Statistical Analysis Plan Cover Page

Official Study Title:	A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of DE-122 in combination with Lucentis® Compared to Lucentis® Monotherapy in Subjects with Wet Age-related Macular Degeneration - AVANTE study
NCT Number:	NCT03211234
Date of the document:	11 Oct 2019

STATISTICAL ANALYSIS PLAN

DE-122 Study 36-002

Protocol Title:	A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of DE-122 in combination with Lucentis® Compared to Lucentis® Monotherapy in Subjects with Wet Age-related Macular Degeneration – AVANTE study
Product:	2.0 mg (20µL of 100 mg/mL) DE-122 injectable solution 4.0 mg (40µL of 100 mg/mL) DE-122 injectable solution
Protocol Number:	36-002 Amendment 07
Sponsor:	Santen Inc.
	6401 Hollis Street, Suite 125 Emeryville, CA 94608 U.S.A.
Date:	October 11, 2019
Status:	Version 1.0

CONFIDENTIAL

APPROVAL SIGN-OFF SHEET

A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of DE-122 in Combination with Lucentis® Compared to Lucentis® Monotherapy in Subjects with Wet Age-related Macular Degeneration – AVANTE Study

DE-122 Study 36-002

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ABBREVIATIONS

Abbreviation	Explanation
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
CNV	Choroidal neovascularization
CRLT	Central retinal lesion thickness
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
FAS	full analysis set
FDA	Food and Drug Administration
HM	horizontal metamorphopsia
IOP	intraocular pressure
ITT	intention-to-treat
IVT	intravitreal
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
µg/mL	microgram per milliliter
mm	millimeter
mmHg	millimeters of mercury
µm	micrometer

ABBREVIATIONS (Continued)

Abbreviation	Explanation
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)
PK	pharmacokinetic/pharmacokinetics
PPS	per-protocol set
RPE	retinal pigment epithelium
SAE(s)	serious adverse event(s)
SADR(s)	serious adverse drug reaction
SAP	statistical analysis plan
SAS	statistical analysis system
SD-OCT	spectral-domain optical coherence tomography
SDTM	study data tabulation model
SHRM	subretinal hyper-reflective material
SOC	system organ classification
US	United States
VEGF	vascular endothelial growth factor
VM	vertical metamorphopsia
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 36-002, Amendment 07, "A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy and Safety of Intravitreal Injections of DE-122 in Combination with Lucentis® Compared to Lucentis® Monotherapy in Subjects with Wet Age-related Macular Degeneration - AVANTE Study". It applies to the study protocol dated 08 January 2019 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 OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective is:

- To assess the safety and efficacy of repeated intravitreal injections of DE-122 (2.0 mg per eye and 4.0 mg per eye) given in combination with Lucentis® in subjects with wet age-related macular degeneration (AMD) compared with Lucentis® alone.

The secondary objectives are

- To evaluate the pharmacokinetics and immunogenicity of DE-122 following repeated IVT injections of DE-122 in subjects with wet AMD in serum samples.
- To evaluate biomarker candidates of DE-122 following repeated IVT injections of DE-122 in subjects with wet AMD in both serum and aqueous humor samples.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 24.

2.2.2. Secondary Efficacy Endpoint

The secondary efficacy endpoints are:

- The proportions of subjects with ≥ 15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (3 line gainers) of BCVA improvement, < 15 letter change (stable), and ≥ 15 letter loss from baseline to week 24.
- Change from baseline in central subfield thickness (CST), macular volume (MV) and central retinal lesion thickness (CRLT) as measured by spectral-domain optical coherence tomography (SD-OCT) assessed at Week 24.
- Change from baseline in total lesion area and total area of choroidal neovascularization (CNV), greatest linear dimension of the total lesion area (GLD) by fluorescein angiogram (FA), as determined by a central reading center at Week 24.

2.2.3. Safety Endpoint

The safety of DE-122 will be evaluated by:

- Adverse events (AEs)
- Slit lamp biomicroscopy
- IOP
- Indirect ophthalmoscopy

- Laboratory assessment including serum chemistry, hematology, and urinalysis
- Vital signs
- Electrocardiogram (EKG)

2.2.4. Pharmacokinetics Endpoint

Pharmacokinetic profile will be assessed by pharmacokinetic parameters including AUC, C_{max}, t_{max}, and $t_{1/2}$.

2.2.5. Immunogenicity Endpoint

Immunogenicity will be assessed by the incidence of DE-122 antibody development in serum.

2.2.6. Biomarker Endpoint

For biomarker investigation, serum samples and aqueous humor samples from the study eye will be measured for levels of angiogenesis-related proteins.

2.2.7. Exploratory Endpoints

2.2.7.1. M-CHARTS™

The degree of metamorphopsia will be explored by vertical metamorphopsia score (VM) and horizontal metamorphopsia score (HM) from the M-CHARTS™.

2.2.7.2. Swept Source OCT Angiography

Swept Source OCT (SS-OCT) angiography will be evaluated for future exploratory research. This exploratory evaluation will be a collaboration between Santen and a third party, and is out of the scope of this document.

2.2.7.3. Subretinal Hyper-Reflective Material and Retinal Pigment Epithelium Elevation

Subretinal hyper-reflective material (SHRM) and retinal pigment epithelium elevation (RPEE) by SD-OCT will be evaluated for future exploratory research.

