STATISTICAL ANALYSIS PLAN
23 September 2015
Version 1.0

A Multi-Center, Open-Label, Parallel-Arm, Randomized, Dose-Ranging Study of ENV515 (travoprost) Intracameral Implant in Subjects with Bilateral Ocular Hypertension or Early Primary Open-Angle Glaucoma

PROTOCOL NUMBER ENV515-01

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LIST OF ABBREVIATIONS

AE	adverse event
CSR	clinical study report
ETDRS	Early Treatment Diabetic Retinopathy Study
ICH	International Conference on Harmonisation
IOP	intraocular pressure
ITT	Intent-to-Treat (population)
LogMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PP	Per-Protocol (population)
SAE	serious adverse event
SD	standard deviation
VA	visual acuity

1. PURPOSE OF THE ANALYSES

The statistical analysis plan (SAP) contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the analysis sets that will be analyzed, the subject characteristics parameters, the efficacy parameters, and the safety parameters. The details of the specific statistical methods that will be used will be provided. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR. Table, figure, and listing specifications are provided in separate documents.

Please note that text within the SAP that comes directly from the protocol will be shown in italics.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The primary objectives of this study are to:

- *Evaluate the safety and tolerability of ENV515 (travoprost) Intracameral Implants in subjects with bilateral ocular hypertension or early primary open-angle glaucoma; and*
- *Evaluate the efficacy of ENV515 (travoprost) Intracameral Implants in lowering intraocular pressure (IOP) in subjects with bilateral ocular hypertension or early primary open-angle glaucoma.*

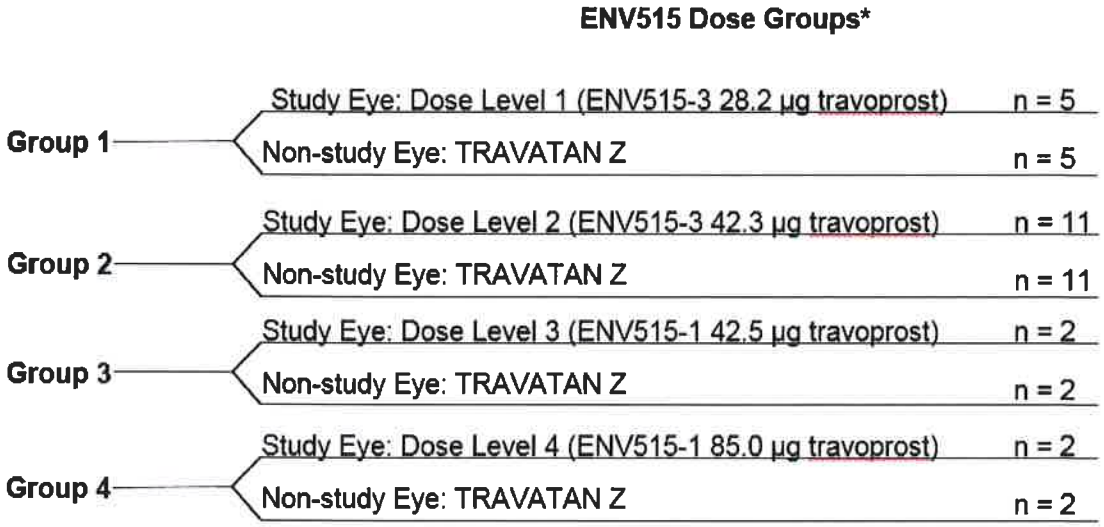
The secondary objectives of this study are to:

- *Determine the pharmacokinetic (PK) levels of travoprost in the aqueous humor at the time of the cataract surgery (4 weeks post-implantation);*
- *Determine the systemic exposure (levels of travoprost in plasma); and*
- *Determine the residual level of travoprost in the implant removed at the time of the cataract surgery (4 weeks post-implantation).*

2.2 Overall Study Design and Plan

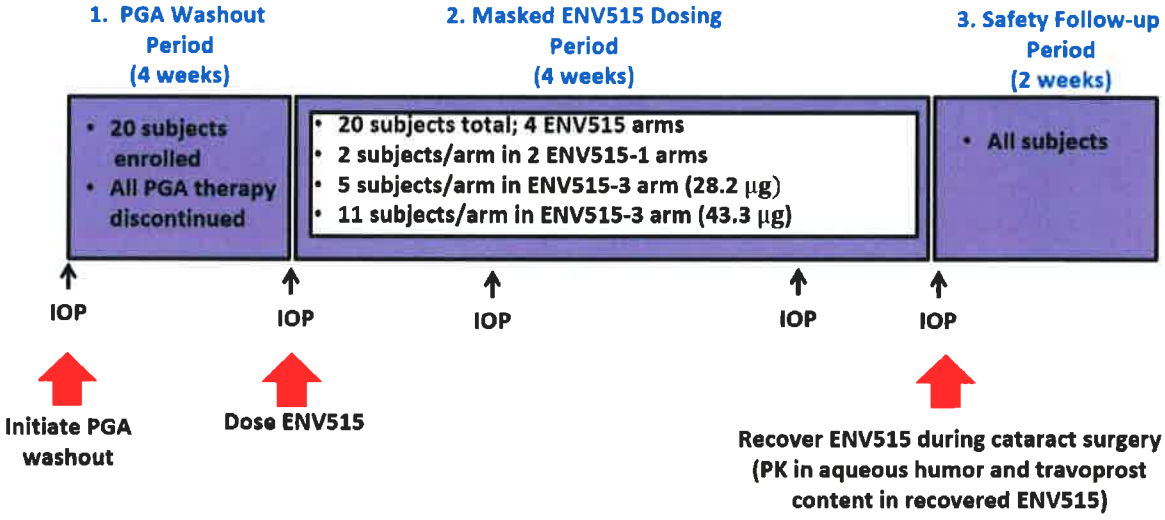
This is a multicenter, randomized, open-label, parallel-group, dose-ranging, 28-day Phase 2a trial to assess the safety, tolerability, efficacy, aqueous humor PK, systemic exposure, and remaining travoprost in ENV515 implants for 4 dose levels of ENV515 intracameral travoprost studied in 20 subjects with bilateral open-angle glaucoma or ocular hypertension who are scheduled for upcoming cataract surgery in a single eye (the study eye). There will be 2 subjects per dose in the 2 ENV515-1 dose groups, 5 subjects per dose in the 2 implants/eye ENV515-3 dose group and 11 subjects per dose in the 3 implants/eye ENV515-3 dose group, evaluating the dose levels of travoprost administered via single, unilateral intracameral injection of ENV515 in the study eye: 28.2 µg/eye (via 2 ENV515-3 implants), 42.3 µg/eye (via 3 ENV515-3 implants), 42.5 µg/eye (via 1 ENV515-1 implant), or 85.0 µg/eye (via 2 ENV-1 implants). All non-study eyes will receive open-label TRAVATAN Z (travoprost ophthalmic solution), 0.004% per their usual treatment regimen (Figure 1). Single doses of ENV515 implants will be administered unilaterally in the study eye (pre-surgical eye) 4 weeks prior to the cataract surgery and the implants will be retrieved during the cataract surgery (Figure 2). The study design includes 11 clinic visits over approximately 10 to 12 weeks depending on the duration of the washout period.

