Statistical Analysis Plan Cover Page

Official Study Title:	A Phase I/II, Open-label, Dose-escalating, Sequential-cohort Study Assessing the Safety, Tolerability, Immunogenicity, and Bioactivity of a Single Intravitreal Injection of DE-122 Injectable Solution for the Treatment of Refractory Exudative Age-related Macular Degeneration- PAVE Study
NCT Number:	NCT02555306
Date of the document:	August 09, 2017

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase I/II, Open-label, Dose-escalating, Sequential-cohort Study Assessing the Safety, Tolerability, Immunogenicity, and Bioactivity of a Single Intravitreal Injection of DE-122 Injectable Solution for the Treatment of Refractory Exudative Age-related Macular Degeneration- PAVE Study
Product:	0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg DE-122 injectable solutions
Protocol Number:	36-001
Sponsor:	Santen Inc. 2100 Powell Street, 16th floor Emeryville, CA 94608 U.S.A.
Date:	August 09, 2017
Status:	Version 2.1

CONFIDENTIAL

APPROVAL SIGN-OFF SHEET

A Phase I/II, Open-label, Dose-escalating, Sequential-cohort Study Assessing the Safety, Tolerability, Immunogenicity, and Bioactivity of a Single Intravitreal Injection of DE-122 Injectable Solution for the Treatment of Refractory Exudative Age-related Macular Degeneration- PAVE Study

DE-122 Study 36-001

TABLE OF CONTENTS

ABBREVIATIONS 1
1. INTRODUCTION 3
2. STUDY OBJECTIVE 4
2.1. Primary Objective and Endpoints 4
2.2. Secondary Objective and Endpoints 4
3. STUDY DESIGN 5
3.1. General Study Design 5
3.2. Randomization and Masking 5
3.3. Sample Size Planning 5
3.4. Visits and Assessments 5
4. DEFINTIONS 8
4.1. Time-Related Terms 8
4.1.1. Baseline Visit 8
4.1.2. Study Day 8
4.1.3. Out-of-Window Measurements and Analysis Window 8
4.1.4. Analysis Visit and Analysis Timepoint 8
4.2. Endpoint-Related Definitions 8
4.2.1. Study Eye and Fellow Eye 8
4.2.2. Baseline Score 9
4.2.3. Change from Baseline 9
4.2.4. Change after Injection 9
4.3. Safety-Related Definitions 9
4.3.1. Adverse Event 9
4.3.1.1. Severity of Adverse Event 9
4.3.1.2. Serious Adverse Event 9
4.3.1.3. Ocular Adverse Event 10
4.3.1.4. Adverse Drug Reaction 10
4.3.1.5. Events of Special Interest 10
4.3.2. Safety Measures 10
4.4. Other Definitions 11
4.4.1. Bioactivity Measures 11

4.4.2. Immunogenicity 11
4.4.3. Biomarker 11
5. STUDY POPULATION 12
5.1. Intention-to-Treat Population 12
6. GENERAL CONSIDERATIONS 13
6.1. Adjustments for Covariates 13
6.2. Handling of Missing Data 13
6.3. Multi-Center Studies 13
6.4. Multiple Comparisons / Multiplicity 14
6.5. Interim Analysis 14
7. SUMMARY OF STUDY POPULATION DATA 15
7.1. Subject Disposition 15
7.2. Demographics and Baseline Characteristics 15
7.3. Medical and Surgical History 15
7.4. Protocol Deviations 15
7.5. Prior and Concomitant Medications 15
8. SAFETY ANALYSES 17
8.1. Adverse Event 17
8.2. Best Corrected Visual Acuity 17
8.3. Slit-lamp Biomicroscopy 17
8.3.1. Iris 17
8.3.2. Lens 17
8.4. Intraocular Pressure 17
8.5. Ophthalmoscopy 18
8.6. Laboratory Assessments 18
8.7. Vital Signs 18
9. BIOACTIVITY ANALYSES 19
10. BIOMARKER ANALYSES 19
11. IMMUNOGENICITY 19
12. REFERENCES 19