3. STUDY DESIGN

3.1. General Study Design

This is a randomized, double masked and active controlled study assessing the safety and efficacy of repeated intravitreal injections of DE-122 (2.0 mg or 4.0 mg) in combination with Lucentis® compared to Lucentis® monotherapy in subjects with wet AMD. Seventy-six (76) subjects wet AMD were randomly assigned to one of three treatment arms in two stages:

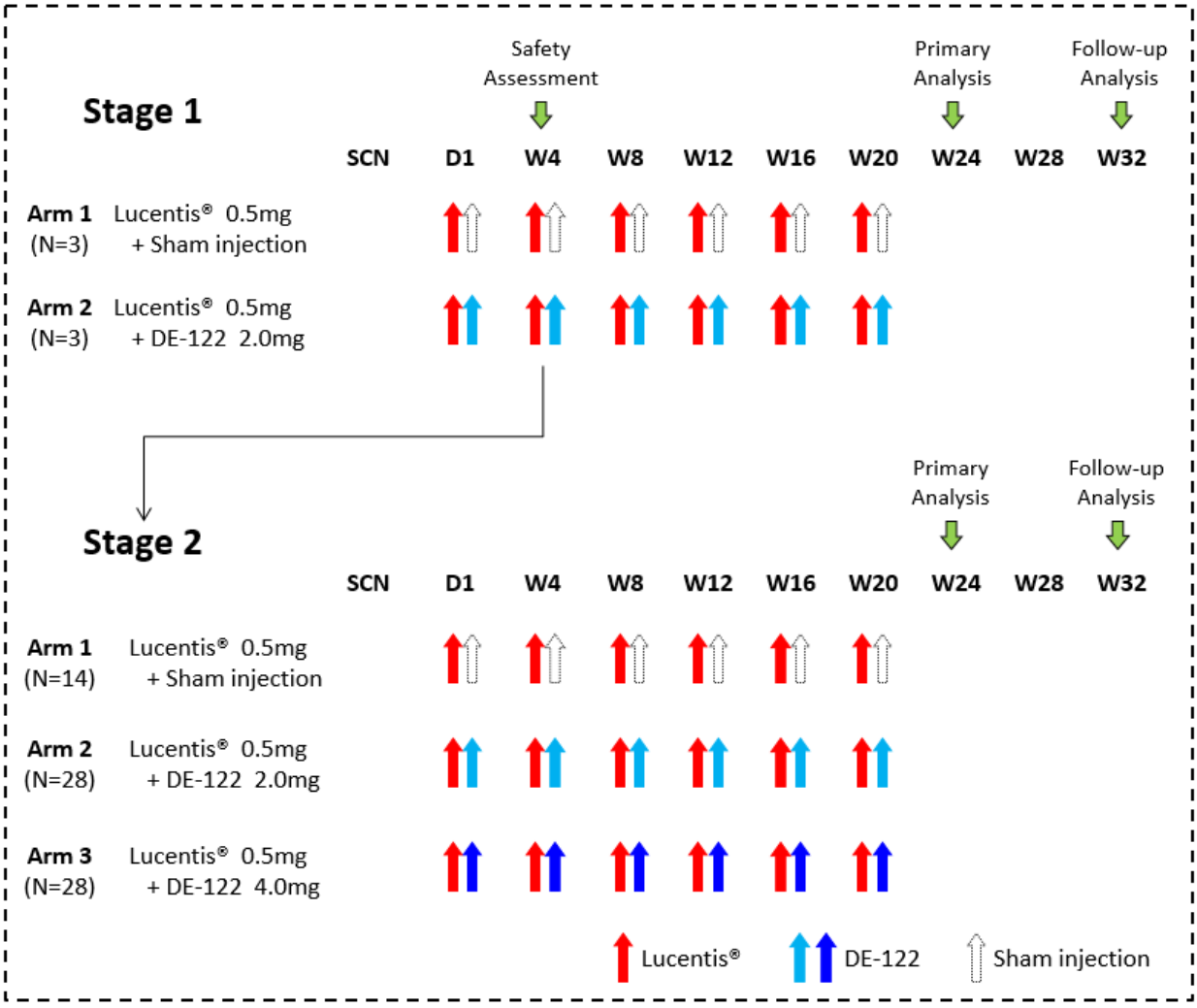
- Arm 1: Sham + Lucentis® 0.5 mg (N=17)
- Arm 2: DE-122, 2.0 mg + Lucentis® 0.5 mg (N=31)
- Arm 3: DE-122, 4.0 mg + Lucentis® 0.5 mg (N=28)

As shown in the Study Design Diagram (Figure 1), this study will consist of two stages. In Stage 1, the first 6 subjects will be randomized to either Arm 1 or Arm 2 in a 1:1 ratio. After all the 6 subjects have completed the Week 4 visit, the Safety Review Team will review the data to determine whether or not the safety and tolerability is acceptable. Subsequently in Stage 2, approximately 70 subjects will be randomized in a 1:2:2 ratios among the three arms.

Subjects will receive, in combination with Lucentis®, either 6 monthly intravitreal injections of DE-122 (2.0 mg), DE-122 (4.0 mg), or Sham in the study eye. The Primary Analysis is planned when all subjects complete the Week 24 visit. The Follow-up Analysis is planned at Week 32 to assess the number of anti-VEGF injections used for Rescue in addition to efficacy and safety data.

To be eligible, a subject must have been previously treated (i.e., At least 3 IVT injections of Anti-VEGF for treatment naïve eyes or eyes adequately maintained on continuous intravitreal anti-VEGF therapy). This condition was not required for subjects who enrolled before Protocol Amendment 06.

Figure 1: Study Design Diagram



3.2. Randomization and Masking

In Stage 1, the first 6 subjects will be randomized to either Arm 1 or Arm 2 in a 1:1 ratio. A blocked randomization with a fixed block size of 2 will be employed.

In Stage 2, approximately 70 subjects will be randomized to all three Arms in a 1:2:2 ratios. A blocked randomization with a fixed block size of 5 stratified by lesion type (polypoidal choroidal vasculopathy [PCV] vs. non-PCV) will be employed. Approximately one third (1/3) of the subjects in each arm are expected to have PCV in Stage 2.

This is a double-masked study, where the subjects and the examiners including the Principal Investigator (PI), are masked to the treatment regimen. However, the designated injecting physician (who is not the PI) will not be masked to the treatment regimen.

