CI calculated using normal approximation for binomial proportion. If the lower limit of the CI is above 0.8, then test is deemed significant.

6.5.6.2.1.2 Percentage of eyes that achieve predictability of MRSE within ± 1.00 D at the time of refractive stability

The null hypothesis (H_0) is that the proportion of eyes that achieve predictability within ± 1.00 D (π) is less than or equal to 0.90 (90%) at the time of refractive stability. The alternative hypothesis (H_1) is that the proportion is greater than 0.90 (90%).

$$H_0: \pi \leq 0.90$$

$$H_1: \pi > 0.90$$

The above hypothesis will be tested using CI calculated using normal approximation for binomial proportion. If the lower limit of the CI is above 0.9, then test is deemed significant.

6.5.6.2.1.3 Percentage of eyes targeted for emmetropia that achieve UCDVA of 20/40 or better at the time of refractive stability

The null hypothesis (H_0) is that the proportion of eyes targeted for emmetropia and that achieve UCDVA of 20/40 or better at the time of refractive stability (π), is less than or equal to 0.88 (88%). The alternative hypothesis (H_1) is that the proportion is greater than 0.88 (88%).

$$H_0: \pi \leq 0.88$$

$$H_1: \pi > 0.88$$

The above hypothesis will be tested using CI calculated using normal approximation for binomial proportion. If the lower limit of the CI is above 0.88, then test is deemed significant.

6.5.6.2.1.4 Statistical Success Criteria for the Study

The study will be statistically successful if all primary effectiveness endpoints in this section are analyzed successfully (i.e., if the null hypotheses are rejected for all primary effectiveness endpoints) at the visit when cohort refractive stability is achieved.

6.5.6.3 Sensitivity Analyses of Primary Effectiveness Endpoints

As sensitivity analyses, the primary effectiveness endpoints will be assessed at the time of cohort refractive stability based on the original dataset (rather than imputed datasets) using the following analyses:

- Observed case analysis: Subjects with both targeted and observed MRSE values available will be used for analysis. Subjects with a non-missing logMAR UCDVA value will be used for analysis. Missing values will not be included in the analysis.
- Best case analysis: Subjects with missing MRSE values will be imputed as "MRSE within ± 0.50" and "MRSE within ± 1.00". Subjects with missing logMAR UCDVA values will be imputed as "UCDVA 20/40 or Better". Subjects with missing values will be imputed as meeting each criterion mentioned above (counted in both the numerator and denominator in percentage calculations).
- Worst case analysis: Subjects with missing MRSE values will be imputed as "MRSE not within ± 0.50" and "MRSE not within ± 1.00". Subjects with missing logMAR UCDVA values will be imputed as "UCDVA Worse than 20/40". Subjects with missing values will be imputed as not meeting each criterion mentioned above (counted in the denominator only in percentage calculations).
- Poolability analysis: The proportion of subjects meeting the MRSE or UDVA criterion will be presented by site and visit without imputation. At each visit, a chi-squared test will be used to test for statistically significant differences among the sites. When a chi-squared test is not appropriate due to sparse data, then a Fisher's exact tests may be substituted.

6.5.6.3.1 Predictability and Refractive Stability Analyses

The following predictability and refractive stability descriptive summaries will be provided for each visit interval starting with the 1- to 3-month interval and continuing to the 6- to 9-month interval for all treated eyes, eyes treated for spherical myopia, and eyes treated for astigmatic myopia unless otherwise specified. Stability analysis will be repeated for Consistent Cohort.

- Eyes that exhibit an absolute change of less than or equal to 0.50 D, 1.00 D, and 2.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart.
- Mean overall change and change per month (calculated as, Difference in MRSE/ Duration in Months, where month = 30 days) in MRSE between consecutive scheduled visits as determined by a paired analysis, with 95% CIs around the mean rate of change based on t-distribution.
    - The mean rate of change in MRSE is expected to decrease monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging.
    - The 95% CI for the mean rate of change in MRSE is expected to include zero or a rate of change attributable to normal aging.
- Mean (± SD) MRSE for the preoperative and each postoperative visit
- Proportion of eyes with residual astigmatic error (absolute shift from Preoperative Visit to each postoperative visit in manifest axis versus residual manifest cylinder magnitude calculated as postoperative cylinder value minus targeted cylinder value in categories of ± 0.5 D, ± 1.0 D, ± >1.0 D) will be presented in a table and also stratified by preoperative diopter of cylinder as specified in Table 1 at Month 1, Month 3, Month 6, and Month 9 for eyes treated for astigmatic myopia.
- Assessment of cylinder stability between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart for correction of spherocylindrical refractive errors, expressed as the proportion of eyes

with an absolute change in cylinder magnitude of 0.00 D, 0.01 D to 0.50 D, 0.51 D to 1.00 D, 1.01 D to 1.50 D, and >1.51 D.