LIST OF TABLES

Table 1: Schedule of Events 7
Table 2: Safety Measures 10

LIST OF FIGURES

Figure 1: Study Design Diagram 6

ABBREVIATIONS

ADaM	Analysis Data Model
ADR(s)	Adverse Drug Reaction(s)
AE(s)	adverse event(s)
AMD	age-related macular degeneration
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the curve
BCVA	best corrected visual acuity
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CSR	clinical study report
CST	central subfield thickness
eCRF	electronic Case Report Form
EKG	electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
ESI(s)	event(s) of special interest
FDA	Food and Drug Administration
IOP	intraocular pressure
ITT	intention-to-treat
LOCF	last-observation-carried-forward
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
µg/mL	microgram per milliliter
mm	millimeter
mmHg	millimeters of mercury
µm	micrometer
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)
PK	pharmacokinetic/pharmacokinetics
SADR(s)	serious adverse drug reactions(s)

ABBREVIATIONS (Continued)

SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD-OCT	spectral-domain optical coherence tomography
SDTM	Study Data Tabulation Model
SOC	system organ classification
US	United States
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope of Santen's Protocol 36-001, "A Phase I/II, Open-label, Dose-escalating, Sequential-cohort Study Assessing the Safety, Tolerability, Immunogenicity, and Bioactivity of a Single Intravitreal Injection of DE-122 Injectable Solution for the Treatment of Refractory Exudative Age-related Macular Degeneration- PAVE Study ". It applies to the study protocol dated 30 June 2016 and provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

2. STUDY OBJECTIVE

2.1. Primary Objective and Endpoints

The primary objective is:

- To assess the safety and tolerability of a single intravitreal injection of four dose levels of DE-122 (0.5 mg/eye, 1.0 mg/eye, 2.0 mg/eye and 4.0 mg/eye) in subjects with refractory exudative age related macular degeneration.

The safety and tolerability of DE-122 will be assessed by

- adverse events (AEs)
- indirect ophthalmoscopy
- best-corrected visual acuity (BCVA)
- slit-lamp biomicroscopy
- intraocular pressure (IOP)
- fundus photography
- fluorescein angiography
- serum chemistry
- hematology
- urinalysis
- physical exam
- electrocardiogram (EKG)
- pregnancy test
- vital signs

Section 4.3.2 gives a detailed description of the safety measures to be collected in this study.

2.2. Secondary Objective and Endpoints

The secondary objective is to evaluate the bioactivity of four dose levels of DE-122 in subjects with refractory exudative age-related macular degeneration.

The bioactivity of DE-122 on resolution of fluid will be assessed using the change in CST based on SD-OCT at each visit post DE-122 treatment as compared to baseline (change in response to anti-VEGF treatment given before Visit 1 (Day 1)).

3. STUDY DESIGN

3.1. General Study Design

This is an open-label, dose-escalating, sequential-cohort study assessing the safety, tolerability, immunogenicity, and bioactivity of a single intravitreal injection of 0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg DE-122 administered in approximately 12 subjects with refractory exudative age-related macular degeneration (AMD). It employs a dose-escalation design to study four cohorts of subjects as shown in the Study Design Diagram (Figure 1).

Four cohorts of subjects each will receive a single intravitreal injection of DE-122 in the study eye. Decisions regarding dose escalation in the next cohort will be based on the recommendations of the Safety Review Team consisting of an external Retina Specialist, the Medical Monitor, and the Drug Safety specialist. Dose-Limiting Toxicity response observed in any cohort will result in termination of the dose escalation.

3.2. Randomization and Masking

This is an open-label cohort study. Randomization is not employed in this study due to the dose-escalation design.

3.3. Sample Size Planning

Approximately 12 subjects (2 or 3 subjects in Cohort 1; 3 subjects in Cohorts 2, 3, and 4) with refractory exudative age related macular degeneration will be enrolled at 5 sites. The final number of subjects enrolled may be adjusted based on the presence of dose limiting toxicities

This sample size is not planned based on statistical considerations.

3.4. Visits and Assessments

Assessments at each visit and visit windows are specified in the Schedule of Event (Table 1).