The Sponsor will have masked and unmasked data review teams. The designated Safety Review Team will review the safety data of the 6 subjects in Stage 1 to determine if the safety and tolerability of the doses at Week 4 are acceptable. In case of a medical emergency, the Principal

Investigator or site staff may reveal the treatment information by unmasking in the Interactive Web Response Systems (IWRS).

3.3. Sample Size Planning

Approximately 76 subjects (Arm 1: 17, Arm 2: 31, Arm 3: 28) with wet AMD will be enrolled at approximately 14 sites. The sample size is not based upon any statistical considerations.

3.4. Visits and Assessments

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

Table 1: Schedule of Events

***Only the subjects who have consented under the protocol prior to Amendment 07 require the grayed-out examinations in the table.**

Visit Number	Visit 0 (SCRN)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 /Exit
Visit Schedule (Time window; days)	D-14 to -1	D1	D3	W1	W4	W8	W12	W16	W20	W20 + 2 days	W20 + 7 days	W24	W28	W32
			D3	D8 (±1)	D29 (±3)	D57 (±3)	D85 (±4)	D113 (±4)	D141 (±4)	W20 + 2 days	W20 + 7(±1) days	D169 (±5)	D197 (±5)	D225 (±5)
Informed consent[a]	X													
Demographics/Eligibility	X													
Medical/surgical history, Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X											X		X
Vital signs	X	X		X	X	X	X	X	X			X	X	X
EKG	X			X							X	X		X
BCVA (ETDRS)	X	X		X	X	X	X	X	X			X	X	X
M-CHARTS™	X	X		X	X	X	X	X	X			X	X	X
Slit-lamp biomicroscopy[b]	X	X		X	X	X	X	X	X			X	X	X
Intraocular pressure (IOP)[c]	X	X		X	X	X	X	X	X			X	X	X
Indirect ophthalmoscopy[b]	X	X		X	X	X	X	X	X			X	X	X
SD-OCT	X	X		X	X	X	X	X	X			X	X	X
SS-OCT angiography[d]	X	X		X	X	X	X	X	X			X	X	X

Table 1: Schedule of Events (Continued)

Visit Number	Visit 0 (SCRN)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 /Exit
Visit Schedule (Time window; days)	**D-14 to -1**	**D1**	**D3**	**W1**	**W4**	**W8**	**W12**	**W16**	**W20**	**W20 + 2 days**	**W20 + 7 days**	**W24**	**W28**	**W32**
			D3	**D8 (±1)**	**D29 (±3)**	**D57 (±3)**	**D85 (±4)**	**D113 (±4)**	**D141 (±4)**	**W20 + 2 days**	**W20 + 7(±1) days**	**D169 (±5)**	**D197 (±5)**	**D225 (±5)**
Fundus photography (FP)	X				X		X					X		X
Fluorescein angiography (FA)	X				X		X					X		X
Urine pregnancy test[e]		X												
Urinalysis[f]	X				X		X					X		X
Serum pregnancy test[e]	X											X		X
Hematology, chemistry serum sample[f]	X				X		X					X		X
PK serum sample[g]		X	X	X	X				X	X	X	X		
Biomarker serum sample[g]		X	X	X	X				X	X	X	X		
Immunogenicity serum sample		X										X		
Pharmacogenomics/genomics blood sample[a, h]		X												
Biomarker aqueous humor sample[a]		X			X				X					

Table 1: Schedule of Events (Continued)

Visit Number	Visit 0 (SCRN)	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13 /Exit
Visit Schedule (Time window; days)	D-14 to -1	D1	D3	W1	W4	W8	W12	W16	W20	W20 + 2 days	W20 + 7 days	W24	W28	W32
			D3	D8 (±1)	D29 (±3)	D57 (±3)	D85 (±4)	D113 (±4)	D141 (±4)	W20 + 2 days	W20 + 7(±1) days	D169 (±5)	D197 (±5)	D225 (±5)
Lucentis® IVT injection[i]		X			X	X	X	X	X					
DE-122 or Sham IVT Injection[i]		X			X	X	X	X	X					
Adverse event		X	X	X	X	X	X	X	X	X	X	X	X	X

SCRN= Screening; D=Day; W=Week; PK=Pharmacokinetic

[a.] Collection and Pharmacogenomics/genomics blood sample collection.
[b.] On days when either Lucentis®/DE-122 or Lucentis®/Sham IVT injections are administered, slit lamp biomicroscopy and indirect ophthalmoscopy will be performed prior to injection and within 30 minutes after DE-122 or Sham injection. This will be also applied for the post IVT injection of Rescue treatment.
[c.] On days when either Lucentis®/DE-122or Lucentis® /Sham IVT injections are administered, IOP will be performed before and after Lucentis® IVT injection. In addition, after DE-122 or Sham injection, IOP will be performed again. This will be also applied for the post injection of Rescue treatment.
[d.] Selected sites will conduct.
[e.] Serum and urine pregnancy tests are to be performed on all females of child-bearing potential.
[f.] Subjects should fast for a minimum of 8 hours prior to urine specimen and blood draw for serum chemistry tests.
[g.] At baseline (Day 1, Visit 1), serum sample for DE-122 concentration (if applicable) and biomarker will be collected
1) prior to the Lucentis® injection;
2) post DE-122 or Sham injection: 3 hours, 48 hours, 1 week and 4 weeks (prior to the Lucentis® injection).
At Week 20, serum sample for DE-122 concentration (if applicable) and biomarker will also be collected
1) prior to the Lucentis® injection;
2) post DE-122 or Sham injection: 3 hours, 48 hours, 1 week and 4 weeks.
[h.] Pharmacogenomics/genomics blood sample can be drawn once at Day 1 or any visit after Visit 1(Day 1) during the study.
[i.] Lucentis® will be administered first, and then DE-122 or Sham will be injected. Rescue treatment with any anti-VEGF IVT injection can be performed during the Week 24 and Week 28 visits.