Figure 1: ENV515 Treatment Arms



Treatment assignment of ENV515 dose level 1-4 randomized to study eye

Figure 2: Study Design for ENV515-01: 4-week Phase 2a Safety, Tolerability, and IOP-Lowering Effects of ENV515 in Glaucoma Subjects in Need of Cataract Surgery



2.3 Study Population

The study population will include 20 subjects between 18 and 85 years of age with a diagnosis of bilateral ocular hypertension or early primary open-angle glaucoma with the need for cataract removal and intraocular lens implantation. The subjects will be enrolled at centers across the United States in this first-in-man Phase 2a trial with ENV515 (travoprost) Intracameral Implants.

2.4 Treatment Regimens

The 4 ENV515 dose levels will be administered in a parallel group design, with each subject participating in only one group. The 4 dose levels will be achieved via the following numbers and sizes of implants: 28.2 µg (2 ENV515-3 implants), 42.3 µg (3 ENV515-3 implants), 42.5 µg (1 ENV515-1 implant), and 85.0 µg (2 ENV515-1 implants). Two subjects per dose in the 2 ENV515-1 dose groups, 5 subjects per dose in the 2 implants/eye ENV515-3 dose group and 11 subjects per dose in the 3 implants/eye ENV515-3 dose group will have the active dose assigned to the pre-surgical eye that is scheduled for cataract removal, with the contralateral eye receiving TRAVATAN Z once daily per package insert from Day 1 through Day 25.

2.5 Treatment Group Assignments or Randomization

Patients will be randomly assigned to 1 of the 4 dose levels of ENV515 within each investigative site. The contralateral eye will receive TRAVATAN Z.

The randomization code for this study will be generated by Envisia or its designee. The subjects, investigators, site staff, and project teams at Envisia and the contract research organization will be unmasked to treatment assignment.

2.6 Sample Size Determination

Since this trial is primarily a dose-finding safety and tolerability study and the first study of ENV515 in human subjects, sample size estimation was not performed. This study will enroll up to 4 arms of2-115 subjects treated unilaterally for a maximum possible 20 subjects.

The proposed number of subjects is typical for a Phase 1/2a clinical trial and should be sufficient to assess the safety and tolerability of the study drug. Assuming that 5 subjects receive pooled active drug within a cohort, the probability of failing to observe a toxicity can be determined for various true underlying toxicity rates from the binomial distribution (Table 1). For example, for a true underlying toxicity rate of 30%, the probability of failing to observe toxicity with 5 subjects would be 0.17. For a true toxicity rate of 40%, the probability of failing to observe toxicity would be 0.08.

Table 1: Toxicity Probabilities (n = 5)

True Toxicity Rate (%)	*10%*	*20%*	*30%*	*40%*	*50%*	*60%*	*70%*	*80%*	*90%*
Probability of Failing to Observe Toxicity	*0.59*	*0.33*	*0.17*	*0.08*	*0.03*	*0.01*	*0.002*	*<0.001*	*<0.001*

Due to the study design and discontinuation criteria in the protocol, subjects who receive the ENV515 dose of study treatment and discontinue from the study for any reason will not be replaced.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)". To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a particular category.
- Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean and median will be reported to one more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.
- All exploratory statistical tests will be 2-sided and nominal significance will be determined at the 0.05 level. All p-values will be rounded to 3 decimal places; p-values that round to "0.000" will be presented as "< 0.001".
- All analyses will be performed using SAS® System version 9.2 or higher.
- Dates will be displayed as ddmmmyyyy (e.g., 24Jan2005).

Since this study has not been powered to allow formal hypothesis testing of toxicity rates or efficacy between dose groups, any examination of treatment differences will be exploratory in nature. For all analyses, subject-level covariates will be summarized within each group by treatment (Table 2). Eye-level covariates will be summarized for each cell in the final row of Table 3.

Table 2: Subject-Level Analyses

Group 1	Group 2	Group 3	Group 4
2 implants ENV515-3 (28.2 µg travoprost)	3 implants ENV515-3 (42.3 µg travoprost)	1 implant ENV515-1 (42.5 µg travoprost)	2 implants ENV515-1 (85.0 µg travoprost)

Table 3: Eye-Level Analyses

Group 1		Group 2		Group 3		Group 4	
2 implants ENV515-3 (28.2 µg travoprost)		3 implants ENV515-3 (42.3 µg travoprost)		1 implant ENV515-1 (42.5 µg travoprost)		2 implants ENV515-1 (85.0 µg travoprost)	
ENV515-3 SE	TRAVA-TAN Z NSE	ENV515-3 SE	TRAVA-TAN Z NSE	ENV515-1 SE	TRAVA-TAN Z NSE	ENV515-1 SE	TRAVA-TAN Z NSE

SE: Study eye; NSE: Non-study eye

4. ANALYSIS POPULATIONS

Intent-to-Treat (ITT) Population

The ITT population will consist of all subjects who are randomized, receive active study drug, and complete at least one post-baseline IOP assessment.

Per Protocol (PP) Population

The PP population will consist of all subjects in the ITT population who complete all study visits and are reasonably compliant with the protocol. Any exclusions from the PP population will be determined prior to database lock.

Safety Population

The Safety population will consist of all subjects who receive at least one dose of study medication.

5. STUDY PATIENTS

5.1 Disposition of Patients

The disposition of subjects will be summarized for all subjects randomized. The number and percentage of subjects in each analysis population, the number and percentage of subjects who complete the study, as well as the number and percentage that discontinue the study and the reasons for study discontinuation will be summarized by dose group.