Figure 1: Study Design Diagram

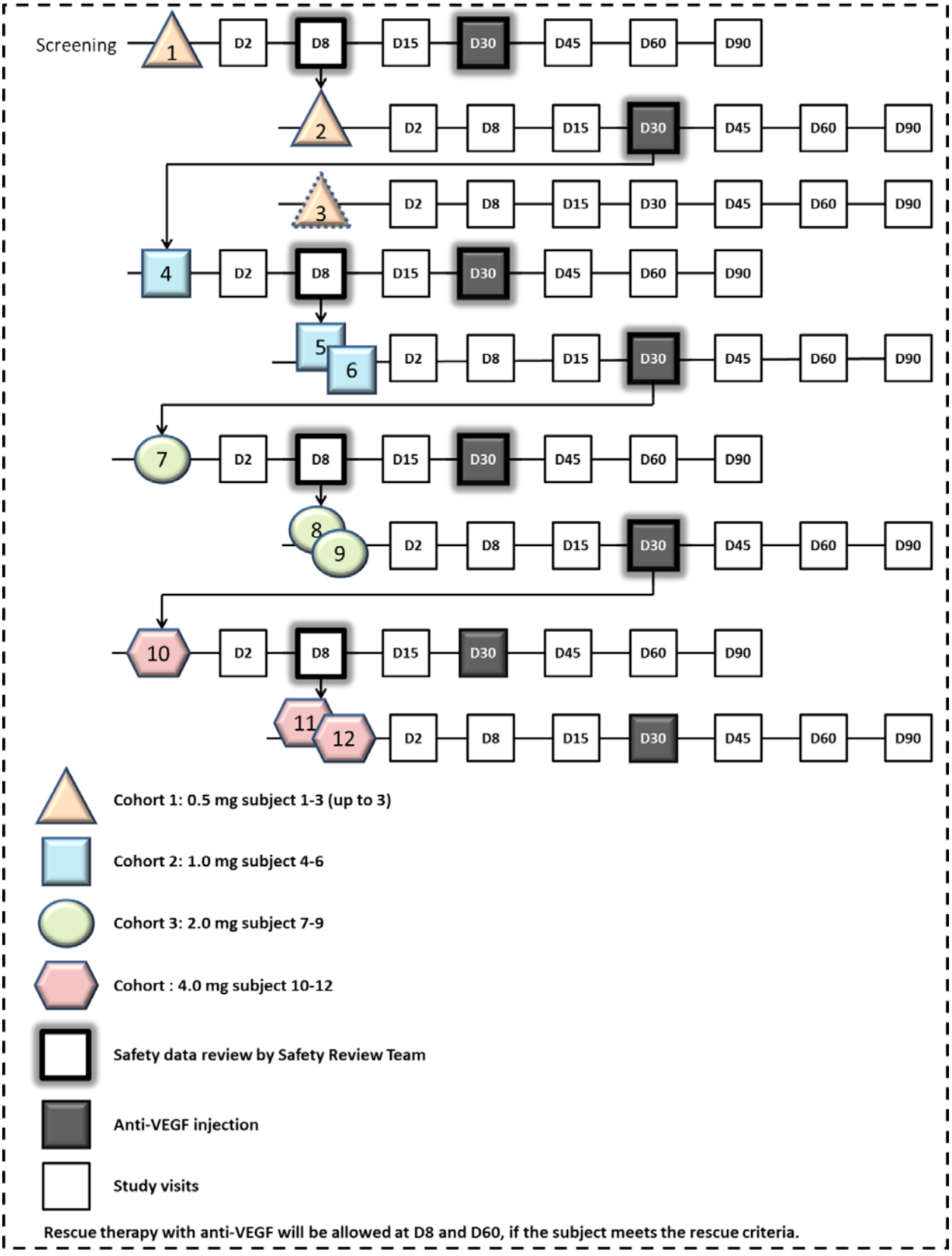

Table 1: Schedule of Events

Visit Number	Visit 0 (SCRN)	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8 /Exit
Visit Schedule (Time window; days)	D-7 to -1	D1		D2	D8 (±1)	D15 (±2)	D30 (±2)	D45 (±3)	D60 (±3)	D90 (±3)
		Pre	Post							
Informed consent[a]	X									
Demographics/Eligibility	X	X								
Medical/surgical history, Concomitant medication	X	X		X	X	X	X	X	X	X
Physical exam	X									X
Vital signs	X	X		X	X	X	X	X	X	X
EKG	X				X		X			X
BCVA (ETDRS)	X	X		X	X	X	X	X	X	X
Slit-lamp biomicroscopy[b]	X	X	X	X	X	X	X	X	X	X
Intraocular pressure[c]	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[b]	X	X	X	X	X	X	X	X	X	X
SD-OCT	X	X		X	X	X	X	X	X	X
Fundus photography	X						X		X	X
Fluorescein angiography	X						X		X	X
Urine pregnancy test[d]							X		X	
Urinalysis[e]	X				X		X			X
Serum pregnancy test[d]	X									X
Hematology, chemistry serum sample[e]	X				X		X			X
Immunogenicity serum sample		X					X			
Biomarker serum sample[f]		X		X	X		X			X
DE-122 IVT Injection		X								
Rescue with anti-VEGF Injection[g]					(X)				(X)	
Anti-VEGF Injection[h]							X			
Adverse events		X	X	X	X	X	X	X	X	X

a. Informed Consent Form - obtain prior to conducting any study-related activities.
b. Slit-lamp biomicroscopy and indirect ophthalmoscopy will be performed prior to DE-122 or anti-VEGF intravitreal injection and within 30 minutes after injection.
c. IOP will be performed before DE-122 or anti-VEGF Intravitreal injection and 40±10 minutes after injection. If IOP is increased ≥ 10 mmHg, repeat IOP measurement 60±10 minutes after the injection.
d. Serum and urine pregnancy tests are to be performed on all women of child-bearing potential.
e. Collect fasting urine and blood specimen.
f. Biomarker serum sample will be collected from the subjects in Cohorts 3 and 4.
g. If subjects meet the following rescue criteria at Visit 3 (Day 8±1) and/or at Visit 7 (Day 60±3): <5 letters gained from baseline BCVA or < 50 microns reduction from baseline CST as measured by SD-OCT.
h. Subjects who do not receive rescue therapy with anti-VEGF medication at Visit 3 (Day 8±1) will receive anti-VEGF treatment at Visit 5 (Day 30±2).

4. DEFINTIONS