- Vector magnitude correction analysis will be summarized including intended refractive correction (IRC), surgically induced refractive correction (SIRC) and correction ratio (CR) calculated as SIRC/IRC, as defined in the Eydelman M paper [2] and also provided in the appendix. These data by study visit will be presented as continuous summary for all eyes treated for astigmatic myopia.
- Cylinder correction (non-vectorial) stratified by preoperative cylinder as specified in Table 1 for all eyes treated for astigmatic myopia will be summarized on a continuous scale in a table by study visit beginning at Month 1 for percent reduction of absolute IRC.

6.5.6.4 Secondary Effectiveness Endpoints

There are no secondary effectiveness endpoints.

6.5.6.5 Tertiary/Supportive/Other Effectiveness Assessments

No imputation for missing data methods will be used for the additional effectiveness assessments presented in subsections of this section. All data will be analyzed using available data only.

Effectiveness analyses will be performed for all treated eyes, eyes treated for spherical myopia, and eyes treated for astigmatic myopia, and data listings for measurements of effectiveness will be presented.

6.5.6.5.1 Additional Effectiveness Analyses

The following effectiveness descriptive summaries will be provided at Month 1, Month 3, Month 6, and Month 9. Primary effectiveness endpoint data will be presented using 1.00 D ranges from -1.00 D to -12.00 D (based on Table 1, the maximum MRSE value that is allowed in the study is -11.5 D) and for preoperative MRSE > -7.0 D versus MRSE ≤ -7.0 D).

- Percentage of eyes that achieve predictability of MRSE within ± 0.50 D
- Percentage of eyes that achieve predictability of MRSE within ± 1.00 D

- Percentage of eyes that achieve UCDVA of 20/40 or better
- Percentage of all eyes that achieve predictability (targeted versus achieved) of MRSE within ± 2.00 D
- Percentage of all eyes targeted for emmetropia that achieve UCDVA of 20/12.5 or better, 20/16 or better, 20/20 or better, 20/40 or better
- Percentage of eyes not targeted for emmetropia that achieve UCDVA of 20/20 or better and of 20/40 or better.
- Percentage of eyes that achieve predictability of manifest spherical refraction within ± 0.50 D, ± 1.00 D, and ± 2.00 D of intended manifest spherical refraction
- Percentage of eyes with predictability of manifest refraction astigmatism within ± 0.50 D, ± 1.00 D, and ± 2.00 D of intended manifest cylindrical refraction
- Percentage of eyes that achieve an UCDVA equal to or better than preoperative BSCVA, including eyes that achieve an UCDVA equal to or better than 20/40 if the preoperative BSCVA was 20/20 or better
- Change from baseline in BSCVA by study visit
- Change from baseline in UCNVA and UCDVA
- Percentage of eyes that are overcorrected or under corrected by > 1.00 D or > 2.00 D MRSE
- Percentage of eyes that achieve a difference between postoperative and preoperative BSCVA of < -2 lines, - 2 lines, -1 line, 0 lines, +1 line, +2 lines, and > +2 lines (line changes will be calculated as integer portion of change from baseline values of Early Treatment Diabetic Retinopathy Study [ETDRS letter] score collected on the CRF divided by 5)
- Percentage of eyes with CR of <= 0.5 D and <= 1.0 D
- Absolute shift in cylindrical axis from preoperative to postoperative visits of 0, <= 5, 5.1 to 10, 10.1 to 15, 15.1 to 30, and >30 deg.
- Eyes as a function of angle of cylindrical error (based on vector analysis. Refer to Appendix 1 for derivation):
    - Eyes with error of angle ≥ -15° and ≤ +15°
    - Eyes with error of angle greater than +15°

- Eyes with error of angle less than -15°

6.5.7 Statistical/Analytical Issues

6.5.7.1 Adjustment for Covariates

No adjustment for covariates will be performed.

6.5.7.2 Handling of Dropouts or Missing Data

The MI methods are as described in Section 6.5.6.2. In addition, analyses based on complete case, best case, worst-case, and complete case without COVID-19 population scenarios for the primary effectiveness endpoints will be performed.

6.5.7.3 Interim Analyses and Data Monitoring

No interim analyses or data monitoring committees are planned during this study. Members of the Sponsor team will review clinical data during the study conduct.

6.5.7.4 Multicenter Studies

This is a multicenter, prospective, open label, non-randomized, single arm study evaluating the safety and effectiveness of the Technolas TENEO 317 Model 2 (Version 1.28 US software) Excimer Laser when used in LASIK surgery to treat myopia or myopic astigmatism. Both eyes of a subject may be enrolled so long as both eyes meet all inclusion/exclusion requirements.

Any extreme or opposite results among centers will be examined.

6.5.7.5 Multiple Comparisons/Multiplicity

All primary effectiveness endpoints must be successful to demonstrate statistical success. Consequently, no adjustment is required for the primary effectiveness endpoints.

6.5.7.6 Use of an "Effectiveness Subset" of Subjects

This section is not applicable to the current analysis.

6.5.7.7 Active-Control Studies to Show Equivalence

This section is not applicable to the current analysis.