5.2 Protocol Deviations

All protocol deviations will be recorded and reported in listings. Major protocol deviations will be identified prior to database lock.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline demographic characteristics such as age and gender and clinical characteristics including VA, IOP, gonioscopy, and corneal thickness will be summarized using descriptive statistics. Baseline will be defined as the last measurement prior to administration of the first dose of study drug. Demographics will be summarized at the patient level, while baseline clinical characteristics will be summarized by study eye and non-study eye. All demographics and baseline clinical characteristics will be listed.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

In this study, the principal investigator administers the investigational treatment into the study eye on the day of randomization. As a result, compliance with the investigational product will be 100%. Compliance information will not be collected for the active control, TRAVATAN Z.

8. EFFICACY EVALUATION

8.1 Overview of Efficacy Analysis Issues

8.1.1 Handling of Dropouts or Missing Data

No adjustments for missing values will be made. Missing values will be noted in the CSR.

8.1.2 Assessment Time Windows

Intraocular pressure will be measured at visit 2 (day -7 to -1) and visit 8 (day 25 +/- 1 day). It will be collected at times 8AM, 10AM and 4PM (all times are +/- 30 minutes).

8.2 Efficacy Variables

The efficacy parameter measured in this study is the IOP time-matched change from pre-dose baseline. The diurnal curve measurements will be made at the Baseline Visit and at Visit 8 (Day 25) and will be collected in both eyes at 8AM, 10AM, and 4PM. Time-matched change from baseline will be calculated separately for each time point at Visit 8 (i.e., 8AM Visit 8 – 8AM Baseline, 10AM Visit 8 – 10AM Baseline, and 4PM Visit 8 – 4PM Baseline).

Three consecutive measurements will be taken at each time point *to determine IOP. All three measurements will be recorded and the median IOP of the three measurements will be recorded and used in the analysis* for that time point.

Additionally, as a safety measure, IOP is also collected in both eyes at 8AM at all other visits.

8.3 Analysis Methods

8.3.1 Primary Efficacy Analyses

The efficacy parameter measured in this study is IOP change from pre-dose baseline. Exploratory analyses comparing the change in IOP over time between treated study pre-surgical eyes and contralateral non-study TRAVATAN Z eyes will be performed. Differences in IOP change from baseline between dose groups will be explored.

The primary endpoint will be the average IOP diurnal curve measurement change from baseline. Intraocular pressure is measured at 8 AM, 10 AM and 4 PM in 3 replicates. The median of the replicates at each of these times will be averaged over the time points to calculate the average IOP diurnal curve measurement. If there were no measurements at either the 8 AM, 10 AM or 4 PM times, then the average IOP diurnal curve measurement will be missing.

Descriptive summary statistics will be presented for average IOP diurnal curve by dose group, study eye and non-study eye, and visit. Descriptive statistics will include mean,

standard deviation, median, interquartile range, minimum and maximum. Both change from baseline and percent change from baseline will be summarized.

Change from baseline in average IOP diurnal curve will be analyzed using an ANCOVA by treatment group and controlling for baseline. This will be done separately for the study eye and non-study eye. Estimates of the slope for each treatment group will be examined along with corresponding p-values for the estimates being non-zero. See Appendix 13.2 for more information.

8.3.2 Other Efficacy Analyses

Descriptive summary statistics will be presented for IOP diurnal curve by dose group, study eye and non-study eye, visit and time point. A comparison of the IOP diurnal curve between treatments will be made. Time-matched change from baseline and percent change from baseline in IOP at each time point for Day 25 will be summarized descriptively. Descriptive statistics will include n, mean, standard deviation, median, minimum, maximum and inter-quartile range.

Time-matched change from baseline in IOP diurnal curve will be analyzed using an ANCOVA controlling for treatment group and time-matched baseline. This will be done separately for each time point and for study eye and non-study eye. The purpose of this analysis will be to examine whether treatment was able to reduce IOP at every time point. Therefore, estimates of the slope for each treatment will be examined along with corresponding p-values for the estimates being non-zero. The See Appendix 13.2 for more information.

Time-matched change from baseline in IOP comparing the treated study-eye with the non-treated study eye will be examined using a paired t-test. This will be done separately for each treatment group and time point. Mean differences and 95% confidence intervals between study eye and non-study eye will be presented.

Summary statistics by time point and study eye and non-study eye will also be presented.

Comparisons of IOP measurements collected at 8AM at all visits will be examined. Summary statistics by visit and study eye versus non-study eye will also be presented. Baseline will be calculated by averaging the 8AM measurements taken at Visit 2 and Visit 3. If subjects had not washed out sufficiently at Visit 2, then they were to come in for an unscheduled visit to have IOP measured. In these cases, baseline will be the average of the Unscheduled Visit and Visit 3. The change from baseline IOP at 8 AM values in the study eye will be analyzed using an ANCOVA with treatment and baseline IOP in the model. This will be done separately for each time point. A similar ANCOVA will be fit for the non-study eye. This analysis will examine the estimates for each treatment group as well as an overall estimate across treatment groups to determine if the estimates are non-zero. Paired t-tests will be done for each treatment group comparing the change from baseline in the study-eye and non-study eye

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

Adverse events, clinical laboratory results, vital signs, and physical exam findings will be tabulated at the subject level. All other safety measurements will be made at the eye level. Unless otherwise noted, baseline will be defined as the last measurement prior to receiving the implant.

9.2 Extent of Exposure

The number of days from implant insertion to implant removal will be summarized using means and standard deviations. The number of days from implant insertion to removal, as well as whether the subject required early removal of the implant, will be available in subject listings. Exposure will be calculated only for the study eye. No exposure information for the TRAVATAN Z eye will be collected.

9.3 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and categorized by system organ class using preferred terms by dose group. Events will be tabulated with respect to their intensity and relationship to the study drug. Only treatment-emergent AEs will be summarized. A treatment-emergent AE will be defined as any AE with onset date on or after the first exposure date. AEs will be tabulated separately for study eye, non-study eye and non-ophthalmic events.

All serious adverse events (SAEs) and other significant events, including withdrawals due to AEs, will be individually summarized in the CSR.

All treatment-emergent AE and SAE data will be presented in subject listings.

