Study Protocol 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
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DE-122
Protocol 36-002
Amendment 07

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

SPONSOR:

SANTEN PHILIPPINES INCORPORATED
Units 2801 to 2802, 28th Floor SM Aura Tower
26th Street corner McKinley Parkway, The Fort,
Taguig City, 1630 Philippines

STUDY DRUG:

- 2.0 mg (20µL of 100 mg/mL) DE-122 injectable solution
- 4.0 mg (40µL of 100 mg/mL) DE-122 injectable solution

I have read the 36-002 protocol and agree to conduct the study as outlined and in accordance with the ethical principles in the Declaration of Helsinki, ICH GCPs, and applicable local regulations. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures.

I understand that my electronic signature on an electronic case report form indicates that the data therein has been reviewed and accepted by me as the Investigator. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

INVESTIGATOR:

Signature/Date: _____ / _____

Name: _____
(Typed or Printed)

Address: _____

_____

Phone: _____

1. PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

2. SYNOPSIS

Name of Sponsor/Company:	**Santen Philippines Incorporated** Units 2801 to 2802, 28th Floor SM Aura Tower, 26th Street corner McKinley Parkway, The Fort, Taguig City 1630 Philippines
Name of Investigational Product: DE-122 injectable solution	
Name of Active Ingredient: DE-122, a chimeric anti-CD105 (Endoglin) IgG1 antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and V_H regions	
Title of Study: A Multi-Center, Randomized, Double Masked and Active Controlled Phase II Study Assessing the Efficacy, 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	
Study Period: Approximately 31 months Estimated date first subject enrolled: July 2017 Estimated date last subject completed: January 2020	**Phase of Development:** Phase II

Primary Objective:

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

Secondary Objective:

- 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.

Methodology:

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. Approximately seventy six (76) subjects with wet AMD will be randomly assigned to one of three treatment arms:

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)

Subjects will receive 6 monthly intravitreal injections of DE-122 (2.0 mg or 4.0 mg) or Sham, in combination with Lucentis®. The primary analysis will be performed when all subjects complete the Week 24 visit.

The first 6 subjects will be randomized to Arm 1 or Arm 2 in a 1:1 ratio in Stage 1. The Safety Review Team will review the safety parameters of the 6 subjects in Stage 1 and determine if the safety and tolerability at Week 4 are acceptable. If so, enrollment will be continued in a 1:2:2 ratio in the three arms for the remaining approximately 70 subjects in Stage 2.

To be eligible, subjects must have a diagnosis of active CNV secondary to AMD, with some subfoveal component (CNV, fluid, or hemorrhage under the fovea) with lesions ≤ 12 disc areas and ≤ 50% hemorrhage in the study eye. Subjects must be 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). Subjects with Polypoidal Choroidal Vasculopathy (PCV) lesions will be allowed, but Retinal Angiomatous Proliferation (RAP) lesions will be excluded from this study. Screening Visit SD-OCT images and Fluorescein Angiography from Investigator-identified eligible subjects will be sent to the central reading center to confirm eligibility based on AMD lesion attributes specified in the protocol. To balance the randomization, subjects will be stratified by subgroups on the reading center's assessment of lesion type, up to approximately one third (1/3) of the subjects in each arm should have PCV in Stage 2. Subjects must satisfy all other inclusion and exclusion criteria.

Subjects must have best corrected visual acuity (BCVA) of 65 to 25 ETDRS letters (equivalent to 20/50 to 20/320 Snellen) in the study eye.

Eligible subjects who are enrolled in the study will be seen for up to 14 visits.

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

Rescue Criteria:

- BCVA decrease of ≥ 5 letters from the last visit
- Central subfield thickness (CST) increase of ≥ 50 μm from the last visit
- The discretion of investigator

Number of Subjects (planned):

Approximately 76 subjects with wet AMD will be enrolled at approximately 14 sites.

Duration of the Study:

The total study period for each subject will include a screening period (up to 14-days), then a treatment and follow up period (up to 32 weeks).

Masking:

This is a double-masked study, with subjects and examiners including the Principal Investigator (PI) masked to the treatment regimen. However, the designated injecting physician (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.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

At Screening (Day -14 to Day -1) and Visit 1 (Day 1), subjects must meet all of the following inclusion criteria:

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
2. Male or female 50 years of age or older on the date of signing the ICF and able and willing to comply with all treatment and follow-up study procedures.
3. Diagnosis of active choroidal neovascularization (presence of subretinal or intraretinal fluid) secondary to wet AMD as assessed by SD-OCT in the study eye.
4. Diagnosis of active leakage secondary to wet AMD as assessed by FA in the study eye.
5. Diagnosis of wet AMD in the study eye prior to Screening visit (Visit 0) treated with repeated

intravitreal anti-VEGF medication (i.e., At least 3 IVT injections of Anti-VEGF for treatment naïve eyes or eyes adequately maintained on continuous intravitreal anti-VEGF therapy).

6. Last treatment with intravitreal injection of anti-VEGF in the study eye > 20 days and < 80 days prior to Screening visit (Visit 0).
7. All lesion types except for Retinal Angiomatous Proliferation (RAP), total lesion size of ≤ 12 disc areas, contain ≤ 50% hemorrhage and no fibrosis or atrophy involving the foveal center in the study eye
8. BCVA of 65 to 25 ETDRS letters (equivalent to 20/50 to 20/320) in the study eye.
9. BCVA of 25 ETDRS letters (equivalent to 20/320) or better in the fellow eye
10. Reasonably clear media and some fixation in the study eye to allow for good quality SD-OCT and fundus photography.