6.5.7.8 Examination of Subgroups

This section is not applicable to the current analysis.

6.5.8 Safety Analyses

The following safety summaries will be provided with descriptive statistics by visit for all treated eyes, eyes treated for spherical myopia, and eyes treated for astigmatic myopia unless otherwise specified.

- Eyes with BSCVA worse than 20/40 among eyes that had a BSCVA of 20/20 or better before surgery at each postoperative study visit, stratified by preoperative MRSE in 1.00-D unit ranges from -1.00 D to -12.00 D; by severity of preoperative myopia with > -7 D and <= -7 D; and by preoperative cylinder for ranges of 0, -0.25 to -0.50 D, -0.51 to -1.00 D, -1.01 D to -2.00 D, and -2.01 D to -3.00 D
- Loss of BSCVA of 1, 2, ≥ 2, and > 2 lines compared to preoperative BSCVA, with 95% CIs around the proportions
- Percentage of eyes that have an increase of manifest refractive astigmatism > 2.00 D compared to the preoperative refraction (since all cylinder values will be converted to minus notation first, this is equivalent to change from baseline in cylinder <= -2 D), stratified by preoperative MRSE, and severity of preoperative myopia. A 95% CI around the percentage of all eyes that have an increase of > 2.00 D will be displayed.
- Incidence of AEs by event type
- Incidence of complications
- Endothelial cell density changes
- Contrast sensitivity changes, mesopic conditions
- Subject symptoms and results for prespecified question domains (from Patient Reported Outcome with LASIK - Preoperative Questionnaire [PROWL-PRQ] [3] and Patient Reported Outcome with LASIK - Postoperative Questionnaire [PROWL-POQ] [4])

6.5.8.1 Extent of Exposure

This section is not applicable to this device study.

6.5.8.2 Adverse Safety Events

Each eye treated must be examined for the presence or absence of adverse safety events at all visits, whether scheduled or not. The collection of safety events begins at the time the subject signs the ICF. For the purposes of this study, adverse safety events are defined broadly to include a range of events encompassing four hierarchical categories of risk: AEs, UADEs, complications/potential AEs, and symptoms. Adverse events represent the key safety events that are surveilled during the study. Unanticipated adverse device events represent rare, unanticipated safety events directly attributable to the device. Other safety events include anticipated complications/potential AEs known to occur following laser refractive surgery and subjective symptoms reported by the subjects.

All AEs, UADEs, and complications/potential AEs will be presented by the AE categories in the eCRF. The data listings by subject will present the categories of AE in the eCRF along with their coded AE term using MedDRA, Version 22.0.

6.5.8.3 Adverse Events and Unanticipated Adverse Device Effects

An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finds) in subjects, users, or other persons, whether or not related to the investigational medical device.

The following AEs are the key safety events surveilled during the study in order to assess conformity to the target values of "Incidence of Adverse Events".

- Loss of > 2 lines (10 letters) BSCVA
- BSCVA worse than 20/40
- BSCVA worse than 20/25 if 20/20 or better preoperatively
- Haze ≥ trace with loss of BSCVA > 2 lines (10 letters)
- Increased manifest refractive astigmatism > 2.0 D
- Corneal epithelial defect involving the keratectomy at one month or later
- Melting of the flap
- Miscreated flap (lost, incomplete, too thin)
- Diffuse lamellar keratitis (Grade 3 or above)
- Corneal infiltrate or ulcer

- Any persistent corneal epithelial defect at one month or later
- Epithelium in the interface with loss of 2 lines (10 letters) or more BSCVA
- IOP with increase of > 10 mmHg above baseline on two consecutive examinations or an IOP greater than 30 mmHg on two consecutive examinations
- Haze beyond 6 months with loss of 2 lines or greater (≥ 10 letters ETDRS) of BSCVA
- Decrease in BSCVA of greater than or equal to 2 lines (≥ 10 letters ETDRS) not due to irregular astigmatism as shown by rigid contact lens refraction at 3 months or later
- Retinal detachment
- Corneal edema at 1 month or later
- Retinal vascular accidents
- Ocular penetration
- Other ocular event

All UADEs are considered to be rare, unanticipated events and have a serious effect on health or safety or represent any life-threatening problem or death caused by the device, if the event has not previously been identified in the investigational plan. A UADE may include, but is not limited to, the following events:

- Device-related death
- Enucleation of treated eye
- Corneal transplant of treated eye

A summary (counts and percentages) of AEs/UADEs will be presented by incidence of AEs for operative visit, each postoperative study visit, and overall (a Total column) using all treated eyes. At a study visit subjects' eyes will be counted only once if they experience multiple AEs/UADEs of the same type and similarly will be counted only once in Total column if they have AEs/UADEs of the same type at multiple study visits.

The number and percentage of eyes with at least one serious, device-related adverse event during the study will be presented along with a two-sided 95% exact CI around the proportion.

All AEs/UADEs will be presented in a data listing by subject. The AEs/UADEs leading to study discontinuation will be listed separately.