9.4 Clinical Laboratory Evaluation

Continuous clinical laboratory values will be summarized using means and standard deviation for reported and change-from-baseline values. Categorical clinical laboratory values will be summarized using shift tables displaying the frequencies of subjects with abnormal or normal results. Clinical laboratory results will be summarized at the subject level. In addition, clinical laboratory data will be presented in subject listings.

9.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1 Vital Signs

Vital sign assessments include measurements of heart rate, blood pressure, and respiration rate. Vital signs will be summarized by study visit and treatment group. All vital sign data will be presented in subject listings.

9.5.2 Physical Examinations

All physical examination data will be presented in listings.

9.5.3 Corneal Thickness (Pachymetry)

Pachymetry will be performed at the Screening Visit, Baseline Visit, Visit 6, Visit 8, and Visit 10. Three measurements will be taken and the average will be used in summary tables. Corneal thickness and change from baseline corneal thickness will be summarized by visit, study eye, and non-study eye. All pachymetry data, including all three measurements for each eye, will be listed.

9.5.4 Visual Acuity (VA)

Visual acuity will be measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart according to the manufacturer's specifications at all study visits. The number of letters missed will be collected and summarized for Visit 2 and Visit 11 by study eye/non-study eye, and treatment group. In addition, the number and proportion of subjects with greater than or equal to 3 lines lost will be summarized. Three lines lost will be defined as greater than or equal to 15 letters missing. All VA data, including manifest refraction, LogMAR, and total letters missed will be presented in subject listings.

9.5.5 Endothelial Cell Count and Morphology

Endothelial cell count and morphology will be collect at Screening, Baseline, Visit 6, Visit 8, and Visit 10. Endothelial cell count will be summarized by visit, study eye/non-study eye, and treatment group. All endothelial data will be presented in subject listings.

9.5.6 Slit Lamp Biomicroscopy Exams

Slit lamp biomicroscopy exams, including corneal staining, will be performed at all study visits. Summary shift tables will be presented by visit, study eye/non-study eye, and treatment. In addition, hyperemia mean and mean change from baseline will be summarized in a table. All slit lamp biomicroscopy findings will be listed.

9.5.7 Pupil Measurements

Pupil Measurements are done at Screening, Baseline, Visit 6, Visit 8 and Visit 10. Pupil measurements will be summarized by visit, study eye/non-study eye, and treatment group. All pupil measurement data will be listed.

9.5.8 Binocular Indirect Ophthalmoscopy (Dilated Fundus Exam)

A dilated fundus exam will performed at the Screening Visit, Baseline visit, Visit 6, Visit 8, and Visit 10. Shift tables of normal/abnormal findings will be presented by visit, study eye/non-study eye, and treatment group. All dilated fundus exam data will be listed.

9.5.9 Visual Field

Visual field assessments will be made at the Screening Visit and Visit 10. Shift tables of normal/abnormal findings will be presented by study eye/non-study eye and treatment group. All visual field data will be listed.

9.5.10 Anterior Segment

Anterior segment photo data will be presented in listings.

9.5.11 Gonioscopy

Gonioscopy is performed at Screening, Baseline, Visit 4, and Visits 6 through 10. All gonioscopy data will be presented in subject listings.

10. PHARMACOKINETIC EVALUATION

A PK sample from the aqueous humor will be collected on the day of surgery from the study eye. In addition, a plasma PK sample will be collected at Visit 10. These data will be summarized by treatment group.

The residual amount of travoprost remaining in the implant after surgical removal will be determined in order to allow for an accurate calculation of travoprost exposure from the implant. This will be calculated by subtracting the residual amount of travoprost in the implant from the original amount in the implant. Travoprost exposure will be summarized by treatment group.

All PK data will be presented in subject listings.

11. LIST OF PLANNED TABLES

Rho Table Identifier	Table No.	Title	Population
DS_TAA	1	Summary of Subject Disposition by Treatment Group	All Subjects
DM_TAA	2	Summary of Demographic and Baseline Characteristics by Treatment Group	Safety
DM_TAB	3	Summary of Disease Baseline Clinical Characteristics by Treatment Group	Safety
EF_TAA	4	Summary of Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group	ITT
EF_TAB	5	Summary of Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group	Per Protocol
EF_TAC	6	Summary of percent Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group	ITT
EF_TAD	7	Summary of percent Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group	Per Protocol
EF_TAE	8	Analysis of Change from Baseline Average Intraocular Pressure Diurnal measurement	ITT
EF_TAF	9	Analysis of Change from Baseline Average Intraocular Pressure Diurnal measurement	Per Protocol

EF_TAG	10	Summary of Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group – Subjects with High Baseline IOP	ITT
EF_TAH	11	Summary of Change from Baseline Average Intraocular Pressure Diurnal Measurement by Treatment Group – Subjects with Low Baseline IOP	Per Protocol
EF_TAI	12	Summary of Change form Baseline Intraocular Pressure Diurnal Measurements by Treatment Group and Time	ITT
EF_TAJ	13	Summary of Percent Change from Baseline Intraocular Pressure Diurnal Measurements by Treatment Group and Time	ITT
EF_TAK	14	Analysis of Change from Baseline Intraocular Pressure Diurnal Measurements by Treatment Group and Time	ITT
EF_TAL	15	Summary of Change from Baseline Intraocular Pressure at 8 AM by Treatment Group and Visit	ITT
EF_TAM	16	Summary of Percent Change from Baseline Intraocular Pressure at 8 AM by Treatment Group and Visit	ITT
EF_TAN	17	Analysis of Change from Baseline Intraocular Pressure at 8 AM by Treatment Group and Time	ITT
EF_TAO	18	Analysis of Change from Baseline Average Intraocular Pressure Diurnal measurement for Study Eye vs Non-Study Eye	ITT
EF_TAP	19	Analysis of Change from Baseline Intraocular Pressure	ITT

		Diurnal Measurements by Treatment Group and Time for Study Eye vs Non-Study Eye	
EF_TAQ	20	Analysis of Change from Baseline Intraocular Pressure at 8 AM by Treatment Group and Time for Study Eye vs Non-Study Eye	ITT
AE_TAA	21	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term – Study Eye	Safety
AE_TAA2	22	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term – Non-Study Eye	Safety
AE_TAA3	23	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class, and Preferred Term – Non-Ophthalmic Adverse Events	Safety
AE_TAB	24	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class and Preferred Term for Study Days 1-7 – Study Eye	Safety
AE_TAB2	25	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class and Preferred Term for Study Days 1-7 – Non-Study Eye	Safety
AE_TAC	26	Number and Percentage of Subjects with Treatment	Safety