Exclusion Criteria:

A subject with any of the following conditions is not eligible to participate in the study:

Ocular:

1. Use of any of the following treatments or anticipated use of any of the following treatments to the study eye:
   - Intravitreal or periocular corticosteroid, within 90 days prior to Visit 1 (Day 1) and throughout the study;
   - Fluocinolone acetonide intravitreal implant, within 12 months prior to Visit 1 (Day 1) and throughout the study;
   - Visudyne photodynamic therapy, within 90 days prior to Visit 1 (Day 1) and throughout the study;
2. Uncontrolled or advanced glaucoma, evidenced by an intraocular pressure (IOP) of > 21 mmHg or cup/disc ratio > 0.8 while on medical therapy, or chronic hypotony (< 6 mmHg) in the study eye.
3. Evidence of any other ocular disease other than wet AMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, pseudovitelliform macular degeneration, moderate/severe myopia).
4. History of vitrectomy in the study eye.
5. Need for ocular surgery in the study eye during the course of the study.
6. YAG laser capsulotomy within 30 days prior to Visit 1 (Day 1) in the study eye.
7. Intraocular surgery, including lens removal or laser, within 90 days prior to Visit 1 (Day 1) in the study eye.
8. Ocular or periocular infection in either eye.
9. Pupillary dilation inadequate for quality stereoscopic fundus photography in the study eye.
10. Media opacity that would limit clinical visualization, intravenous fluorescein angiography, or SD-OCT evaluation in the study eye.

11. History of herpetic infection in the study eye or adnexa.
12. Presence of known active toxoplasmosis, inactive toxoplasmosis or toxoplasmosis scar in either eye.
13. Presence of any form of ocular malignancy including choroidal melanoma in either eye.

Non-Ocular:

14. Prior treatment with DE-122 injectable solution.
15. Use of any of the following treatments or anticipated use of any of the following treatments during the study:
    - Systemic treatment with anti-VEGF agents (e.g., bevacizumab)
    - Agents targeting the endoglin pathway
16. Allergy or hypersensitivity to study drug product, fluorescein dye, or other study related procedures/medications.
17. Inadequate renal function: e.g., serum creatinine > 1.3 mg/dL and BUN > 2 x the upper limit of normal (ULN).
18. Inadequate hematologic function: e.g., hemoglobin < 10 g/dL; platelet count < 130 x 10^9 /L; WBC < 3.8 X 10^9 /L or > 10.9 X 10^9 /L.
19. Inadequate liver function: e.g., serum bilirubin > 1.5 mg/dL, GGT, SGOT/ALT, SGPT/AST, and alkaline phosphatase outside 2 x ULN.
20. History of bone marrow suppression.
21. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia).
22. History of hemorrhage, epistaxis, hemoptysis (> ½ teaspoon bright red blood), or treatment with anticoagulants within 90 days prior to Visit 1 (Day 1).
23. Myocardial infarction, stroke or history of transient ischemic attacks within 180 days prior to Visit 1 (Day 1).
24. Major surgery within 90 days prior to Visit 1 (Day 1). Major surgery is defined as any surgery involving a risk to the life of the subject, including any operation upon an organ within the cranium, chest, abdomen, or pelvic cavity.
25. Therapeutic radiation to the head or neck within 90 days prior to Visit 1 (Day 1).
26. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 (Day 1) or planning to participate in other investigational drug or device clinical trials for the duration of the study. This includes both ocular and non-ocular clinical trials.
27. Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 while subject is sitting). If a subject's initial reading exceeds these values, a second reading may be taken 30 or more minutes later. If a subject's blood pressure needs to be controlled by antihypertensive medication, the subject can be eligible if medication is taken continuously for at least 30 days prior to Visit 1 (Day 1).

28. Atrial fibrillation not controlled by the subject's primary care physician or cardiologist within 30 days prior to Visit 1 (Day 1).
29. Clinically significant concurrent illness, laboratory or EKG abnormality.
30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
31. Any systemic infection within 30 days prior to Visit 1 (Day 1).
32. Females who are pregnant or lactating and females of child-bearing potential who are not using adequate contraceptive precautions (i.e., IUD, oral contraceptives, barrier method, or other contraception deemed adequate by the Clinical Investigator). Men who do not agree to practice an acceptable method of contraception throughout the course of the study.
33. Use of marijuana or illegal medication within 30 days prior to Visit 1 (Day 1) and throughout the study.
34. Unable to comply with study procedures or follow-up visits.

In addition, the Clinical Investigator or Santen Medical Monitor may declare a subject ineligible for any sound reason.

Study Eye

The study eye must meet all inclusion and exclusion criteria, including confirmation by the central reading center. If both eyes are eligible based on inclusion and exclusion criteria, the study eye of an eligible subject is defined as the eye with the worse vision. If both eyes have the same vision, the right eye (OD) should be determined as the study eye.

Investigational product, dosage and mode of administration:

Subjects will receive 6 monthly intravitreal injections of DE-122 (2.0 mg or 4.0 mg) or Sham in combination with Lucentis®. Subjects will be randomly assigned to one of three treatment arms as follows:

Stage 1:

- Arm 1: Sham + Lucentis® 0.5 mg (50 µL)
- Arm 2: DE-122, 2.0 mg (20 µL of 100 mg/mL) + Lucentis® 0.5 mg (50 µL)

Stage 2:

- Arm 1: Sham + Lucentis® 0.5 mg (50 µL)
- Arm 2: DE-122, 2.0 mg (20 µL of 100 mg/mL) + Lucentis® 0.5 mg (50 µL)
- Arm 3: DE-122, 4.0 mg (40 µL of 100 mg/mL) + Lucentis® 0.5 mg (50 µL)

Lucentis® will be administered first. DE-122 2.0 or 4.0 mg, or Sham injection will be administered after Lucentis® administration.

Route of Administration of Investigational product:

Intravitreal injection in the study eye.