6.5.8.4 Complications/Potential Adverse Events

Complications/Possible AEs are known to potentially occur in association with laser refractive surgery and include the safety events listed below:

- Allergic conjunctivitis
- Blepharitis
- Conjunctivitis
- Corneal abrasion
- Corneal edema between 1 week to less than 1 month after procedure
- Corneal flap lifting between 1 day to 1 month post-surgery for wrinkled flap
- Corneal haze
- Corneal scar
- Debris in the interface
- Diffuse lamellar keratitis (grade 2 or less)
- Double/ghost images in operative eye
- Dry eye
- Enhancement not done due to flap fibrosis
- Epithelium at the flap edge
- Epithelium in the interface
- Flap is not of the size and shape as initially intended or resultant flap is misaligned
- Foreign body sensation at 1 month or later
- Iritis
- Loose epithelium
- Meibomian gland dysfunction

- Mucus under edge of flap
- Pain at 1 month or later
- Peripheral corneal epithelial defect at 1 month or later
- Possible allergic reaction to plugs or eye drops
- Postoperative flap complications
- Punctal plug inserted
- Punctal plug replaced
- Rough epithelium
- Superficial punctate keratopathy (SPK)
- Steroid induced IOP increase
- Subconjunctival hemorrhage
- Transient light-sensitivity syndrome (TLSS)
- Trace microstriae
- Trace corneal haze
- Vitreous floaters
- Other

Complications/potential AEs will be summarized in a similar manner as AEs/UADEs for operative visit, each postoperative visit, and overall (a Total column) using all treated eyes.

All complications/potential AEs also will be presented in a data listing by subject. The complications/potential AEs leading to study discontinuation will be listed separately.

6.5.8.5 Endothelial Cell Density (ECD) Sub-Study

Preoperative and postoperative (Month 6) corneal ECDs will be measured by specular microscopy for both eyes (regardless whether one or both eyes are treated) of up to approximately 90 subject eyes undergoing LASIK surgery at two or more clinical sites. To determine ECD, sites will submit all preoperative and Month 6 postoperative images to the central reading center for image analysis.

A table will be provided for change from baseline in ECD at Month 6 and categorical percent loss in ECD including > 0%, > -10% to <= 0%, > -20% to <= -10%, > -30% to <= -20%, > -40% to <= -30%, > - 50% to <= -40%, and <= -50%

A data listing by subject and by study visit will be provided for the date ECD was performed and the mean ECD result will be provided by the central reading center for up to three analyzable images taken at a study visit.

6.5.8.6 Contrast Sensitivity Testing Sub-Study

At least approximately 50 subjects will have their eyes enrolled in a sub-study to have monocular and binocular contrast sensitivity testing performed, testing which will be conducted at three or more clinical sites. The subjects in this sub-study may be, although are not required to be, any of the subjects in the specular microscopy testing sub-study. Testing will be conducted using a commercially available contrast sensitivity instrument of the same make and model at each of the two or more clinical sites. Each instrument will be calibrated according to the manufacturer and capable of conducting binocular mesopic (approximately 3.0 ± 2.0 cd/m^2) contrast sensitivity measurements with and without glare at spatial frequencies of 1.5, 3, 6, and 12 cpd. The contrast sensitivity measurements will be made at the optimal distance recommended by the instrument manufacturer.

Subjects will practice the contrast sensitivity test once at each of two randomly selected spatial frequencies under mesopic conditions without glare before beginning tests for recorded data. Contrast sensitivity will be assessed twice for each subject at each test condition at the Preoperative Visit and postoperatively at the Month 6 Visit. Mean contrast sensitivity of the two assessments at each visit and change from baseline results will be summarized in a table using all treated subjects.

A data listing by subject of contrast sensitivity results will be provided.

6.5.8.7 Schirmer's Test

Appropriate commercial paper strips for conducting a Schirmer's test without anesthesia are placed in the inferior fornix extending outward of both eyes and subjects are instructed to close their eyes for 5 minutes. The test strips are then removed, and the migration distance of strip wetness is measured in mm. No topical anesthetic may be used.

Schirmer's test is conducted in each eye at the Preoperative Visit and postoperatively at the Month 6 Visit. Tear fluid secretion from the Schirmer's test will not be summarized in a table.

A data listing by subject of Schirmer's test results will be provided.

6.5.8.8 Intraocular Pressure (IOP)

The measurement of eye pressure is part of a routine eye examination in which the IOP is determined. Goldmann applanation tonometry is the most accurate method and as such is the preferred method for study subjects. However, if an alternative method (e.g., Tonopen) is required at any site, it will be allowed. In any event, the same testing method is to be employed for all study visits for each subject to facilitate reliable comparisons from visit to visit. If cycloplegic refraction is measured the same day as IOP, the IOP should be measured following the refraction to avoid disturbing the corneal surface.