4.1. Time-Related Terms

4.1.1. Baseline Visit

For this study, the *baseline visit* is the Day 1 visit when the injection of DE-122 is scheduled.

4.1.2. Study Day

The *study day* variable describes the relative day of the observation starting with the reference date as Day 1. In this study, the initial injection date (visit 1data) of the study medication is the reference day and the study day will be calculated as:

- For days prior to the injection date, Study Day = Date – Injection Date
- For days on/after the injection date, Study Day = Date – Injection Date + 1

Note that there is no Study Day 0.

4.1.3. Out-of-Window Measurements and Analysis Window

A measurement collected at a visit is an *out-of-window* measurement if the study day of the visit falls outside of a visit window specified in Table 1, or a *within-window* measurement otherwise.

If there are many *out-of-window* measurements for a visit, then a window wider than the specified visit window may be defined for analysis purposes to minimize missing data. Such wider windows for analysis (i.e., *analysis windows*), if needed, will be determined by the Medical Monitor and the Study Statistician based on the review of all *out-of-window* measurements before the database lock.

For analyses involving post-baseline visits, if there are two or more measurements that fall into the same analysis window of a post-baseline visit, then the measurement closest to the target assessment day will be selected for that visit. In the case that two measurements are closest and equidistant to the target assessment day, i.e., one is before and one is after the target assessment day, the later one will be selected for that visit.

4.1.4. Analysis Visit and Analysis Timepoint

Analysis visit and *analysis time point* are timing variables to be defined in the ADaM specifications document for analyses involving visits. Possible values of these timing variables may vary depending on which assessment is considered.

4.2. Endpoint-Related Definitions

4.2.1. Study Eye and Fellow Eye

The *study eye* of a subject is the eye with worse vision. It will be chosen by the Clinical Investigator at Day 1 (Baseline).

Fellow eye is the non-study eye.