Criteria for Evaluation:

Efficacy:

The primary efficacy variable assessed at Week 24:

- Mean change from baseline in BCVA

The secondary efficacy variables assessed at Week 24:

- Change from baseline in CST, macular volume and central retinal lesion thickness by SD-OCT, as determined by a reading center
- Proportion of subjects with BCVA: 1) gain of ≥ 15 ETDRS letters (3-line gainers); 2) < 15 letters change (stable); and 3) ≥ 15 letter loss
- Change from baseline in total lesion area and total area of CNV by fluorescein angiogram (FA), as determined by a central reading center
- Change from baseline in greatest linear dimension of the total lesion area by FA, as determined by a central reading center

A Follow-up Analysis is planned when all subjects complete the Week 32 visit. The Analysis will include the number of anti-VEGF injections used for Rescue in addition to efficacy and safety data.

Safety:

The safety assessments will include adverse events (AEs), slit lamp biomicroscopy, indirect ophthalmoscopy, BCVA, IOP, fundus photography, fluorescein angiography, serum chemistry, hematology, urinalysis, vital signs, physical examination, EKG, and pregnancy.

Immunogenicity:

ADA titer will be measured in all subjects at prior to the Lucentis® injection of Day 1, and at Week 24.

Pharmacokinetics (PK):

Levels of DE-122 in serum will be determined and pharmacokinetic assessments will be performed on a subset of subjects.

Pharmacogenomics/genomics:

Subjects who have consented will provide a blood sample for a future Pharmacogenomics/genomics laboratory research. The purpose of this Pharmacogenomics/genomics analysis is future exploratory research to identify possible genetic markers, associated with the study drug(s) and/or ophthalmologic disease conditions. Blood sample will be collected once at Day 1 or any visit after Day 1 during the study.

Biomarker Candidates:

The exploratory investigation of biomarker candidates will be examined in serum and aqueous humor in subjects who give their consent. The samples will also be stored for future exploratory research to identify possible biomarkers associated with the study drug(s) and/or ophthalmologic disease conditions. Serum samples and aqueous humor samples (optional) will be collected on certain scheduled visits. SS-OCT angiography images will be taken at selected sites and stored.

Statistical Methods:

The primary analysis will be performed at Week 24. All safety and efficacy data will be summarized by treatment arms with descriptive statistics. BCVA and CST data will also be presented graphically.

Due to the exploratory nature of this study, the sample size was not calculated for a statistical power.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation/Term	Definition
ADA	anti-drug antibody
AE(s)	adverse event(s)
ALKs	activin receptor-like kinases
ALT	alanine amino transferase
AMD	age-related macular degeneration
AST	aspartate amino transferase
BCVA	best corrected visual acuity
BMP	bone morphogenic protein
BUN	blood urea nitrogen
CD105	endoglin
CNV	choroidal neovascularization
CST	central subfield thickness
CRLT	central retinal lesion thickness
DE-122	a chimeric anti-CD105 (endoglin) IgG1 antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and V_H regions for ophthalmology studies
dL	deciliter
eCRF(s)	electronic case report form(s)
EDC	electronic data capture
EKG	Electrocardiogram (= ECG)
ETDRS	Early Treatment of Diabetic Retinopathy Study
ESI(s)	event(s) of special interest
FA	Fluorescein Angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
HIF-1-α	hypoxia-inducible factor-1-α
ICF	informed consent form

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation/Term	Definition
ICH	International Conference on Harmonization
IEC	independent ethics committee
IOP	intraocular pressure
IRB	institutional review board
ITT	intention-to-treat
IUD	intrauterine device
IVT	intravitreal
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µL	microliter
mL	milliliter
mmHg	millimeter of mercury
MV	macular volume
SS-OCT Angiography	swept source optical coherence tomography angiography
PCV	Polypoidal Choroidal Vasculopathy
RAP	Retinal Angiomatous Proliferation
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SD-OCT	spectral domain optical coherence tomography
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
TGF-β	transforming growth factor-β
TRC105	a chimeric anti-CD105 (endoglin) IgG1 antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and V_H regions for oncology studies
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

5. INTRODUCTION

AMD is the leading cause of irreversible vision loss in developed countries. AMD is characterized by extracellular matrix deposits, known as drusen, accumulating between the retinal pigment epithelium and Bruch's membrane. In exudative or wet AMD unwanted blood vessels grow into the macula which leads to hemorrhage and subretinal fluid. In addition, retinal pigment epithelial detachment, retinal tears, fibrovascular scarring and vitreous hemorrhage may occur. The aberrant growth of leaky vessels is the result of local inflammatory responses leading to disruption of the balance of cytokines that control angiogenesis (Lim et al., 2008).

Angiogenesis is a complex and coordinated process of the growth and sprouting of new blood vessels from pre-existing vasculature. Although several angiogenic factors have been identified, VEGF family proteins, their receptors and intracellular signaling molecules appear to be the key mediators of angiogenesis (Kane et al., 2008).

Exciting advances have been made in understanding the pathogenesis of AMD in recent years. Since 2004, several anti-VEGF medications, such as ranibizumab (Lucentis®), pegaptanib (Macugen®) and aflibercept (Eylea®) have been approved by the FDA for patients with wet AMD. Although Eylea®, which is the most recently approved anti-VEGF medication for wet AMD, showed more than 95% of the subjects maintained vision defined as losing < 15 ETDRS letters for 12 months, only 30% of subjects gained > 15 ETDRS letters. Moreover, approximately 30% of subjects still showed cystic intraretinal edema and subretinal fluid after 12 months of treatment (Heier et al., 2012). Therefore, anti-VEGF treatment may not represent the only pathway towards anti-angiogenesis. New or novel approaches to inhibit angiogenesis are needed to elicit further improvements in visual acuity, macular edema, and quality of life in wet AMD patients.

Endoglin (also known as CD105) is a member of the TGF-β receptor family that is expressed by proliferating endothelial cells and is considered as one of the essential factors for angiogenesis. Normal levels of endoglin are needed for endothelial cell proliferation (Guo et al., 2004; Warrington et al., 2005). Endoglin expression is increased by cellular hypoxia through the production of hypoxia-inducible factor-1-α (HIF-1-α), and endoglin protects hypoxic cells from apoptosis (Li et al., 2003).