Intraocular pressure is measured at the Preoperative Visit and postoperatively at the Month 1, Month 3, Month 6, and Month 9 Visits. The IOP measurements and changes from baseline for each eye will not be summarized in a table.

A data listing by subject of IOP results will be presented.

6.5.8.9 PROWL Questionnaire

The PROWL-PRQ and PROWL-POQ will be administered to all subjects. Subjects will complete PROWL questionnaires at the Preoperative Visit and postoperatively at the Month 3, Month 6, and Month 9 Visits.

Results obtained both pre- and post-LASIK surgery will be assessed for selected topic domains of near vision, far vision, eye dryness, subject symptoms, driving, and vision clarity. **Table 3** describes the specific pre-operative PROWL-PRQ and post-operative PROWL-POQ questions to be analyzed for each of these topic domains. Normalization of individual or domain scores, if required, will be done as described in the Hays RD paper [5] or relevant primary references annotated in the PROWL questionnaire reference. Domain score for each subject will be provided as the average score of all questions within a domain after normalization as shown in **Table 3a**.

Normalized results for other PROWL-PRQ and/or PROWL-POQ categories of vision satisfaction, vision clarity, and satisfaction with LASIK surgery will be analyzed. **Table 4** describes the specific PROWL-PRQ and PROWL-POQ questions to be summarized for each of these categories with normalization score details provided in **Table 4a**.

Domains presented in Tables 3 and 4 will be summarized by study visit using continuous descriptive statistics including change from baseline.

Table 3. PROWL Topic Domain Categories and Domain Questions to be Analyzed

Topics - Pre and Post LASIK surgery	**PROWL-PRQ questions**	**PROWL-POQ questions**
Far Vision	16-18 and 28-29	10-12 and 22-23
Near Vision	19 and 24-27	13 and 18-21
Eye Dryness	65-72	62-69
Subject Symptoms	45-64	42-61
Driving	12-18	6-12
Vision Clarity	34-36a	28-30a

Table 4a. Normalized Scores for PROWL Questions in Table **3**

Topics - Pre and Post LASIK surgery	**PROWL-PRQ questions**	**PROWL-POQ questions**	**Normalized Score**
Far Vision	16-17	10-11	No difficulty at all =100 A little difficulty = 75 Moderate difficulty = 50 A lot of difficulty = 25 Never drive at night because of vision, or Never drive in these condition because of vision = 0 Never drive at night for other reasons or Never drive in these condition for other reasons = N/A
	18 and 28-29	12 and 22-23	No difficulty at all =100 A little difficulty = 200/3 Moderate difficulty = 100/3 A lot of difficulty = 0
	Domain score = (sum of scores of all questions within the domain)/(total number of questions answered) Note: Questions with answers as N/A will be treated as not answered and excluded from the mean domain score calculation.		
Near Vision	19	13	No difficulty at all =100

			A little difficulty = 200/3 Moderate difficulty = 100/3 A lot of difficulty = 0
	24-26	18-20	No difficulty at all =100 A little difficulty = 75 Moderate difficulty = 50 A lot of difficulty = 25 Never try to do these activities because of vision or Never try to do this because of vision = 0 Never do these activities for other reasons or Never do this for other reason = N/A
	27	21	Yes, many = 0 Yes, one or a few = 50 No = 100
	Domain score = (sum of scores of all questions within the domain)/(total number of questions answered) Note: Questions with answers as N/A will be treated as not answered and excluded from the calculation.		
Eye Dryness	65-72	62-69	None of the time = 4 Some of the time = 3 Half of the time = 2 Most of the Time = 1 All of the Time = 0
	Domain score = [(sum of scores of all questions within the domain) x 100]/[(total number of questions answered) x 4].		
Subject Symptoms (including 4 symptom groups, double images, glare, halo, and starbursts)	45-64 Double Images: 45-49 Glare: 50-54 Halo: 55-59 Starburst: 60-64	42-61 Double Images: 42-46 Glare: 47-51 Halo: 52-56 Starburst: 57-61	Scoring should always value best health as = 100, and other optional choices to range down to = 0. Scoring steps then should recognize the number of steps from 0 to 100 units. Example 1) PRQ61a: In the last 7 days, how often have you seen starbursts when you are wearing your best vision correction (glasses or contact lenses)? I do not wear glasses or contact lenses = N/A Never = 100 Rarely = 75 Sometimes = 50

			Often = 25 Always = 0 Example 2). PRQ60: In the last 7 days, have you seen any starbursts? Yes, but ONLY when NOT wearing glasses or contact lenses = 100/3 Yes, but ONLY when wearing glasses or contact lenses = 200/3 Yes, when wearing AND when not wearing glasses or contact lenses = 0 No, not at all = 100
	Domain score = (sum of scores of all questions within the domain)/(total number of questions answered) Note: Calculate domain score for each symptom group. Questions with answers as N/A will be treated as not answered and excluded from the calculation.		
Driving	12-13	6-7	Yes or no, no scoring needed
	14	8	Mainly vision Mainly other reason Both vision and other reasons No scoring needed
	15-17	9-11	No difficulty = 100 A little difficulty = 75 Moderate difficulty = 50 Extreme difficulty = 25 Never drive during the daytime because of vision, or Never drive at night because of vision or Never drive in these conditions because of vision = 0 Never drive during the daytime for other reasons, or Never drive at night for other reasons, or Never drive in these conditions for other reasons = N/A
	18	12	No difficulty at all =100 A little difficulty = 200/3 Moderate difficulty = 100/3 A lot of difficulty = 0
	Domain score = (sum of scores of scores of all questions)/(total number of questions answered)		