		Emergent Adverse Events by Treatment Group, System Organ Class and Preferred Term for Study Days 19-25 – Study Eye	
AE_TAC2	27	Number and Percentage of Subjects with Treatment Emergent Adverse Events by Treatment Group, System Organ Class and Preferred Term for Study Days 19-25 – Non-Study Eye	Safety
AE_TAD	28	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity – Study Eye	Safety
AE_TAD2	29	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity – Non-Study Eye	Safety
AE_TAD3	30	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity – Non-Ophthalmic Adverse Events	Safety
AE_TAE	31	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity for Study Days 1-7 – Study Eye	Safety
AE_TAE2	32	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity for Study Days 1-7 – Non-	Safety

		Study Eye	
AE_TAF	33	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity for Study Days 19-25 – Study Eye	Safety
AE_TAF2	34	Number and Percentage of Subjects with Adverse Events by Treatment Group, System Organ Class, Preferred Term and Severity for Study Days 19-25 – Non-Study Eye	Safety
AE_TAG	35	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group, System Organ Class, Preferred Term and Relationship to Study Treatment – Study Eye	Safety
AE_TAG2	36	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group, System Organ Class, Preferred Term and Relationship to Study Treatment – Non-Study Eye	Safety
AE_TAG3	37	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group, System Organ Class, Preferred Term and Relationship to Study Treatment – Non-Ophthalmic Adverse Events	Safety
AE_TAH	38	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group System Organ Class, Preferred Term and Relationship to Study Treatment for Study Days 1-	Safety

		7 – Study Eye	
AE_TAH2	39	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group System Organ Class, Preferred Term and Relationship to Study Treatment for Study Days 1-7 – Non-Study Eye	Safety
AE_TAI	40	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group System Organ Class, Preferred Term and Relationship to Study Treatment for Study Days 19-25 – Study Eye	Safety
AE_TAI2	41	Number and Percentage of Subjects with Treatment-Related Adverse Events by Treatment Group System Organ Class, Preferred Term and Relationship to Study Treatment for Study Days 19-25 – Non-Study Eye	Safety
VS_TAA	42	Mean and Mean Change from Baseline in Vital Sign Values by Treatment Group and Visit	Safety
LB_TAA	43	Mean and Mean Change from Baseline in Blood Chemistry Values by Treatment Group and Visit	Safety
LB_TAB	44	Mean and Mean Change from Baseline in Hematology Values by Treatment Group and Visit	Safety
LB_TAC	45	Mean and Mean Change from Baseline in Continuous Urinalysis Values by Treatment Group and Visit	Safety
LB_TAD	46	Summary of Categorical	Safety

		Urinalysis Values: Shift from Baseline to Each Visit by Treatment Group	
CT_TAA	47	Mean and Mean Change from Baseline in Corneal Thickness by Treatment Group and Visit	Safety
EC_TAA	48	Mean and Mean Change from Baseline in Endothelial Cell Count by Treatment Group and Visit	Safety
SL_TAA	49	Summary of Change from Baseline in Hyperemia Score by Treatment Group and Visit	Safety
SL_TAB	50	Shift from Baseline in Slit Lamp Biomicroscopy by Visit and Treatment Group	Safety
DF_TAA	51	Shift from Baseline in Dilated Fundus Exam Finding to Each Visit by Treatment Group	Safety
VF_TAA	5	Shift from Baseline in Visual Field to Each Visit by Treatment Group	Safety
VA_TAA	53	Mean and Mean Change from Baseline in Visual Acuity (EDTRS Letters Missed)) by Treatment Group and Visit	Safety
VA_TAB	54	Proportion of Subjects with 3 or More Lines Lost by Treatment Group	Safety
PM_TAA	55	Mean and Mean Change from Baseline in Pupil Measurement by Treatment Group and Visit	Safety
PK_TAA	56	Summary of Pharmacokinetics and Implant Information by Treatment Group	Safety

12. LIST OF PLANNED DATA LISTINGS

Listing No.	Title
1	Subject Disposition
2	Protocol Deviations
3	Demographics
4	Baseline Clinical Characteristics
5	Intraocular Pressure Measurement
6	Travoprost Implant Exposure
7	Adverse Events
8	Hematology Results
9	Chemistry Results
10	Urinalysis Results
11	Vital Signs
12	Physical Examinations
13	Pachymetry
14	Visual Acuity
15	Endothelial Cell Count and Morphology
16	Slit Lamp Biomicroscopy
17	Pupil Measurements
18	Dilated Fundus Examination
19	Visual Field
20	Anterior Segment
21	Goinoscopy
22	Pharmacokinetics

13. APPENDICES

13.1 Schedule of Events

Procedure	Screening V1 Day -35 to -28	Baseline V2 -7 to -1 Days	Randomization/ Treatment V3 Day 1	Treatment V4 Day 3 +/- 1 day	Treatment V5 Day 7 +/- 1 day	Treatment V6 Day 14 +/- 1 day	Treatment V7 Day 21 +/- 1 day	Treatment V8 Day 25 +/- 1 day	Su D
Informed consent review	X								
Demographics/ medical & ocular history	X								
Concomitant medication query	X	X	X	X	X	X	X	X	
Adverse events query	X	X	X	X	X	X	X	X	
BCVA – (ETDRS)	X	X	X	X	X	X	X	X	
Pupil measurement	X	X				X		X	
Slit-lamp biomicroscopy	X	X	X	X	X	X	X	X	
Corneal staining	X	X	X	X	X	X	X	X	
IOP check (8:00 a.m.)	X	X	X	X	X	X	X	X	
Gonioscopy	X	X		X		X	X	X	
Pachymetry (contact)	X	X				X		X	
Specular microscopy (non-contact)	X[1]	X				X		X	
Visual field	X								
Anterior segment OCT	X	X		X		X		X	
IOP diurnal curve		X[2]						X[2]	
Dilated fundus exam	X	X				X		X	
Physical exam	X	X							

Procedure	Screening V1 Day -35 to -28	Baseline V2 -7 to -1 Days	Randomization/ Treatment V3 Day 1	Treatment V4 Day 3 +/- 1 day	Treatment V5 Day 7 +/- 1 day	Treatment V6 Day 14 +/- 1 day	Treatment V7 Day 21 +/- 1 day	Treatment V8 Day 25 +/- 1 day	Su D
Vitals	X	X							
Lab tests	X	X[3]				X[3]			
Pregnancy test	X	X	X						
Study drug administration			X						
Cataract surgery									
Aqueous humor collection									
Implant recovery									
Dispense TRAVATAN Z			X						
Collect TRAVATAN Z								X	
Receive pre-surgical medications								X	
Dismiss subject, complete exit form									

1 Non-contact specular microscopy can be performed anytime during the site visit.
2 IOP will be measured at 8 a.m., 10 a.m., and 4 p.m. for the diurnal curve endpoint.
3 Blood draws will be conducted prior to the daily administration of the TRAVATAN Z into the non-study eye. Samples col additionally be used to determine the systemic exposure to travoprost as described in Section **Error! Reference source no Reference source not found.** of the protocol.