4.2.2. Baseline Score

For any measure, the *baseline score* is the last observed measurement prior to the injection of study medication. For this study, the baseline score would be the measurement prior to the initial injection at baseline visit.

4.2.3. Change from Baseline

For any measure, the change from baseline at a post-baseline visit will be derived as:

Change from Baseline at a Post-Baseline Visit = (Score at the Post-Baseline Visit) – (Baseline Score).

For any measure assessed pre- and post-injection at Baseline, only the pre-injection score will be used to derive the change-from-baseline variable.

4.2.4. Change after Injection

For any measure assessed pre- and post-injection at Baseline, the change after injection will be derived as:

Change after Injection = Post-Injection Score – Pre-Injection Score.

The last pre-injection score and the first post-injection score will be used to derive the change after injection variable.

4.3. Safety-Related Definitions

4.3.1. Adverse Event

As defined in 21 CFR 312.32(a), an AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. AEs reported on the AE electronic Case Report Form (eCRF) will be assessed according to the recently amended FDA regulations 21 CFR Parts 312 and 320.

An AE will be considered as a treatment-emergent AE if the AE onset date is on or after the injection. In other words, an AE will not be counted as a treatment-emergent AE if it can be determined that the AE occurred prior to injection. For AE summaries, only the treatment-emergent AEs will be tabulated.

Each AE will be classified into a system organ classification (SOC) and coded to a preferred term using MedDRA Version 18.0.

4.3.1.1. Severity of Adverse Event

Each AE will be graded by the Clinical Investigator as Mild, Moderate, or Severe based on the criteria specified in Section 11.1.1.1 of the protocol.

4.3.1.2. Serious Adverse Event

An AE will be counted as a serious adverse event (SAE) if the Clinical Investigator answered "Yes" to the AE eCRF question "Is the adverse event serious?"

4.3.1.3. Ocular Adverse Event

An AE will be counted as an ocular AE if the Clinical Investigator selected "OD", "OS", or "OU" for "Event Location" on the AE eCRF.

4.3.1.4. Adverse Drug Reaction

An AE will be counted as an ADR if the Clinical Investigator answered "Related" to the AE eCRF question "Relationship to Study Drug?"

4.3.1.5. Events of Special Interest

Events of special interest (ESIs) such as pregnancy, study medication administration error and ocular telangiectasia and bleeding will be identified throughout the study.

4.3.2. Safety Measures

Table 2 below lists the safety measures to be evaluated in this study.

Table 2: Safety Measures

Safety Measure	Note
Best-corrected visual acuity	BCVA measures the acuteness or clearness of the best-corrected vision, with a range of [0, 97] in ETDRS letters. An increase in BCVA indicates an improvement in the best-corrected vision.
Slit-lamp biomicroscopy findings: lid Redness, lid edema, conjunctival hyperemia, conjunctival Edema, corneal edema, anterior chamber cells, anterior chamber flare	Anterior Chamber Cells will be graded as 0 = No cells, 0.5 = 1-5 cells, 1 = 6-15 cells, 2 = 16-25 cells, 3 = 26-50 cells, or 4 = >50 cells. Anterior Chamber Flare will be graded as 0 = None, 1 = Faint, 2 = Moderate, 3 = Marked, or 4 = Intense. The other six biomicroscopy parameters will be graded as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe.
Iris	The iris status of an eye will be graded as either Normal or Abnormal.
Lens description	The lens of an eye will be classified as phakic, aphakic, or pseudophakic.
Phakic lens severity score	The status of a phakic lens will be graded as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe.
Intraocular pressure	IOP, the fluid pressure inside the eye, is recorded in mmHg. The IOP of an eye is derived as the mean/median of two or three consecutive IOP measurements. In this study, the IOP increase of ≥ 10 mmHg from baseline needs to be reported as an AE.