	Note: Questions with answers as N/A will be treated as not answered and excluded from the calculation. Questions PRQ12, 13, 14 (or POQ6, 7, 8) are excluded from the domain score calculation.		
Vision Clarity	34, 35, 36	28, 29, 30	Yes = 0 No = 100
	34a, 35a, 36a	28a, 29a, 30a	Very = 0 Somewhat = 25 A little = 50 Not at all = 75
	Domain score = (sum of scores of all questions within the domain)/(total number of questions answered) Note: When 34 is No, 34A should not be answered. However, in case 34 is No and 34A is answered, ignore 34 result from the domain score calculation and only use 34a result. Apply the same rule when the discrepancy happens to 35 (35A), or 36 (36A), or 28 (28A), or 29 (29A), or 30 (30A).		

Table 5. PROWL Question Categories and Questions to be Analyzed

Topics - Table Summary with Descriptive Statistics	**PROWL-PRQ Questions**	**PROWL-POQ Questions**
Vision Satisfaction	37	34
Vision Clarity	5	5
Satisfaction with LASIK Surgery		71-78

Table 6a. Normalization Scores for PROWL Questions in Table 4

Topics - Table Summary with Descriptive Statistics	**PROWL-PRQ Questions**	**PROWL-POQ Questions**	**Normalized Score**
Vision Satisfaction	37	34	Completely satisfied = 100 Very satisfied = 80 Somewhat satisfied = 60 Somewhat dissatisfied = 40 Very dissatisfied = 20 Completely dissatisfied = 0
Vision Clarity	5	5	Perfectly clear = 100 Pretty clear = 200/3 Somewhat clear = 100/3 Not clear at all =0
Satisfaction with LASIK Surgery		71-78	Scoring of each of these questions should be provided as percentages for each possible response.

			Example 1) POQ72: Currently, how satisfied or dissatisfied are you with how long it took to see improvement in your vision after LASIK surgery? Completely satisfied = 100 Very satisfied = 80 Somewhat satisfied = 60 Somewhat dissatisfied = 40 Very dissatisfied = 20 Completely dissatisfied = 0 Never had any improvement in any vision after LASIK surgery = 0 Example 2) POQ 73: Currently, how satisfied or dissatisfied are you with how long it took to see improvement in your post-operative symptoms of discomfort after LASIK surgery? Completely satisfied = 100 Very satisfied = 80 Somewhat satisfied = 60 Somewhat dissatisfied = 40 Very dissatisfied = 20 Completely dissatisfied = 0 Never had any post-operative symptoms of discomfort after LASIK surgery = 100
	Domain score = (sum of scores of scores of all questions)/(total number of questions answered)		

A data listing by subject of PROWL-PRQ responses and PROWL-POQ responses by study visit also will be presented.

6.5.8.10 Corneal Topography

Corneal topography of subject eyes will be measured at the Preoperative Visit and postoperatively at the Month 1, Month 3, Month 6, and Month 9 Visits. The data will not be summarized in a table.

A data listing by subject of corneal topography findings will be provided.

6.5.8.11 Pupil Size

Pupil size will be measured at the Preoperative Visit and postoperatively at the Month 3, Month 6, and Month 9 Visits. Pupil size and changes from baseline for each eye will not be summarized in a table.

A data listing by subject of pupil size will be provided.

6.5.8.12 Slit Lamp Examinations

Slit lamp examinations will be performed at the Preoperative Visit and postoperatively at the Day 1, Week 1, Month 1, Month 3, Month 6, and Month 9 Visits. The slit lamp findings will include examinations of the lid, conjunctiva, cornea clarity, SPK, corneal edema, corneal epithelium, corneal stroma, corneal flap, corneal interface, diffuse lamellar keratitis, anterior chamber cells, anterior chamber flare, and iris/pupil. Slit lamp findings will not be summarized in a table.

A subject data listing of slit lamp examination findings will be provided.

6.5.8.13 Other Safety Measurements

Keratometry, pachymetry, and cycloplegic refraction are performed only at the Preoperative Visit. Keratometry and pachymetry may be performed at a postoperative visit to assess anomalous results. No summaries will be provided but data listings by subject of these assessments will be provided.

Dilated fundoscopic examinations will be performed at the Preoperative Visit but are only required postoperatively if loss of BSCVA occurs compared to preoperative BSCVA. No summaries will be provided, while a data listing by subject of all dilated fundoscopic examination findings will be presented.