4. DEFINTIONS

4.1. Time-Related Terms

4.1.1. Screening Visit

The screening visit is Visit 0 when the subject provided written informed consent.

4.1.2. Baseline Visit

The *baseline visit* is Visit 1 (Day 1) visit when the subject is randomized.

4.1.3. Study Day

The *study day* variable is the relative day of the observation with respect to the reference date, which is set to Day 1. In this study, the reference date is the baseline visit date, and the study day will be defined as:

- For days prior to the injection date, study day = date – baseline visit date
- For days on/after the injection date, study day = date – baseline visit date + 1

Note that there is no study day 0.

4.1.4. Analysis Periods

Analysis periods for the efficacy and safety analysis are defined in Table 2.

Table 2: Analysis Periods

Analysis Period	Analysis Period Start Date	Analysis Period End Date
On-treatment Period	The date of the first Lucentis® injection	The date of the Week 24 visit, or the Study Exit date, whichever came first
Follow-up Period	The date of the first day after Week 24 visit	The Study Exit date
Entire Study	Efficacy: the date of randomization; Safety: the date of the first Lucentis® injection	The Study Exit date

4.1.5. Out-of-Window Measurements, Analysis Window and Analysis Visit

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.

Analysis visit is a timing variable which will be used for all analyses involving visits. For each analysis visit, an analysis window is provided in order to determine which of the analysis visit a measurement should be mapped to. The analysis visit of a measurement will be determined by the study day of the measurement and the specified analysis windows. The study visit, assigned when the measurement was collected, will not necessarily agree with the analysis visit.

The following analysis windows for post-baseline visits will be applied to minimize the amount of missing data for analysis purposes:

Table 3: Post-Baseline Analysis Visit and Analysis Window

Post-Baseline Analysis Visit (Target Assessment Date)	Visit Window	Analysis Window
Week 1 (Day 8)	[7, 9]	[2, 18]
Week 4 (Day 29)	[26, 32]	[19, 43]
Week 8 (Day 57)	[54, 60]	[44, 71]
Week 12 (Day 85)	[81, 89]	[72, 99]
Week 16 (Day 113)	[109, 117]	[100, 127]
Week 20 (Day 141)	[137, 145]	[128, 155]
Week 24 (Day 169)	[164, 174]	[156, 183]
Week 28 (Day 197)	[192, 202]	[184, 211]
Week 32 (Day 225)	[220, 230]	[212, 253]

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 at visit with any injection will be selected. If there is no visit with any injection, then the measurement closest to the target assessment day will be selected for that visit. In the case that two measurements are 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.

4.1.6. Days on Treatment

Days on treatment measures the duration of exposure to a study medication received during the study. For this study, the days on treatment is defined as:

- Days on treatment = (date of last dose – date of first dose) + 1

4.2. Efficacy-Related Definitions

4.2.1. Study Eye and Fellow Eye

The *study eye* of a randomized, treated subject is the eye that was injected with study medication at baseline (Day 1). For subjects who were randomized but not treated, the study eye is the eye determined to be injected by the Clinical Investigator at baseline (Day 1). The Clinical Investigator selected “OD” or “OS” for “Study Eye” on the Primary Diagnosis eCRF.

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 initial injection of study medication at the baseline visit.

4.2.3. Change and Percent Change from Baseline

The change and the percent change from baseline in a measure at a post-baseline visit will be defined as:

- Change = score at the post-baseline visit – baseline score.
- Percent change from baseline = 100 × change / (baseline score).

4.2.4. Efficacy Measures

Table 4 lists all the efficacy measures to be evaluated for this study.

Table 4: Efficacy Measures

Efficacy Measures	Note
Best corrected visual acuity (BCVA)	BCVA measures the acuteness or clearness of the best-corrected vision, with a range of [0, 110] in ETDRS letters. The total number of corrected letters will be measured at both 4 meters and 1 meter. The sum of the total number of corrected letters at both 4 meters and 1 meter will be used for analysis. If a subject cannot read the ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded. BCVA will be 0 for these situations in any analysis. An increase in BCVA indicates improvement in the best-corrected vision. A 5-letter difference in visual acuity is equivalent to one Snellen line. A BCVA score of 85 ETDRS letters is equivalent to 20/20 vision, which is considered normal vision.
Central subfield thickness (CST)	CST, also known as foveal thickness, measures the central portion of macular in micrometer (μm), with a range of [0, 2000] without decimals. CST is defined as the average retinal thickness in the central 1 millimeter (mm) diameter of the macular. 'Ungradable' may be selected when the SD-OCT image is unable to measure for any reason.
Macular volume (MV)	Macular volume measures the sum of the volumes of the neural retina in the central 6 mm of the macula in mm3 (one to four digits with two digits to the right of the decimals). 'Ungradable' may be selected when the SD-OCT image is unable to measure for any reason.
Central retinal lesion thickness (CRLT)	CRLT is the distance between the inner limiting membrane of the retina and the Bruch's membrane. In this study, CRLT will be measured at the sum of the neurosensory retinal thickness (RET) at the foveal centerpoint, subretinal fluid thickness (SRF) at the foveal centerpoint, SHRM at the foveal centerpoint, and RPE+RPEE thickness at the foveal centerpoint. Each of the four individual thickness components will be measured in μm with a range of [0, 2000] without decimals. If "Ungradable" was selected for RPE + RPEE and SHRM measurement, for example the RPE is absent or disrupted, measurement from Bruch's membrane to the inner border of SHRM and enter that value will be used together with the RET and SRF measurement for CRLT. CRLT is determined by FA.