Endoglin acts to modulate signaling of multiple kinase receptor complexes of the TGF-β superfamily, including TGF-β receptors, bone morphogenic protein (BMP) receptors, activin receptor-like kinases (ALKs) and activin receptors (Barbara et al., 1999). In the absence of endoglin, activation of TGF-β receptors results in phosphorylation of SMAD 2/3 proteins that inhibit endothelial cell growth. However, activation of endoglin by BMP modulates SMAD protein phosphorylation, through phosphorylation of SMAD 1/5/8 (Nolan-Stevaux et al., 2012). The end result is release of the growth inhibitory effects of TGF-β receptor activation on endothelial cells (Lebrin et al., 2004). Similarly, endoglin is required for proliferation of endothelium in response to BMP. BMP-9 and BMP-10 bind to endoglin and phosphorylate SMAD 1/5/8 to signal endothelial cell proliferation (Park et al., 2008).

A recent study has demonstrated that endoglin is highly expressed in choroidal neovascularization (CNV) membranes surgically excised from wet AMD patients (Yasukawa et al., 2000).

TRC105 is an anti-angiogenic mouse/human chimeric antibody against human endoglin developed by TRACON Pharmaceuticals, Inc. TRC105 binds endoglin on proliferating endothelial cells to inhibit ligand binding by BMP, interrupting signal transduction, resulting in growth inhibition and apoptosis. TRC105 also mediates antibody-dependent cell-mediated cytotoxicity (ADCC).

A series of pharmacology studies in the TRACON oncology program have characterized TRC105 as a potent anti-angiogenic agent. TRC105 alone inhibits VEGF- and bFGF-induced endothelial cell proliferation, suggesting that TRC105 can achieve similar therapeutic effects as anti-VEGF agents but through a different mechanism and specific or shared signaling pathway.

It may be that TRC105 and anti-VEGF agents work synergistically to inhibit neovascularization and that TRC105 suppresses the escape mechanism underlying resistance to the long-term anti-VEGF treatment, both of which are mediated by overexpression of endoglin.

Several clinical trials for various cancer patients have been conducted by TRACON Pharmaceuticals, Inc. As of December 06, 2015, over 438 patients had been treated with TRC105. The majority of the patients have been Caucasian with ages ranging from 18 to 87 years. TRC105 has been well tolerated and exhibited a remarkably consistent adverse event profile, whether dosed as a single agent or dosed in combination with VEGF inhibitors or chemotherapy. Activity of TRC105 in combination has been particularly noteworthy and represents the current development strategy.

Santen is developing an ophthalmic formulation of TRC105, DE-122 injectable solution, suitable for intravitreal injection for the treatment of wet AMD.

Santen has conducted a Phase I/II, open-label, dose-escalating, sequential cohort study assessing the safety, tolerability, immunogenicity, and bioactivity of a single IVT injection of DE-122 injectable solution in the study eye of approximately twelve subjects with refractory wet AMD (Protocol 36-001). Four dose levels of DE-122 were assessed in this Phase I/II study, 0.5 mg/eye, 1.0 mg/eye, 2.0 mg/eye and 4.0 mg/eye. The doses selected for use in this study were based on the results from non-clinical studies. Additional information regarding the non-clinical studies is provided in the Investigator's Brochure.

As of July 2017, all 12 subjects completed the study. There were no reported SAEs. No dose-dependent events were reported and no new safety concerns were identified at all investigated doses. Ocular AEs were reported in 5 subjects (41.7%). Most common AE was Subconjunctival haemorrhage (3 subjects, 25%) and all were considered to be due to the injection procedure.

Santen believes that the Phase I/II study results mentioned above, in addition to the results of the non-clinical studies, supports the use of repeated IVT injections of the 2.0 mg and 4.0 mg concentrations of DE-122 in humans in the Phase II clinical trial (Protocol 36-002).

6. OBJECTIVES

Primary Objective:

- To assess the safety and efficacy of repeated IVT injections of DE-122 (2.0 mg/eye and 4.0 mg/eye) given in combination with Lucentis® in subjects with wet AMD compared with Lucentis® alone.

Secondary Objective:

- 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.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

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. Approximately seventy six (76) subjects with wet AMD will be randomly assigned to one of three treatment arms:

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)

Subjects will receive 6 monthly intravitreal injections of DE-122 (2.0 mg or 4.0 mg) or Sham in the study eye, in combination with Lucentis®.

The first 6 subjects will be randomized to Arm 1 or Arm 2 in a 1:1 ratio in Stage 1. The Safety Review Team will review the safety parameters of the 6 subjects in Stage 1 and determine if the safety and tolerability at Week 4 are acceptable. If so, enrollment will be continued in a 1:2:2 ratio in the three arms for the remaining approximately 70 subjects in Stage 2.

To be eligible, subjects must have a diagnosis of active CNV secondary to AMD, with some subfoveal component (CNV, fluid, or hemorrhage under the fovea) with lesions ≤ 12 disc areas and ≤ 50% hemorrhage in the study eye. Subjects must be 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). Subjects with Polypoidal Choroidal Vasculopathy (PCV) lesions will be allowed, but Retinal Angiomatous Proliferation (RAP) lesions will be excluded from this study.

Screening Visit SD-OCT images and Fluorescein Angiography from Investigator-identified eligible subjects will be sent to the central reading center to confirm eligibility based on AMD lesion attributes specified in the protocol. To balance the randomization, subjects will be stratified by subgroups on the reading center's assessment of lesion type, up to approximately one third (1/3) of the subjects in each arm should have PCV in Stage 2. Subjects must satisfy all other inclusion and exclusion criteria.