6.5.9 Determination of Sample Size

6.5.9.1 Assumptions

Prior clinical experience with the TENEO 317 excimer laser in Europe showed that 94.5% of eyes were within 0.50 D and 99% of eyes were within 1.00 D of targeted MRSE 1 month after surgery. In addition, 100% of eyes achieved UCDVA of 20/40 or better at 1 month [6].

6.5.9.2 Percentage of Eyes That Achieve Predictability of MRSE within ± 0.50 D at the Time of Refractive Stability

A one group χ^2 test with a 2.5% one-sided significance level will have > 99.99% power to detect the difference between the Null hypothesis proportion, π_0, of 0.80 and the alternative proportion, π_1, of 0.945 when the sample size is 300.

6.5.9.3 Percentage of Eyes That Achieve Predictability of MRSE within ± 1.00 D at the Time of Refractive Stability

A one group χ^2 test with a 2.5% one-sided significance level will have > 99.99% power to detect the difference between the Null hypothesis proportion, π_0, of 0.90 and the Alternative proportion, π_1, of 0.99 when the sample size is 300.

6.5.9.4 Percentage of Eyes Targeted For Emmetropia That Achieve UCDVA of 20/40 or Better at the Time of Refractive Stability

A one group χ^2 test with a 2.5% one-sided significance level will have > 99.99% power to detect the difference between the Null hypothesis proportion, π_0, of 0.88 and the Alternative proportion, π_1, of 0.99 when the sample size is 300.

6.5.9.5 Overall Enrollment

Approximately three hundred thirty-four eyes (334) eyes will be treated to evaluate 300 eyes at the time of refractive stability, as recommended by the ANSI Z80.11-2012 (R2017) standard. This will allow for losses of up to 10%. Enrollment of each eye will be monitored to achieve the minimum marginal distribution of preoperative refractive errors given for study eyes.

Enrollment will be successive without staging of enrollment since substantial prior clinical experience with the TENEO 317 model 2 excimer laser was obtained after the device received CE marking status.

6.6 Changes in Planned Analyses

- "UDVA" is changed to "UCDVA" to be consistent with "UCNVA".
- "Predictability (attempted versus achieved)" is replaced with "Predictability (calculated as postoperative refraction minus targeted refraction. If targeted refraction is emmetropic, then it is equal to postoperative refraction)" for clarity in the primary endpoint definition.
- The multiple imputation method is updated from Markov Chain Monte Carlo (MCMC) to FCS as FCS has greater flexibility than MCMC.
- The following bullet points in Section 9.6.3.2 of the protocol are deleted in the SAP due to redundancy:

    - Change in MRSE between Month 1 and Month 3, between Month 3 and Month 6, and Month 6 and Month 9 and change per month as determined by a paired analysis
    - Percentage of eyes that achieve a change in MRSE less than or equal to +0.50 D between Month 1 and Month 3, between Month 3 and Month 6, and Month 6 and Month 9

- Poolability analysis will be done as an additional sensitivity analysis as specified in Section 6.5.6.3.
- The following bullet points in Section 6.5.6.3.1 in the SAP are not specified in the protocol:

    - Proportion of eyes with residual astigmatic error (absolute shift from preoperative visit to each postoperative visit in manifest axis versus residual manifest cylinder magnitude calculated as postoperative cylinder value minus targeted cylinder value in categories of +/- 0.5 D, +/- 1 D, +/- > 1 D) will be presented in a table and also stratified by preoperative diopter of cylinder as specified in Table 1 at Month 1, Month 3, Month 6, and Month 9 for eyes treated for astigmatic myopia.

    - Vector magnitude correction analysis will be summarized including intended refractive correction (IRC), surgically induced refractive correction (SIRC) and correction ratio (CR) calculated as SIRC/IRC, as defined in the Eydelman M paper. These data by study visit will be presented as continuous summary for all eyes treated for astigmatic myopia.
    - Cylinder correction (non-vectorial) stratified by preoperative cylinder as specified in Table 1 for all eyes treated for astigmatic myopia will be summarized on a continuous scale in a table by study visit beginning at Month 1 for percent reduction of absolute IRC.

- The key effectiveness variables stratified by preoperative manifest cylinder power as stated in Section 9.6.3.1 of the protocol will not be summarized.
- 95% CIs for percentage of eyes with the loss of BSCVA of 1, 2, ≥ 2, and > 2 lines compared to preoperative BSCVA and for percentage of eyes that have an increase of manifest refractive astigmatism > 2.00 D compared to the preoperative refraction will be presented.
- The percentage of eyes with at least one serious, device-related adverse event during the study along with 95% CI will be presented.
- Contrast sensitivity results will not be reported as graphs as stated in the protocol but will be summarized in a table.
- Schirmer's test results will not be summarized in a table.
- Intraocular pressure results will not be summarized in a table.
- Changes to questionnaire data analysis.
    - In the protocol, Table 3 has questions for topics Visual Functions and Near Vision overlapped. In SAP, topic Vision Functions is removed, and questions are combined under Near Vision.
    - Topic Expectation of LASIK Surgery in protocol Table 4 is considered a subjective measure that may have potential threats to the validity. The results will not be summarized but only provided in questionnaire listing.
    - Questions not covered in protocol Table 3 and Table 4 are not the main interest to the study. The results will not be summarized but only provided in questionnaire listing.