Table 4: Efficacy Measures (Continued)

Efficacy Measures	Note
Total lesion area	Total lesion area is defined as the entire complex of lesion components (mm2), which is the sum of total CNV area and the areas of each of the non-CNV lesion components. Total lesion area will be determined by FA.
Total area of choroidal neovascularization (CNV)	The total area of CNV measures the total area of new blood vessels that originate from the choroid and extend through Bruch's membrane into the subretinal pigment epithelium (sub-RPE). The total area of CNV will be measured in mm2. 'Ungradable' may be selected when the FA image is unable to measure for any reason.
Greatest linear dimension of the total lesion area (GLD)	GLD of the total lesion area is measured from the total lesion area (mm) determined by FA.

4.3. Safety-Related Definitions

4.3.1. Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study drug(s).

An on-study AE can occur at any time after the date of informed consent through the last study visit. An AE will be considered as treatment-emergent if the AE onset occurs on or after the analysis period start date and prior to or on the on-treatment analysis period end date as defined in Section 4.1.4. Treatment-emergent AEs are a subset of on-study AEs. Both on-study and treatment-emergent AEs are to be recorded, but only treatment-emergent AEs will be tabulated.

Each AE will be classified into a system organ class (SOC) and coded to a preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 published in 2017.

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 12.1.1.1 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. Suspected Adverse Reaction

An AE will be counted as a suspected adverse reaction (SAR) 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 (ESI) such as pregnancy, study medication administration error, ocular telangiectasia and bleeding events will be identified throughout the study. An event will be counted as ESI if the Clinical Investigator selected "Yes" to the AE eCRF question "Is it a protocol defined Event of Special Interest (ESI)?"

4.3.2. Safety Measures

Table 5 lists the safety measures to be evaluated in this study.

4.3.3. Rescue Therapy

Subjects are eligible for rescue with any anti-VEGF IVT injection during the Week 24 and Week 28 if one of the following rescue criteria is met:

- BCVA decrease of ≥ 5 letters from the last visit score
- CST increase from the last visit of ≥ 50µm
- The discretion of investigator

4.3.4. Baseline Score

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

4.3.5. Change and Percent Change from Baseline

The *change and the percent change from baseline* in a measure at a post-baseline visit will be defined as:

- Change = score at the post-baseline visit – baseline score.
- Percent change from baseline = 100 × change / (baseline score)

For any measure assessed pre and post injection at visits with injection(s), only the pre-injection scores at the visit will be used to derive the change-from-baseline variable.

4.3.6. Change after Injection

For any measure assessed pre and post injection, the *change after injection* is defined as:

- Change after injection = post-injection score at the visit – pre-injection score at the visit.

If multiple post-injection scores are available at the visit, then the first observation will be used to derive the change after injection.

If more than one injection were given to the subject at the same visit, change after injection in IOP will be performed for each injection.

Table 5: Safety Measures

Safety Measure	Note
Intraocular pressure (IOP)	IOP will be measured by applanation tonometry and reported in millimeters of mercury (mmHg). The IOP of an eye is derived as the mean/median of two or three consecutive IOP measurements. IOP will be measured before Lucentis® and 40 (±10) minutes after Lucentis® injection. If applicable, IOP will be measured again 60 (±10) minutes following Lucentis® injection. Any increase of ≥ 10 mmHg in IOP at 60 (±10) minutes post-injection will be reported as an AE. The procedure will be also applied for DE-122 or Sham injection, and any post IVT injection of rescue treatment.
Slit-lamp biomicroscopy findings: lid Redness lid edema conjunctival hyperemia conjunctival edema corneal edema anterior chamber cells anterior chamber flare iris pupil lens phakic lens severity	Slit-lamp biomicroscopy will be performed prior to Lucentis® injection and within 30 minutes after DE-122 or Sham injection, and any post IVT injection of rescue treatment. 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 iris and pupil status of an eye will be graded as either normal or abnormal. The lens of an eye will be classified as phakic, aphakic, or pseudophakic. The rest biomicroscopy parameters will be graded as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe.

Table 5: Safety Measures (Continued)

Safety Measure	Note
Ophthalmoscopy findings: cup/disc ratio retina macula choroid vitreous	Indirect ophthalmoscopy will be performed prior to Lucentis® injection and within 30 minutes after DE-122 or Sham injection, and any post IVT injection of rescue treatment. Cup/disc ratio will be recorded with two decimal points (e.g., 0.80). The retina, macula and choroid will be graded as either normal or abnormal. Vitreous haze and opacification 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 4+ = Dense opacity obscures the optic nerve head.
Laboratory test: urinalysis hematology serum chemistry	Laboratory test results will be graded as: 1 = Normal 2 = Not Clinically Significant Abnormality 3 = Clinically Significant Abnormality 4 = No Results/Invalid Results 5 = Sample Not Collected Refer to Section 23.4.16 of the protocol for the list of the minimum blood parameters and urine parameters.
Vital signs: systolic blood pressure diastolic blood pressure heart rate	Systolic blood pressure and diastolic blood pressure will be measured in mmHg. Heart rate will be measured by beats/minute. The average of two or three readings will be used.

Table 5: Safety Measures (Continued)

Safety Measure	Note
EKG	EKG report will be reviewed by the Clinical Investigator and will be graded as: 1 = Normal 2 = Abnormal, Clinically Insignificant 3 = Abnormal, Potentially Clinically Insignificant 4 = Abnormal, Potentially Clinically Significant 5 = Abnormal, Potentially Exclusionary 6 = Abnormal, Clinically Significant 7 = Unable to Evaluate 8 = Unable to evaluate but measurements provided are correct

4.4. Other Definitions

4.4.1. Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, a *prior medication* is defined as any non-study medication taken that ended prior to the treatment start date. A concomitant medication is defined as any non-study medication taken concurrently while on the study medication, i.e., the treatment period of a concomitant medication taken by a subject's needs to overlap with his/her treatment period of the study medication.

4.4.2. Pharmacokinetic Measures

Table 6 lists all the PK measures to be estimated.