Subjects must have best corrected visual acuity (BCVA) of 65 to 25 ETDRS letters (equivalent to 20/50 to 20/320 Snellen) in the study eye.

Eligible subjects who are enrolled in the study will be seen for up to 14 visits.

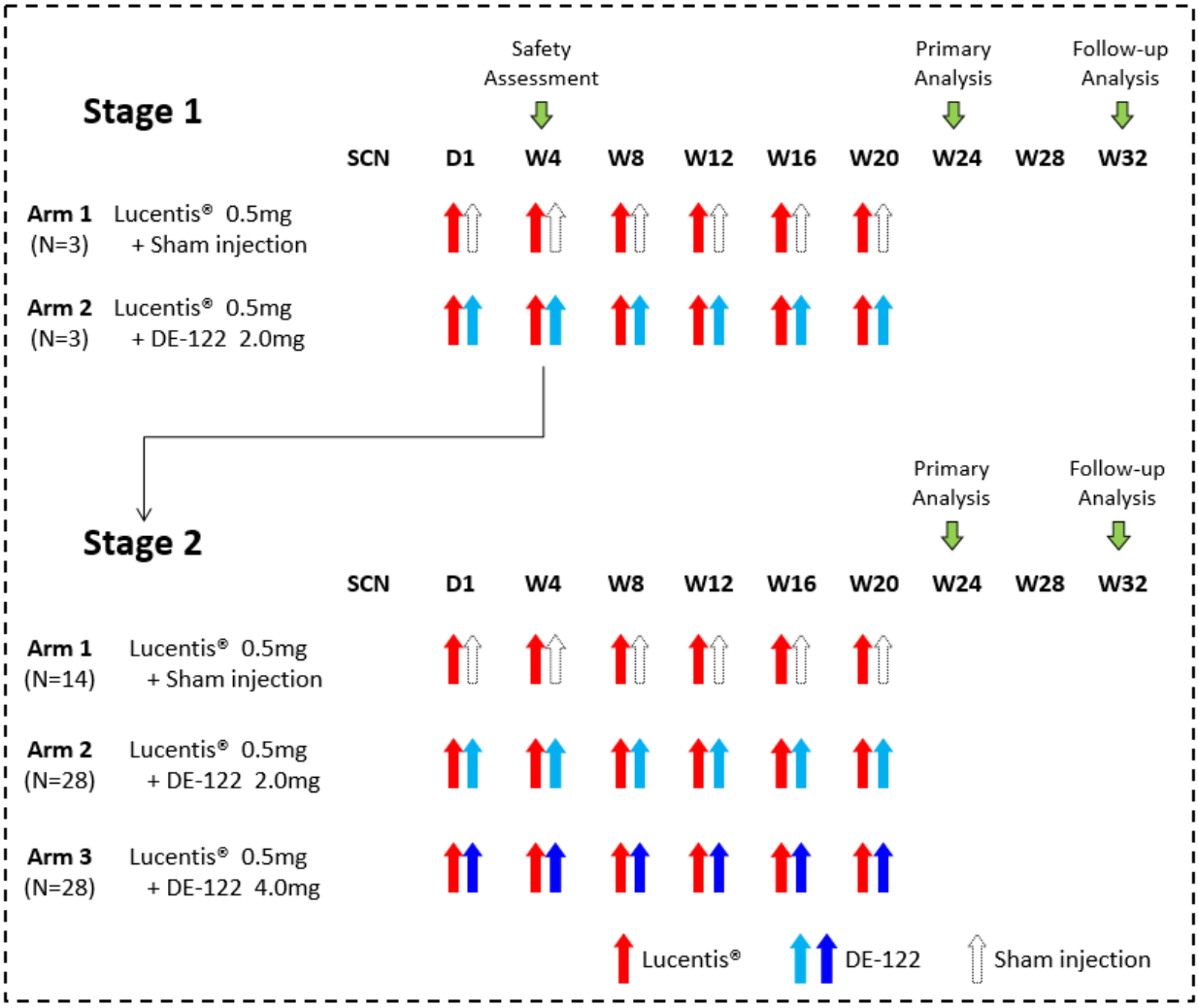
The Primary Analysis is planned when all subjects complete the Week 24 visit. The Follow-up Analysis is planned at Week 32 to assess the number of anti-VEGF injections used for Rescue in addition to efficacy and safety data.

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:

Rescue Criteria:

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

Figure 1: Study Schematic



7.1.1. Selection of Concentrations in the Study

In this clinical study, two dose levels of DE-122 (2.0 mg and 4.0 mg) are being tested in subjects with wet AMD. The maximum amount of DE-122 that a subject can possibly receive is 24 mg over a 20 week period. Systemic exposure of DE-122 in this study given 6 times by IVT injection is anticipated to be significantly lower than the systemic exposure in over 500 cancer

subjects (most of whom received 10 mg/kg of TRC105 by weekly intravenous infusion). Therefore, no concerns regarding systemic toxicity are anticipated in this study.

In pre-clinical studies, the highest tested DE-122 IVT dose of 5 mg/injection in the monkey eye would correlate to 10 mg/eye in human eyes due to the difference in volume, hence the difference in vitreous volume between human and monkey (2:1 ratio) conveys a margin of safety.

In the mouse model of laser-induced CNV efficacy study, animals were given an IVT injection of DE-122 at 0.5, 1.5 and 5.0 μg/eye. DE-122 inhibited CNV in a dose-dependent manner. The highest effective dose was 5 μg/eye. Considering the vitreous volume difference between human and mouse (~1000:1 ratio), a range of 0.5 to 5 mg/eye is considered a logical effective dose level for humans.

In Phase I/II clinical study (Protocol 36-001), four dose levels of DE-122 (0.5 mg, 1.0 mg, 2.0 mg and 4.0 mg) were tested in subjects with refractory wet AMD. No dose-dependent events were reported and no new safety concerns were identified at all investigated doses. Most common AE was Subconjunctival haemorrhage (3 subjects, 25%) and all were considered to be due to the injection procedure.