Table 2: Safety Measures (Continued)

Indirect Ophthalmoscopy findings: *cup/disc ratio, retina, macula and choroid, vitreous*	Cup/disc ratio will be recorded with two decimal points (e.g., 0.80). Retina (including macular) and choroid will be graded as either Normal or Abnormal. Vitreous haze will be graded as: 0 = Clear, Trace or 0.5+ = Trace, 1+ = Few opacities, mild blurring, 2+ = Significant blurring but still visible, 3+ = Optic nerve visible, no vessels seen, and 4+ = Dense opacity obscures the optic nerve head.
Fundus Photography	Optic disc, Macula.
Fluorescein Angiography	Optic disc, Macula.
Laboratory assessments: *hematology, chemistry and urinalysis*	Refer to Section 21.4.15 of the protocol for the list of the minimum blood parameters and urine parameters.
Vital signs: *systolic blood pressure, diastolic blood pressure, heart rate*	For systolic blood pressure (mmHg), if two measurements collected at a visit differ by 5 mmHg or less, then the average of the two will be used as the recorded pressure; otherwise, a third measurement will be taken and the average of the three will be used as the recorded pressure. Same rules apply to diastolic blood pressure (mmHg). The average of the two (or three, if performed) heart rate measurements will be used as the recorded heart rate (beats per minute).

4.4. Other Definitions

4.4.1. Bioactivity Measures

Bioactivity measures in this study include CST (μm) and macular volume (mm^3) measured by SD-OCT. Bioactivity of DE-122 will be considered evident if a considerable decrease in CST or macular volume is observed.

4.4.2. Immunogenicity

ADA titer will be measured in serum samples collected at Visit 1 (Day 1) and Visit 5 (Day 30±2).

4.4.3. Biomarker

Serum samples will be collected in Cohorts 3 and 4, and measured for levels of endoglin-related proteins. Changes from baseline in levels of biomarkers will be summarized descriptively by dose level of DE-122.

5. STUDY POPULATION

5.1. Intention-to-Treat Population

The Intention-to-Treat (ITT) Population will include all subjects in the study.

6. GENERAL CONSIDERATIONS

Besides data listings, all measures will be summarized by dose level and/or overall. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, minimum, and maximum. Categorical variables will be tabulated using frequency (n), sometimes along with percentage (%). Percentages will not be displayed for summaries by dose level due to the small sample size.

All data manipulations and descriptive summaries will be implemented using SAS®, Version 9.3 or later.

6.1. Adjustments for Covariates

Covariate adjustments are not applicable to this study.

6.2. Handling of Missing Data

For safety measures, missing scores will not be imputed for data summaries.

For bioactivity measures, the last-observation-carried-forward (LOCF) approach may be used to impute missing post-injection values. However, baseline scores will not be carried forward.

Completely or partially missing onset and resolution dates of medical events including AEs will be conservatively imputed as follows:

Date	***Type of Missing Date***	***Handling of Missing Date***
Event onset date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied.
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the onset date
	YYYY and MM are available but DD is missing	Use the first day of MM to impute the missing date part of the onset date
Event resolution date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied.
	Only YYYY is available	Use the last day of YYYY to impute the missing month and date parts of the resolution date
	YYYY and MM are available but DD is missing	Use the last day of MM to impute the missing date part of the resolution date

Same rules will be followed to impute completely or partially missing start and end dates of non-study medications.

6.3. Multi-Center Studies

This is a multi-center study enrolling subjects from 5 US sites. No pooling algorithm will be applied.

6.4. Multiple Comparisons / Multiplicity

Multiplicity adjustment is not applicable to this study.

6.5. Interim Analysis

No formal interim analysis is planned for this study.

7. SUMMARY OF STUDY POPULATION DATA

Percentages will not be displayed for summaries by dose level due to the small sample size.

7.1. Subject Disposition

The subject disposition will be summarized by dose level and overall. The summary will include the number of subjects in the ITT Population, as well as the numbers and percentages of completers and non-completers.

7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for the ITT Population by dose level and overall. Specifically for subject demographics, the following variables will be summarized:

- Age at entry (continuous and categorical: < 65 years or ≥ 65 years)
- Sex
- Race
- Ethnicity

For baseline characteristics, the following variables will be summarized for study eyes:

- Baseline BCVA
- Baseline IOP
- Baseline CST
- Baseline macular volume

7.3. Medical and Surgical History

The medical and surgical history will be summarized for the ITT Population. Subjects reporting any medical and surgical history at baseline will be tabulated by body system for each dose level and overall.