Table 6: Pharmacokinetic Measures

Pharmacokinetic Measure	Note
Area under the curve (AUC)	AUC (μg/mL × day) reflects the extent of exposure to DE-109 after injection. It equals the integral of the concentration-time curve.
C_{max}	C_{max} denotes the peak plasma concentration of DE-109 observed after injection.
t_{max}	t_{max} denotes the time to reach C_{max}.
Elimination half-life ($t_{1/2}$)	$t_{1/2}$ is the time required for the concentration of DE-109 to reach half of its original value.

PK parameters will be estimated for each of the following time intervals based on plasma concentrations collected during the corresponding time interval:

- Day 1 to Week 4 visit
- Week 20 to Week 24 visit

4.4.3. M-CHARTS™

Narrow Dotted Lines with one line (Type I) and Bold Dotted Lines with one line (Type B) are used in this study to measure the severity of metamorphopsia in macular lesions. VM and HM of Type I and Type B in each eye will be examined three times. The median from the 3 measurements will be used. The VM and HM of Type I range from 0 to 2 while 0 to 2.4 for Type B. The VM and HM scores in normal eyes without metamorphopsia are 0. A large score indicates more sever metamorphopsia.

4.4.4. Subretinal Hyper-Reflective Material and Retinal Pigment Epithelium Elevation

SHRM is a morphological change seen on OCT as hyper-reflective material located external to the retina, or subretinal fluid if it is present, and internal to the RPE. SHRM will be graded as "Yes" if there is any SHRM, "No" if there is no SHRM, "Ungradable" if there is any reason it would be unable to grade because of pathology or reasons unrelated to quality of the image, and "Ungradable/Quality" if there are quality reasons that it is indeterminable that SHRM is present. An RPEE refers to RPE that is separated from Bruch's membrane. The material external to the elevated RPE may be hypo-reflective, or have reflective material that could be pigment, blood, or CNV. The RPE may also be elevated by drusen. RPEE will be graded as "Yes" if there is any RPEE on any scan, "No" if there is no RPEE on any scan, "Ungradable" if there is any reason that it would be unable to grade because of pathology or reasons unrelated to quality of the image, and "Ungradable/Quality" if there are quality reasons that it is indeterminable that RPEE is present.

5. STUDY POPULATION

5.1. Intention-to-Treat Population

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

5.2. Safety Population

The *Safety Population* will include all subjects who received at least one injection of the study medication. It will be the study population for safety analyses performed with subjects as treated.

5.3. Full Analysis Set

The *Full Analysis Set (FAS)* will include all subjects who received at least one injection of the study medication (DE-122 or Lucentis®) and provided at least one post-baseline BCVA measurement of the study eye during the study. It will be the population used for efficacy analyses performed with subjects as randomized.

5.4. Per-Protocol Set

The *Per-Protocol Set (PPS)* is a subset of the FAS. It includes all FAS subjects without protocol violations that could affect the primary efficacy endpoint. It will be the analysis population for some sensitivity analyses performed with subjects as randomized.

Before the unmasking of treatment assignment, Santen's study team will review all protocol deviations, identify subjects with any protocol deviation that could impact the efficacy outcome, and determine whether or not to exclude the subject from the PPS.

5.5. PK Population

The *Pharmacokinetic (PK) Population* will include all subjects who receive at least one DE-122 and have at least one quantifiable post-injection PK serum assessment. It will be the study population for PK analyses.

5.6. Biomarker Population

The *Biomarker Population* will include all subjects who receive at least one DE-122 and have at least one quantifiable post-injection biomarker serum assessment. It will be the study population for biomarker analyses.

6. GENERAL CONSIDERATIONS

Besides data listings, all measures will be summarized by randomized arm 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 (%).

All data manipulations and descriptive summaries will be implemented using SAS®, Version 9.4 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 efficacy measures, the last-observation-carried-forward (LOCF) approach may be used to impute missing post-baseline values in sensitivity analysis. Baseline scores will not be carried forward.

Completely or partially missing onset and resolution dates of medical events, i.e., medical history events and AEs will be imputed in a conservative fashion 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 day of the onset date
	YYYY and MM are available but DD is missing	Use the first day of MM to impute the missing day 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 day of the resolution date
	YYYY and MM are available but DD is missing	Use the last day of MM to impute the missing day 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. Handling of Special Measurement Values

For BCVA, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be set to 0 letter in the analysis.

For measures determined by SD-OCT and FA, “Ungradable” will be treated as missing data.

For M-CHARTS™, any VM and HM with "Unmeasurable" in Type I and Type B will be set to 2 and 2.4, respectively.

6.4. Multi-Center Studies

This is a multi-center study enrolling subjects from up to 14 sites. No pooling algorithm will be applied.

6.5. Multiple Comparisons / Multiplicity

Multiplicity adjustment is not applicable to this study.

6.6. Interim Analysis

An interim analysis was planned in Protocols Amendment 06 and previous versions but was removed from Protocol Amendment 07. Therefore, no formal interim analysis will be conducted.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The subject disposition will be summarized by treatment arm and overall for all randomized subjects. The summary will include the number of subjects in the ITT Population, the numbers and percentages of subjects in the Safety Population, FAS, PPS, PK Population and Biomarker Population. The summary will also include the numbers and percentages of completers and non-completers at Week 24 (Visit 11) and Week 32 (Visit 13), as well as the number and percentage of non-completers by primary discontinuation reason. The number of percentages of subjects enrolled prior to Protocol Amendment 06 and on/after Protocol Amendment 06 will also be provided.