13.2 SAS Code

Below is an example of SAS code to be used for examining whether the treatment effect for the control (TRAVATAN Z) is non-zero.

```
Proc mixed data=dset;

Where eye=study eye;

By timepoint;

Class treatment;

Model IOPChange=treatment baseline;

Lsmeans treatment /cl;

Run;
```

STATISTICAL ANALYSIS PLAN
January 21, 2019

A Multi-Center, Three-Stage, Open-Label, Prospective, Active-Comparator-Controlled Phase 2a Study of ENV515 (travoprost) Intracameral Implant in Patients with Bilateral Ocular Hypertension or Early Primary Open Angle Glaucoma

PROTOCOL NUMBER ENV515-01

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LIST OF ABBREVIATIONS

AE	adverse event
CSR	clinical study report
ETDRS	Early Treatment Diabetic Retinopathy Study
IND	Investigational New Drug Application
IOP	intraocular pressure
MedDRA	Medical Dictionary for Regulatory Activities
NSE	non-study eye
SAP	statistical analysis plan
SD	standard deviation
SE	study eye
VA	visual acuity

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) contains detailed information to aid in the implementation of the statistical analysis and reporting of the study data for use in the abbreviated clinical study report (CSR). An abbreviated CSR is being created because the Investigational New Drug Application (IND) is being withdrawn. This SAP will address the analysis for Cohorts 2 and 3 of the study. A separate SAP was created for Cohort 1.

2. PROTOCOL SUMMARY

ENV515-01 is a multicenter, open-label, prospective, active-comparator-controlled Phase 2a study of ENV515 (travoprost) Intracameral Implant comprising three stages:

- The completed Cohort 1 was a 28-day study focused on evaluation of the initial safety, efficacy, and pharmacokinetic properties of ENV515 conducted in glaucoma patients scheduled for cataract removal during which the ENV515 implant is removed during the cataract procedure 28 days after implantation. This cohort was covered in a separate SAP and no further mention of this cohort will be made in this SAP.

- Cohort 2 is a 12-month study with a 6-month optional Extension 1 followed by an additional 3-month optional Extension 2 (for a total of up to 21 months) that is focused on evaluation of the long-term safety and efficacy in glaucoma patients during which the two ENV515-3 implants are followed through their biodissolution while the duration of intraocular pressure (IOP)-lowering efficacy is assessed.

- Cohort 3 is a 12-month study with a 6-month optional Extension 1 followed by an additional 6-month optional Extension 2 (for a total of up to 24 months) that is focused on evaluation of the long-term safety in glaucoma patients during which one or two ENV515-3-2 implants per study eye are followed through their biodissolution.

2.1 Study Objectives

Evaluate in a dose-escalating design the long-term safety and tolerability of a single, unilateral low dose of two ENV515-3 (travoprost) intracameral implants/eye in Cohort 2; and low and high doses of one and two ENV515-3-2 (travoprost) intracameral implants/eye, respectively, in Cohort 3 in patients with bilateral ocular hypertension or primary open-angle glaucoma.

2.2 Overall Study Design and Plan

Cohorts 2 (5 patients) and 3 (15 patients) are 12-month, prospective, open-label, active-comparator-controlled, multicenter, dose-escalating cohorts of this Phase 2a trial. Cohort 2 had a 6-month optional Extension 1 followed by an additional 3-month optional Extension 2 (for up to a total of 21 months), increasing the total study duration to approximately 23 months. Cohort 3 has a 6-month optional Extension 1 followed by an additional 6-month optional Extension 2 (for a total of 24 months), increasing the total study duration to approximately 26 months. Cohorts 2 and 3 were designed to assess the long-term safety, tolerability, and systemic exposure to travoprost after a single low dose (ENV515-3) in Cohort 2, and single low or high doses (ENV515-3-2) in Cohort 3 in

patients with bilateral open-angle glaucoma or ocular hypertension (see Inclusion Criteria in Section 11.1 of the protocol). For the purposes of the Cohorts 2 and 3, patients are eligible if in the opinion of the investigator they have an IOP in both eyes that is considered to be adequately controlled at the screening visit, can be safely withdrawn from IOP medications in both eyes during the washout period, and are not considered to be at significant risk for disease progression throughout the trial. The dose levels of travoprost in Cohorts 2 and 3 of this study are achieved by administration of a single, unilateral intracameral injection of each formulation with 28.2 µg travoprost/eye in Cohort 2; and 26.1 µg and 52.2 µg travoprost/eye in Cohort 3. These dose levels will be achieved via two implants per eye for low dose of ENV515-3 in Cohort 2, and one and two implants per eye for the low and high doses of ENV515-3-2, respectively, in Cohort 3. The study eye is prospectively defined as the eye with higher IOP or the left eye if IOP values are equal in both eyes on Dosing Visit (Day 1). All non-study eyes will receive open-label timolol maleate 0.5% ophthalmic solution administered twice a day (Figure 1 and Figure 2).