7.4. Protocol Deviations

Subjects with any protocol deviation(s) will be listed by dose level and subject ID.

7.5. Prior and Concomitant Medications

Prior medications are medications taken and ended prior to injection. Concomitant medications are non-study medications a subject took during the study on or after injection. For this study, all prior and concomitant medications will be coded using WHO-DDE (Enhanced, March 2015 Version format B2). Each prior or concomitant medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO-DDE preferred drug name.

Subjects taking any prior medication in the Safety Population will be tabulated by ATC level and preferred drug name. A subject will be counted at most once for each prior medication, even if

the subject took the same prior medication on multiple occasions. Subjects taking any concomitant medications will be tabulated similarly.

8. SAFETY ANALYSES

The safety-related measures collected in this study include AEs, BCVA, slit-lamp biomicroscopy variables, IOP, indirect ophthalmoscopy variables, laboratory tests (hematology, chemistry, and urinalysis), vital signs, physical exam, and EKG. The Safety Population will be used for all safety summaries performed with subjects as treated.

8.1. Adverse Event

Subjects with any AE(s) (or ADR(s)) will be tabulated by SOC and preferred term specified in MedDRA Version 18.0. They will also be tabulated by SOC, preferred term, and maximum severity. In these AE tables, a subject who experienced multiple AEs (or ADR(s)) within a SOC or preferred term will be counted only once at the maximum severity for that SOC or preferred term; in addition, ocular AEs (or ADRs) will be presented first to be separated from non-ocular AEs (or ADRs).

AEs, SAEs, AEs leading to discontinuation, and deaths, if any, will be listed separately by dose level, subject ID, and onset time.

ESI(s) will be listed by event type, dose level, and subject ID.

8.2. Best Corrected Visual Acuity

BCVA scores and changes from baseline in BCVA score will be summarized by dose level and analysis visit. The overall number and proportion of subjects maintaining vision will be obtained.

8.3. Slit-lamp Biomicroscopy

Rating scores and changes from baseline in rating score will be summarized by dose level, biomicroscopy parameter, and analysis visit. Subjects with any worsening (increase) of ≥ two units from baseline will be listed by biomicroscopic parameter, dose level, and subject ID.

8.3.1. Iris

Iris statuses and changes from baseline in iris status will be summarized by dose level and analysis visit. Subjects with any worsening from Normal at baseline to Abnormal at any post-baseline visit will be listed by dose level and subject ID.

8.3.2. Lens

Subjects with any worsening (increase) of ≥ 2 units from baseline in phakic lens severity score will be listed by dose level and subject ID.

8.4. Intraocular Pressure

IOP scores and changes from baseline in IOP will be summarized by dose level and analysis visit. Subjects with an increase of ≥ 10 mmHg from baseline in IOP will be listed by dose level and subject ID.

8.5. Ophthalmoscopy

The cup/disc ratio, retina, macula and choroid, as well as vitreous scale will be summarized by dose level and analysis visit.

8.6. Laboratory Assessments

For each type of laboratory assessments (chemistry, hematology, or urinalysis), any worsening from baseline in laboratory result will be listed by dose level and laboratory test.

8.7. Vital Signs

Subjects with any worsened vital signs after injection will be listed by dose level for each type of vital signs (blood pressure or heart rate).

9. BIOACTIVITY ANALYSES

All bioactivity analyses will be performed on the ITT population. For BCVA, CST and macular volume, scores and changes from baseline will be summarized descriptively by dose level and analysis visit.

10. BIOMARKER ANALYSES

The following descpritive analysis is planned by dose level of DE-122:

- Individual Patient listing of biomarker level for each visit, both numeric and graph.
- Individual Changes from baseline in levels of biomarkers for each post-baseline visit, both numeric and graph.
- Summary analysis of above two by the two dose levels.

11. IMMUNOGENICITY

ADA titer will be measured in serum samples collected at Visit 1 (Day 1) and Visit 5

(Day 30±2). Change from baseline in ADA titer, as well as other related analyses will be perfomed per request.

12. REFERENCES

None.