7.2. Number of Subjects

Approximately 76 subjects (Arm 1: 17 subjects, Arm 2: 31 subjects, Arm 3: 28 subjects) with wet AMD will be enrolled at approximately 14 sites in the Philippines and the US. The final number of subjects enrolled may be adjusted up to 80 based on drop-out rate.

7.3. Treatment Assignment

Two dose levels of DE-122 and Lucentis® will be administered by IVT injection in the study eye.

- DE-122 injectable solution 2.0 mg (20 μL of 100 mg/mL)
- DE-122 injectable solution 4.0 mg (40 μL of 100 mg/mL)
- Ranibizumab (Lucentis®) 0.5 mg (50 μL of 10 mg/mL)

7.4. Dose Adjustment Criteria

The Safety Review Team will review safety parameters after the 6 subjects in Stage 1 have completed Week 4. If the safety criteria for adjusting or stopping doses and the criteria for study termination are not met, the remaining subjects in three Arms will be enrolled in the study.

7.4.1. Safety Criteria for 6 Subjects in Stage 1

If more than one of the following events is observed by Week 4 visit in Stage 1, planned doses may be adjusted or stopped by the Safety Review Team.

- Visual acuity loss from baseline defined as:
  - Loss of best corrected visual acuity (BCVA) of 30 or more letters not due to vitreous hemorrhage or injection procedure **OR**
  - Transition to no light perception (NLP) not due to injection procedure
- Clinically significant inflammation defined as:

  - > 3+ vitreous haze as measured by the National Eye Institute Grading Scheme (Nussenblatt et al., 1985) **OR**
  - Sterile endophthalmitis (including the presence of hypopyon)
- Severe IOP elevation as measured by tonometry, on two separate exams, at least one day apart, excluding day of injection (despite pharmaceutical intervention):
  - > 35 mmHg **OR**
  - Increase of > 15 mmHg from baseline
- Retinal non-perfusion of the study eye/vascular occlusion
- Vasculitis
- Retinitis
- > 2+ disc edema
- > 2 quadrants of retinal hemorrhage

If there is insufficient safety information in either in the 6 subjects in Stage 1, the Safety Review Team may decide to treat additional subjects before continuing enrollment in the study.

Criteria for Study Termination

Unacceptable safety signals that prevent continuing to other subjects in all arms or result in stopping the study may include any of the following, if deemed to be related to DE-122 study drug (not DE-122 administration procedures):

- Pattern of systemic AEs
- Any of the following AEs in any 2 subjects in any cohort:
  - Retinal non-perfusion of the study eye/vascular occlusion
  - Vasculitis
  - Retinitis
  - > 2+ disc edema
  - > 2 quadrants of retinal hemorrhage

7.5. Study Procedures

All subjects must sign a written ICF before participating in any study-related activity, and the subject will be assigned a unique screening number. Central randomization will occur at Visit 1 (Day 1) after a subject meets all eligibility requirements at Screening. Each randomized subject will be assigned a unique subject number. If a subject is discontinued from the study for any reason, the subject number will remain in effect and will not be reused.

A Schedule of Events can be found below and detailed procedures for examinations can be found in Section 23.4, Appendix D – Procedures for Examinations.

Table 3: Schedule of Events

***Only the subjects who have consented under the protocol prior to Version 4.0 (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
Fundus photography	X				X		X					X		X
Fluorescein angiography	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		

Table 3: 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)
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					
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. Informed Consent - obtain prior to conducting any study-related activities. Separate informed consent is required to participate in the ancillary Biomarker aqueous humor sample 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.

7.5.1. Screening Phase

7.5.1.1. Visit 0/Screening (Day -14 to Day -1)

- Explain the purpose and details of the study to the subject and obtain written informed consent prior to the subject's participation in any study related activity.
- Obtain separate informed consent for participant in the ancillary Biomarker aqueous humor sample collection and Pharmacogenomics/genomics blood sample collection. Ensure that the subject understands that if they do not wish to provide aqueous humor sample and blood sample for the Biomarker research study and the Pharmacogenomics/genomics study that it will not affect the subject's enrollment in the trial.
- Obtain subject's demographic information, medical, surgical and medication history.
- Perform the following assessments: (all ophthalmic procedures to be performed OU). The procedures of each assessment are described in Section 23.4, Appendix D.
  - Physical examination (if not performed by external internist)
  - Vital signs
  - EKG
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
  - Fundus photography
  - Fluorescein angiography
- Review the inclusion and exclusion criteria. Do not continue screening any subject who does not meet the screening eligibility requirements.
- If the subject continues to be eligible for the study, collect more than 8 hours fasting urine and blood specimen for the following examinations:
  - Urinalysis
  - Serum pregnancy test (for females of child-bearing potential)
  - Hematology, chemistry serum sample
- If subject has not been fasting, schedule the subject as soon as possible for fasting blood draw and urine specimen.

- Upload collected images (Fluorescein angiography, Fundus photography and SD-OCT) of both eyes to the central reading center for confirmation of subject eligibility.
- Schedule the subject to return for Visit 1 (Day 1).