7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for the FAS Population by planned treatment arm and overall, safety population by actual treatment and overall. Specifically, for subject demographics, the following variables will be summarized:

- Age at randomization (continuous and categorical: < 65 years or ≥ 65 years)
- Sex (categorical: Male or Female)
- Race (categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other/Multiracial)
- Ethnicity (categorical: Hispanic/Latino or Not)
- Country (categorical: Philippine or US)

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

- Lesion type (PCV or non-PCV)
- Prior anti-VEGF treatment in the study eye (Yes or No)
  - If yes, refractory to anti-VEGF treatment or not (Yes or No)
  - And, how long since the first anti-VEGF treatment
  - And, the type of most recent prior anti-VEGF treatment (type 1: Lucentis or Ranibizumab; type 2: Avastin or Bevacizumab; type 3: Eylea or Aflibercept)
- Baseline BCVA
- Baseline FA readings including total lesion area, total area of CNV, and greatest linear dimension of the total lesion area
- Baseline CST, MV and CRLT
- Baseline IOP
- Baseline lens status (aphakic, pseudophakic or phakic)

Summaries of demographic and baseline characteristics will be repeated on the following subgroups:

- Country
- Lesion type (PCV or non-PCV)
- Prior anti-VEGF treatment in the study eye (Yes or No)
- Protocol version (before Amendment 06 or on/after Amendment 06)

7.3. Medical and Surgical History

For this study, medical and surgical history (i.e., medical events) will be coded using MedDRA 20.0, 2017. Each medical event will be classified into a SOC and mapped to a PT.

The medical and surgical history will be summarized for the FAS population. Subjects reporting any medical and surgical history at baseline will be tabulated by SOC and PT for each planned treatment and overall.

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Safety issues
- Consent issues
- Enrollment issues
- Protocol implementation issues
- Other deviations

A protocol deviation is considered major if it may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Santen's study team will review all protocol deviations and determine the list of major protocol deviations prior to database lock. All randomized subjects with any major protocol deviation(s) will be tabulated by deviation category for each planned treatment and overall. In addition, all protocol deviations will also be listed.

7.5. Prior and Concomitant Medications

For this study, non-study medications, including prior and concomitant medications, will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) (March 2017). Each non-study medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO-DDE preferred drug name.

Non-study medications will be summarized for the Safety population. Subjects taking any prior medications will be tabulated by ATC level 3, level 4 and preferred drug name for each actual treatment received and overall. 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. In addition, prior medications and concomitant medications will also be listed, separately.

Any prior medications taken for target disease will be summarized and listed.

7.6. Exposure to Study Medication

The treatment exposure to DE-122 will be reflected by the number of DE-122 injections received (1 to 6). For Safety subjects, the exposure will be summarized by frequency and percentage for actual treatment received and overall.

7.7. Treatment Compliance

A subject will be considered fully compliant if the study eye was injected with the planned treatment at each visit when the injection is scheduled per protocol. If the subject skipped the injection of DE-122 at the investigator's decision with the corresponding AE reported, then this subject will still be considered as treatment compliant. Treatment compliance will be summarized for the FAS population by planned treatment and overall. The treatment compliance statuses will also be listed by planned treatment, subject ID, and injection visit.

8. EFFICACY ANALYSES

Unless specified otherwise, the efficacy analyses will be performed on the FAS, where subjects are classified by planned treatment, irrespective of the actual treatment received.

Unless specified otherwise, all efficacy analyses will be performed on the study eye, and the data on fellow eye will not be used.

8.1. Primary Endpoint

8.1.1. Primary Analysis

The primary efficacy endpoint is mean change from baseline in BCVA at Week 24. No formal statistical hypothesis testing will be implemented for the primary endpoint. Descriptive summaries will be provided by each planned treatment arm. The differences in mean change between Arm 2 or 3 and Arm 1, as well as the corresponding 95% confidence intervals based on t-test without multiplicity adjustment will also be provided. Descriptive summaries of BCVA measured at Week 28 and Week 32 will be provided, in which any records after the rescue injection(s) will be censored.

The primary analyses will be performed on the FAS. Besides the summary tables, plots of BCVA measures versus analysis visit will be provided. BCVA score, and percent change from baseline will also be summarized.

8.1.2. Sensitivity Analysis

To assess the robustness of the primary analysis results, the same analysis may be repeated on the PPS with observed cases, and FAS with missing data imputed by the LOCF approach.

In addition, if the scheduled injection was skipped at a visit, BCVA measured at the first visit after that visit will be censored. Descriptive summaries will be performed based on the censored dataset to assess the impact of missing injection on the primary analysis results.

8.2. Analyses of Secondary Endpoints

8.2.1. Primary Analysis

Frequency and percentage of subjects with BCVA improvement of ≥ 15 ETDRS letters (3-line gainers); within 15 letters change (stable) and loss of ≥ 15 letters from baseline at Week 24 will be provided based on FAS. The differences in proportion between Arm 2 or 3 and Arm 1, as well as the corresponding 95% confidence intervals based on t-test without multiplicity adjustment will be provided. Besides the summary table, bar plot will be performed.

Change from baseline in CST, MV, CRLT, total lesion area, total area of CNV, and GLD of the total lesion area at Week 24 will be summarized descriptively by treatment arms based on observed data. The differences in mean change between Arm 2 or 3 and Arm 1, and the corresponding 95% confidence intervals based on t-test without multiplicity adjustment will be provided. Scores and percent change from baseline will be provided. Plots of measurement and

change from baseline versus analysis visit will also be provided. Frequency and percentage of subjects with 'ungradable' data will be provided.

8.2.2. Sensitivity Analysis

To assess the robustness of the primary analysis results, the same analysis may be repeated on the PPS with observed cases.

In addition, if the scheduled injection was skipped at a visit, the efficacy data measured at the first visit after that visit will be censored. Descriptive summaries will be performed based on the censored dataset to assess the impact of missing injection on the primary analysis results.

8.3. Subgroup Analyses

To assess the homogeneity of treatment effects among subgroups, primary endpoint will be analyzed for the following subgroups:

- Age group (< 65, or ≥ 65 years)
- Sex (males or females)
- Country (Philippine or US)
- Lesion type (PCV or non-PCV)
- Prior anti-VEGF treatment in the study eye (yes or no)
- Type of most recent prior anti-VEGF treatment in the study eye (type 1: Lucentis or Ranibizumab; type 2: Avastin or Bevacizumab; type 3: Eylea or Aflibercept)
- Protocol version (before or on/after Amendment 06)
- Lens status (phakic or non- phakic).