Documentation of revision to the SAP will commence after approval of Version 1.0.

7 REFERENCES

1. ANSI Z80.11-2012 (R2017) standard – Laser Systems for Corneal Reshaping
2. Eydelman M, Hilmantel G, Tarver ME, et al. Symptoms and satisfaction of patients in the patient-reported outcomes with laser in situ keratomileusis (PROWL) studies. JAMA Ophthalmol 2017, 135:13-22.
3. LASIK Pre-Operative Questionnaire (PRQ). (2015, June 4). Retrieved from https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/UCM528837.pdf
4. LASIK Post-Operative Questionnaire (POQ). (2015, June 2). Retrieved from https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/SurgeryandLifeSupport/LASIK/UCM528841.pdf
5. Hays RD, Tarver ME, Spritzer KL, et al. Assessment of the psychometric properties of a questionnaire assessing patient-reported outcomes with laser in situ keratomileusis (PROWL). JAMA Ophthalmol 2017; 135:3-12.
6. Engineering Report ER-100022264: Data analysis report of patients with preoperative only spherical myopia or myopic astigmatism, Technolas Document #100022264.

8 APPENDIX 1

Vector analyses

The following pre-analysis transformations will be done:

1. Convert manifest refraction to positive cylinder notation.
2. Convert all manifest refraction data from the spectacle to the corneal plane (adjusting for vertex distance) using the following formula:

$$MRC = \frac{1000\ (Sph + Cyl)}{1000 - 13\ (Sph + Cyl)} - \frac{1000\ Sph}{1000 - 13\ Sph}$$

   Where
   MRC = Refractive cylinder at the corneal plane
   Sph = Manifest refractive sphere
   Cyl = Manifest refractive cylinder
3. Adjust left eye axis as follows:

$$Adjusted\ Axis = 180^o - Original\ axis$$

Vector Analysis Variables:

1. The intended refractive correction vector (IRC) is defined as the vector difference between the preoperative astigmatic correction vector and the target postoperative cylinder vector (preoperative - target). If the target refractive state is emmetropia, the IRC vector is equal to the preoperative cylinder (i.e., MRC) and angle.
2. Surgically induced refractive correction (SIRC) vector is the vector difference between the preoperative and postoperative astigmatic correction vectors (preoperative - postoperative).

Methods for calculating the refractive error analysis variables (from here onwards, C = MRC and A for left eye is the adjusted axis):

1. Convert the preoperative astigmatic correction to X and Y vector components:
   $X_{preop} = C_{preop} * \cos(2 * A_{preop})$
   $Y_{preop} = C_{preop} * \sin(2 * A_{preop})$
2. Convert the postoperative astigmatic correction to X and Y vector components:
   $X_{postop} = C_{postop} * \cos(2 * A_{postop})$
   $Y_{postop} = C_{postop} * \sin(2 * A_{postop})$
3. Find the magnitude of the SIRC
   $$|SIRC| = \sqrt{[Xpreop - Xpostop]^2 + [Ypreop - Ypostop]^2}$$
4. Find the axis of the SIRC, A_{SIRC}, using the preoperative and postoperative X and Y comments (where $X_{SIRC} = X_{preop} - X_{postop}$ and $Y_{SIRC} = Y_{preop} - Y_{postop}$).
   $$\theta = 0.5 * \arctan\left[\frac{YSIRC}{XSIRC}\right]$$
   Then, find A_{SIRC} using the X and Y components of SIRC:
   If $Y_{SIRC} \geq 0$ and $X_{SIRC} > 0$ then $A_{SIRC} = \theta$
   If $Y_{SIRC} < 0$ and $X_{SIRC} > 0$ then $A_{SIRC} = \theta + 180°$
   If $X_{SIRC} < 0$ then $A_{SIRC} = \theta + 90°$
   If $X_{SIRC} = 0$ and $Y_{SIRC} > 0$ then $A_{SIRC} = 45°$
   If $X_{SIRC} = 0$ and $Y_{SIRC} < 0$ then $A_{SIRC} = 135°$
5. Find error of angle (EA) by subtracting A_{IRC} from A_{SIRC}.
   $EA = A_{SIRC} - A_{IRC}$, if $|A_{SIRC} - A_{IRC}| < 90°$
   $EA = A_{SIRC} - A_{IRC} - 180°$, if $A_{SIRC} - A_{IRC} > 90°$
   $EA = A_{SIRC} - A_{IRC} + 180°$, if $A_{SIRC} - A_{IRC} < -90°$
   $EA = 0°$, if $A_{SIRC} - A_{IRC} = \pm 90°$.