Figure 1: ENV515 Treatment, Cohort 2

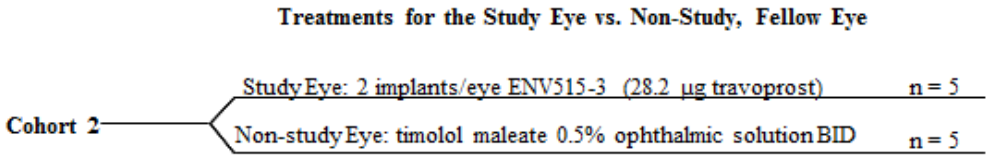
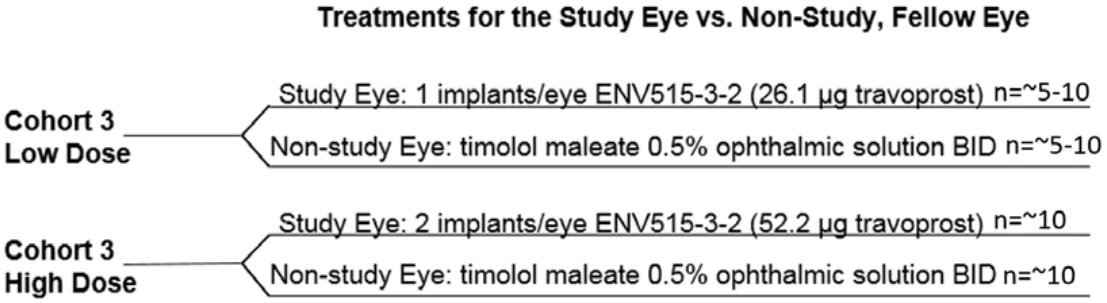
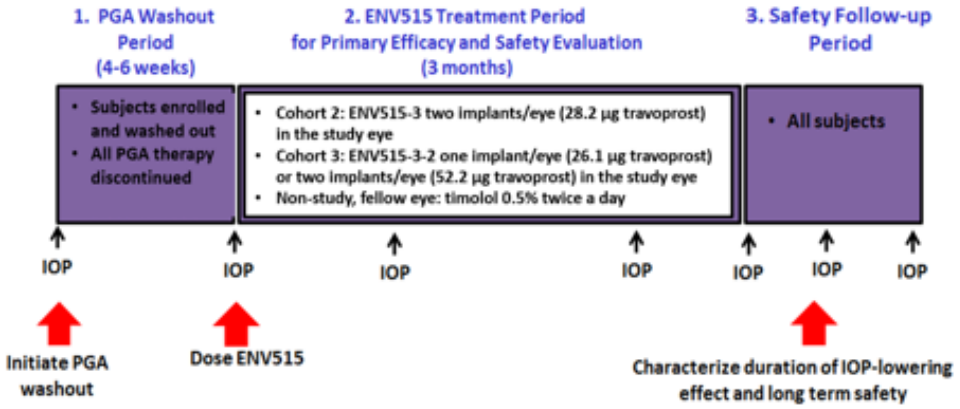


Figure 2: ENV515 Treatment, Cohort 3



On the Day 1 Dosing (Visit 3), low dose of ENV515-3 in Cohort 2, or low or high doses of ENV515-3-2 in Cohort 3 will be administered. Following the completion of the rest of the study treatment period Month 4 (Visit 8) to Exit/Early Exit (Visit 16, Visit 22, or Visit 25) for the Cohort 2 alone, all safety and tolerability analyses will be conducted (Figure 3).

Figure 3: Study Design for ENV515-01 (Cohorts 2 and 3)



For Cohort 2, the study design included up to 26 clinic visits over approximately 23 months (12 months of Cohort 2, 6-month optional Extension 1, and 3-month optional Extension 2). For Cohort 3, the study design includes up to 28 clinic visits over approximately 26 months (12 months of Cohort 3, 6-month optional Extension 1, and 6-month optional Extension 2). Following the Screening Visit, patients will be required to washout current glaucoma medication(s) for 4 weeks with up to an additional 2-week extension or 6 weeks depending on Cohort. Patients will be required to return for an IOP baseline check during the Baseline Visit (Visit 2/Day -7 to -1) following the wash-out period. A single dose of ENV515-3 (two implants/eye) or ENV515-3-2 (one or two implant(s)/eye) will be given via intracameral injection during Dosing Visit 3/Day 1.

Diurnal IOP curves will be measured at select study visits with the exception of the abbreviated visits at the Screening Visit (Days -49 to -442 for Cohort 2 and Days -56 to -42 for Cohort 3), Dosing Visit 3 (Day 1), Treatment Visit 4 (Day 2), Treatment Visit 5a (Day 28), and selected visits depending on the cohort and extensions(s).

2.3 Study Population

This study enrolled subjects between 18 and 85 years of age with a diagnosis of bilateral ocular hypertension or primary open-angle glaucoma. For additional information on inclusion and exclusion criteria, see Section 11 of the protocol.

2.4 Treatment Regimens

Patients will receive the following investigational product doses in the study eye on Day 1 Dosing (Visit 3) and will receive timolol maleate 0.5% ophthalmic solution to use in the nonstudy eye twice daily starting on the evening of Day 1 and continuing through the day prior to Month 12 (Visit 16), Month 18 (Visit 22), or Month 21 (Visit 25) for Cohort 2 or Month 24 (Visit 28) for Cohort 3.

- Cohort 2 low dose level: two implants/eye of ENV515-3 (28.2 µg/eye)
- Cohort 3 low and high dose levels:
    - One implant/eye of ENV515-3-2 (26.1 µg/eye)
    - Two implants/eye of ENV515-3-2 (52.2 µg/eye)

2.5 Treatment Group Assignments or Randomization

No randomization was conducted as these are open-label cohorts.

2.6 Sample Size Determination

Since this trial is primarily a dose-finding safety and tolerability study and the first study of the full duration of IOP-lowering effect of ENV515-3 for Cohort 2, sample size estimation was not performed. This study will enroll 5 patients in a single arm for Cohort 2, and 15 patients in Cohort 3.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied for this study.

- Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)". To ensure completeness, summaries for categorical and discrete variables will include all categories, even if no subjects had a response in a particular category.
- Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean and median will be reported to one more level of precision than the original observations, and the SD will be reported to 2 more levels of precision than the original observations. The minimum and maximum will be the same precision as the original data.
- All analyses will be performed using SAS® System version 9.4 or higher.
- Dates will be displayed as ddmmmyyyy (e.g., 24Jan2005).