7.5.2. Treatment/follow-up phase

7.5.2.1. Visit 1 (Day 1)

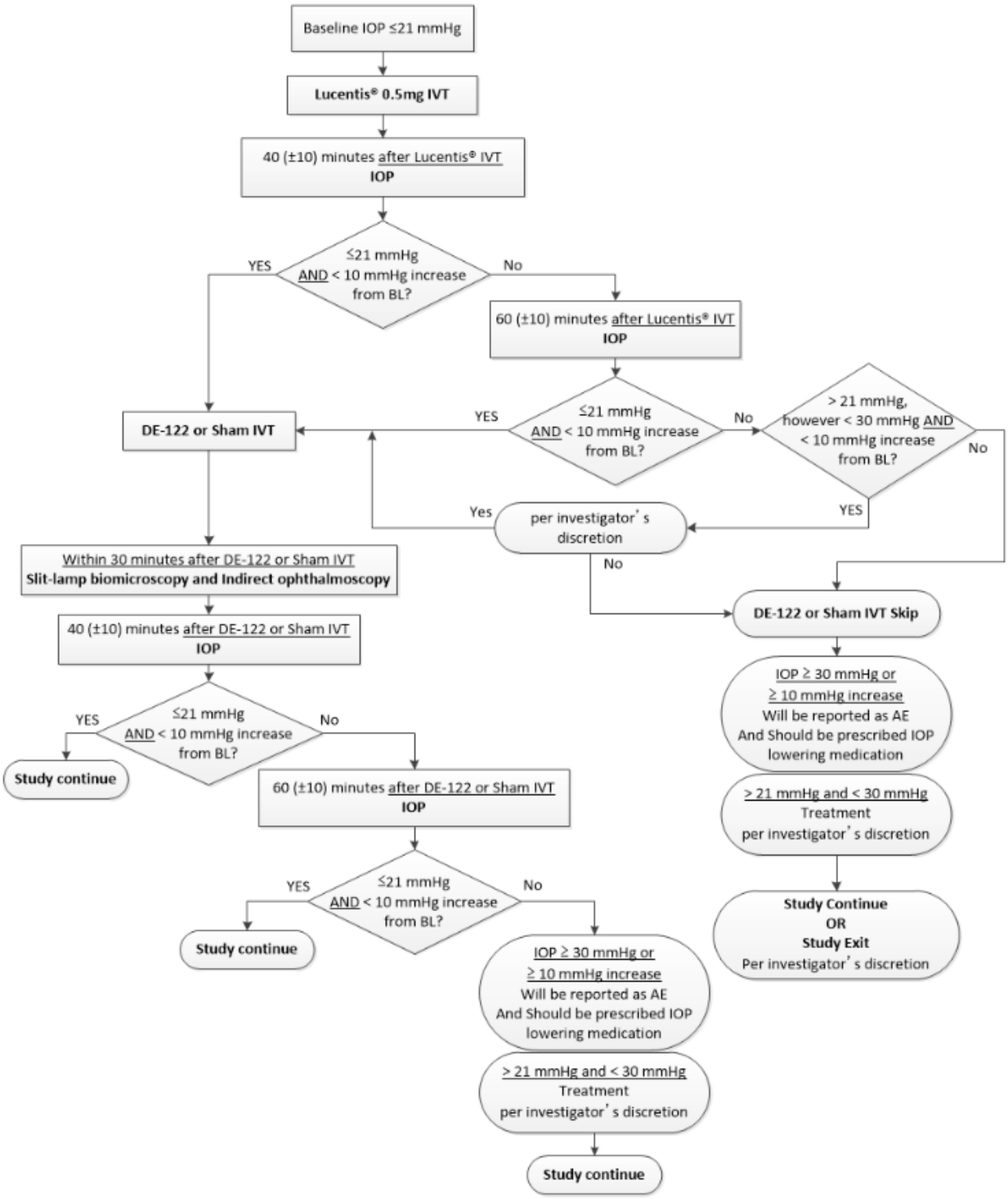
- **Review** results of the following procedures performed at Screening (Day -14 to Day -1) to determine continuation in the study:
  - Physical examination
  - EKG
  - Urinalysis
  - Blood chemistry and hematology tests
  - Serum pregnancy test (for females of child-bearing potential)
  - Eligibility determination by the central reading center
- If the subject continues to be eligible for the study, the following assessments must be performed prior to administration of study drugs to confirm eligibility and obtain baseline characteristics: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
- If the subject continues to be eligible for the study, collect urine and blood specimen for the following examinations:
  - Urine pregnancy test (for females of child-bearing potential)
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Immunogenicity serum sample

- Biomarker serum sample

- If the subject has consented to the Pharmacogenomics/genomics study, collect blood sample for the Pharmacogenomics/genomics study. Blood collection for the Pharmacogenomics/genomics study can be alternatively collected once at any visit during the study after Visit 1(Day 1).
- Perform final review of inclusion/exclusion criteria. If the subject has met all eligibility criteria, including confirmation of the lesion eligibility by the central reading center (which will also confirm lesion type), determine the study eye. The subject is then randomized, via IWRS.
- After the subject has been randomized to a treatment Arm, Lucentis® will be administered as per drug labeling.
- If the subject has consented to the Biomarker aqueous humor sample collection, collect the aqueous humor sample before Lucentis® administration.
- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
      If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion. In addition, the Clinical Investigator has the discretion on whether to have the subject continue or exit the study.
    - **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT will not be administered.** The subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the event will be reported as

an AE. In addition, the Clinical Investigator has the discretion on whether to have the subject continue or exit the study.

- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.
- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU)
  - Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after each IVT injection.
- Collect blood specimen for the following examinations at 3 hrs (±10 mins) post DE-122 or Sham injection. If DE-122 or Sham IVT injection is skipped, the blood sampling will be done at 3 hrs (±10 mins) post Lucentis® administration.
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- Upload collected images (SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 2 (Day 3) or Visit 3 (Week 1 (D8±1)).