Other subgroup analyses may be performed as suggested by the data.

9. SAFETY ANALYSES

The safety-related measures collected in this study include AEs, IOP, slit-lamp biomicroscopy variables, indirect ophthalmoscopy variables, laboratory tests (hematology, chemistry, and urinalysis), vital signs, physical exam, fundus photography, fluorescein angiography, EKG, and pregnancy.

The Safety population will be used for all safety summaries, where subjects will be classified by actual treatment received.

9.1. Adverse Event

Subjects with any AE(s), SAE(s), SAR(s), serious SAR(s) and ESI(s) will be tabulated for each actual treatment received. Besides the overall AE summary, subjects with any AE(s) will be tabulated by SOC and PT specified in MedDRA Version 20.0. Subjects with any AE(s) will also be tabulated by SOC, PT and maximum severity. A subject who experienced multiple AEs within a SOC or PT will be counted only once at the maximum severity for that SOC or PT. SAEs, SARs, and Serious SARs will be tabulated similarly.

Summaries for ocular AEs and non-ocular AEs will also be performed. Ocular AEs, ocular SAEs and ocular SARs will be summarized for study eyes and fellow eyes separately. Any ocular AE that occurred simultaneously to both eyes will be counted once for both the study eye and the fellow eye.

All AE tabulations will be performed on the Safety population for the On-treatment period, Follow-up period and entire study.

AEs, AEs leading to death, AEs leading to discontinuation, SAEs, and ESIs, if any, will be listed separately.

9.2. Slit-lamp Biomicroscopy

Frequency and percentage of severity rating score will be summarized by actual treatment received and analysis visit for study eyes. In addition, subjects with any clinically significant worsening from baseline, defined as from normal to abnormal for iris and pupil, or worsening (increase) of 2 units or more for the rest biomicroscopy parameters, will be summarized and listed. For anterior chamber cells, rating score from 0 to 0.5 is considered as 1 unit of increase, and from 0 to 1 is considered as 2 unit of increase. The summaries of cataract severity score apply to phakic lens only.

For all biomicroscopy parameters, subjects with any worsening of 2 units or more after injection will be summarized and listed.

9.3. Ophthalmoscopy

For cup to disc ratio, scores and changes from baseline will be summarized by actual treatment received and analysis visit for study eyes.

For binary ophthalmoscopy parameters (retina, macular and choroid), subjects with any change from Normal at baseline to Abnormal in status will be tabulated by actual treatment received and analysis visit for study eyes. In addition, a listing will be provided.

For vitreous haze, frequency and percentage of severity rating score will be summarized by actual treatment received and analysis visit for study eyes. In addition, subjects with worsening (increase) of 2 units or more from baseline will be summarized and listed.

For all ophthalmoscopy parameters, subjects with any worsening of 2 units or more after injection will be summarized and listed.

9.4. Intraocular Pressure

IOP scores, changes from baseline and percent change from baseline in pre-injection IOP will be summarized by actual treatment received and analysis visit.

Change after injection in IOP will be summarized repeatedly at 40 (±10) and 60 (±10) minutes following injection. Subjects with an increase of ≥ 10 mmHg at 60 (±10) minutes post-injection in IOP will be listed by treatment arm and subject ID. These analyses will be performed for the injection of Lucentis and DE-122, respectively.

9.5. Rescue Therapy

Frequency and percentage of subjects who received rescue therapy will be summarized. Subjects who received rescue therapy will be listed.

9.6. Electrocardiogram (EKG)

Any worsening from normal/not clinically significant abnormality at baseline to clinically significant abnormality will be summarized by actual treatment received and analysis visit. Subjects with clinically significant abnormality will be listed.

9.7. Vital Signs

Blood pressures and pulse rate, and changes from baseline will be summarized by actual treatment received and analysis visit.

9.8. Laboratory Assessments

For each type of laboratory assessments (chemistry, hematology, or urinalysis), any worsening from normal/not clinically significant abnormality at baseline to clinically significant abnormality will be summarized by actual treatment received and analysis visit. Subjects with clinically significant abnormality will be listed.

10. PHARMACOKINETIC ANALYSES

All PK analyses will be performed on the PK population, with subjects as treated. Pharmacokinetic parameters (AUC, C_{max}, t_{max}, and $t_{1/2}$) will be summarized descriptively by actual treatment arm and analysis interval.

11. IMMUNOGENICITY ANALYSIS

To assess immunogenicity, the incidence of DE-122 antibody development in each arm will be summarized by frequency counts and percentages.

12. BIOMARKER ANALYSIS

Translational Research will provide the report of biomarker investigation. Scores, changes from baseline and percent change from baseline in levels of potential biomarkers will be summarized descriptively by actual treatment received and analysis visit. Besides the summary tables, plots of biomarker measures versus analysis visit will be provided. Pearson's correlation between change from baseline in BCVA and each biomarker will be analyzed by actual treatment and analysis visit. The 95% confidence interval of the correlation coefficient based on Fisher's Z transformation will be provided.

13. OTHER ANALYSES

13.1. M-CHARTS™

Score and change from baseline in VM and HM in study eye will be summarized by planned treatment received and analysis visit for Type I and Type B, separately. The same analysis will be repeated using the average of MV and MH, and the worst (larger) of MV and MH.

13.2. SS-OCT Angiography

The analysis of SS-OCT angiography will be conducted by a third party.

13.3. Subretinal Hyper-Reflective Material and Retinal Pigment Epithelium Elevation

Frequency and percentage of subjects who had the presence of SHRM and RPEE in the study eye will be summarized by planned treatment received and analysis visit.

14. REFERENCES

None.