Patient-level analyses will be presented with the following columns:

Cohort 2	Low Dose Cohort 3	High Dose Cohort 3
2 implants ENV515-3 (28.2 µg travoprost)	1 implant ENV515-3-2 (26.1 µg travoprost)	2 implants ENV515-3-2 (52.2 µg travoprost)

Eye-level analyses will be presented with the following columns:

Cohort 2		Low Dose Cohort 3		High Dose Cohort 3	
2 implants ENV515-3 (28.2 µg travoprost)		1 implant ENV515-3-2 (26.1 µg travoprost)		2 implants ENV515-3-2 (52.2 µg travoprost)	
ENV515-3 SE	Timolol maleate 0.5% NSE	ENV515-3 SE	Timolol maleate 0.5% NSE	ENV515-3 SE	Timolol maleate 0.5% NSE

Note: SE=study eye, NSE=non-study eye

4. ANALYSIS POPULATIONS

The safety population will be defined as any patient receiving at least one dose of study medication in the study. The safety population will be used for all analyses.

5. STUDY PATIENTS

5.1 Disposition of Patients

The disposition of subjects will be summarized for all subjects enrolled in Cohorts 2 and 3. The number and percentage of subjects in the safety population, the number and percentage of subjects who complete the study, as well as the number and percentage that discontinue the study and the reasons for study discontinuation will be summarized by cohort dose.

5.2 Protocol Deviations

All protocol deviations will be reported in listings. Protocol deviations will be defined prior to locking the database.

5.3 Medical History

All medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and presented in listings.

5.4 Prior and Concomitant Medications

All prior and concomitant medications will coded using WHO Drug Enhanced version 2016.01 and be presented in listings.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Age, gender, race, ethnicity, and iris color will be summarized by cohort dose. All demographics data will be presented in subject listings.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

In this study, the principal investigator administers the investigational treatment into the study eye on the day of randomization. As a result, compliance with the investigational product will be 100%. Compliance information will not be collected for the active control.

8. EFFICACY EVALUATION

8.1 Primary Efficacy Analysis

The primary efficacy endpoint for this study is the change from baseline in time-matched IOP measurements for the study and non-study eye. Intraocular pressure is collected at 8 am. Values for IOP and change from baseline will be summarized by visit and time, cohort dose group, and eye as specified in Section 3. Baseline will be defined as the last IOP measurement prior to implantation and will be time-matched. No formal statistical testing will be done.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

Adverse events, clinical laboratory results, vital signs, and physical exam findings will be tabulated at the subject level. All other safety measurements will be made at the eye level. Unless otherwise noted, baseline will be defined as the last measurement prior to receiving the implant.

9.2 Extent of Exposure

The number of days from implant insertion to implant dissolution or removal will be summarized descriptive statistics. All other exposure data will be available in subject listings. Exposure will be calculated only for the study eye. No exposure information for the TRAVATAN Z eye will be collected.

9.3 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and categorized by system organ class using preferred terms. Events will be tabulated overall and by ocular/non-ocular status. Treatment related adverse events and severe adverse event will also be summarized. Serious adverse events will be summarized.

9.4 Clinical Laboratory Evaluation

Continuous clinical laboratory values will be summarized using descriptive statistics for reported and change from baseline values. Baseline will be the last measurement prior to implantation. Categorical clinical laboratory values will display the frequencies of patients with abnormal and normal results.

9.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.5.1 Vital Signs

Vital sign assessments include measurements of heart rate, blood pressure, and respiration rate. Vital signs will be summarized using descriptive statistics by study visit and treatment group. All vital sign data will be presented in subject listings.

9.5.2 Physical Examinations

All physical examination data will be presented in listings.

9.5.3 Visual Acuity (VA)

Visual acuity will be measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart according to the manufacturer's specifications. The number of letters missed will be collected and summarized by cohort group and eye for each visit. Visual acuity data, including best corrected distance, will be presented in subject listings.

9.5.4 Other Safety Parameters

Safety data were also collected for anterior chamber optical coherence tomography, gonioscopy, specular microscopy, corneal thickness, endothelial cell count and morphology, slit lamp biomicroscopy exam findings, corneal staining, binocular indirect ophthalmoscopy, visual field assessment, and pupil measurements. These data will be presented in data listings.

10. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

This analysis plan is for an abbreviated CSR. Therefore, the primary endpoint will be summarized, but no formal statistical testing will be done. There will be no summaries for secondary endpoints. The planned summaries in the protocol for changes in corneal thickness, VA, endothelial cell count and morphology, slit lamp biomicroscopy exam findings, binocular indirect ophthalmoscopy, visual field assessment, anterior segment photos, and pupil measurement will not be created. These data will instead be available in listings.

11. LIST OF PLANNED TABLES

Rho Table Identifier	Table No.	Title	Population
DS-TAA	14.1.1	Disposition	Safety
DM-TAA	14.1.2	Demographics	Safety
EF-TAA	14.2.1	Summary of Intraocular Pressure by Visit and Time Point	Safety
AE-TAA	14.3.1.1	Summary of Adverse Events	Safety
AE-TAB	14.3.1.2	Summary of Adverse Events by System Organ Class and Preferred Term	Safety
AE-TAC	14.3.1.3	Summary of Ocular Adverse Events by System Organ Class and Preferred Term	Safety
AE-TAD	14.3.1.4	Summary of Related Adverse Events	Safety
AE-TAE	14.3.1.5	Summary of Severe Adverse Events	Safety
AE-TAF	14.3.1.6	Summary of Serious Adverse Events	Safety
LB-TAA	14.3.2.1	Summary of Chemistry by Visit	Safety
LB-TAB	14.3.2.2	Summary of Hematology by Visit	Safety
LB-TAC	14.3.2.3	Summary of Urinalysis by Visit	Safety
VS-TAA	14.3.3.1	Summary of Vital Signs by Visit	Safety
VA-TAA	14.3.4.1	Summary of Visual Acuity	Safety
EX-TAA	14.3.5.1	Summary of Exposure	Safety

12. LIST OF PLANNED DATA LISTINGS

Listing No.	Title
16.1.1	Disposition
16.1.2	Demographics
16.1.3	Protocol Deviations
16.1.4	Prior and Concomitant Medications
16.1.5	Medical History
16.2.1	Intraocular Pressure
16.3.1	Adverse Events
16.3.2.1	Chemistry
16.3.2.2	Hematology
163.2.3	Urinalysis
16.3.3	Vital Signs
16.3.4.1	Visual Acuity
16.3.4.2	Endothelial Cell Count and Morphology
16.3.4.3	Slit Lamp Biomicroscopy
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16.3.4.9	Specular Microscopy
16.3.4.10	Corneal Thickness
16.3.4.11	Pupil Measurements
16.4.5	Exposure