Baseline IOP ≤21 mmHg
Lucentis® 0.5mg IVT
40 (±10) minutes after Lucentis® IVT
IOP
YES
≤21 mmHg
AND < 10 mmHg increase
from BL?
No
60 (±10) minutes after Lucentis® IVT
IOP
YES
≤21 mmHg
AND < 10 mmHg increase
from BL?
No
> 21 mmHg,
however < 30 mmHg AND
< 10 mmHg increase
from BL?
No
YES
DE-122 or Sham IVT
Yes
per investigator's
discretion
No
Within 30 minutes after DE-122 or Sham IVT
Slit-lamp biomicroscopy and Indirect ophthalmoscopy
40 (±10) minutes after DE-122 or Sham IVT
IOP
YES
≤21 mmHg
AND < 10 mmHg increase
from BL?
No
Study continue
60 (±10) minutes after DE-122 or Sham IVT
IOP
YES
≤21 mmHg
AND < 10 mmHg increase
from BL?
No
Study continue
IOP ≥ 30 mmHg or
≥ 10 mmHg increase
Will be reported as AE
And Should be prescribed IOP
lowering medication
> 21 mmHg and < 30 mmHg
Treatment
per investigator's discretion
Study continue
DE-122 or Sham IVT Skip
IOP ≥ 30 mmHg or
≥ 10 mmHg increase
Will be reported as AE
And Should be prescribed IOP
lowering medication
> 21 mmHg and < 30 mmHg
Treatment
per investigator's discretion
Study Continue
OR
Study Exit
Per investigator's discretion

7.5.2.2. Visit 2 (Day 3)

For only the subjects who have consented under the protocol prior to Version 4.0

- Perform the following assessments:
  - Query for AEs
  - Update medical history and medications
- Collect blood specimen for the following examinations at 48 (±2) hrs post DE-122 or Sham injection. If DE-122 or Sham IVT injection was skipped at Visit 1, blood specimen will be collected at 48 (±2) hrs post Lucentis® IVT injection.
  - PK serum sample
  - Biomarker serum sample
- Schedule the subject to return for Visit 3 (Week 1 (D8±1)).

7.5.2.3. Visit 3 (Week 1 (D8±1))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - EKG
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
- Collect blood specimen for the following examinations:
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- Upload collected images (SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 4 (Week 4 (D29±3)). Remind subjects to fast 8 hours prior to next visit.

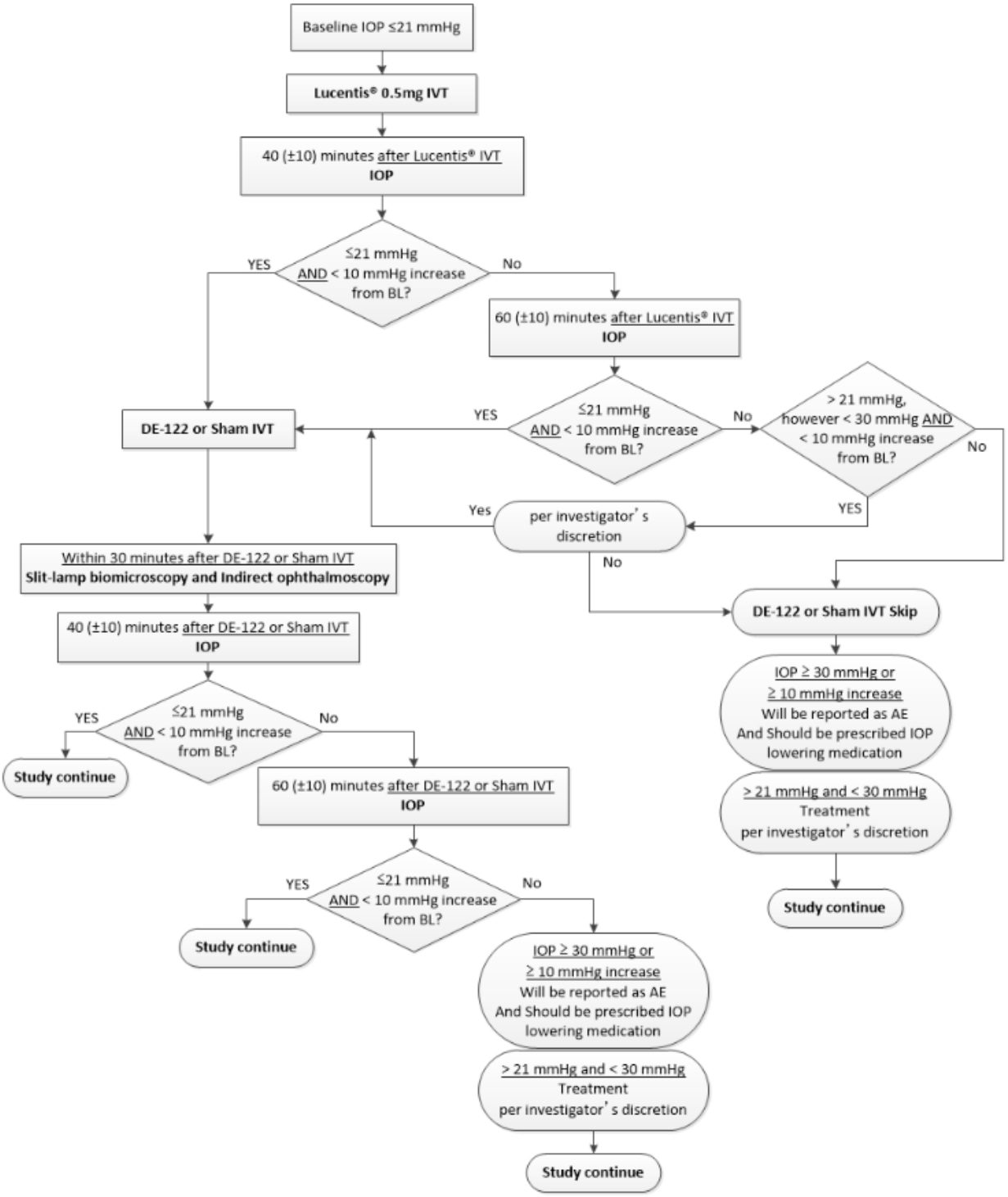
7.5.2.4. Visit 4 (Week 4 (D29±3))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
  - Fundus photography
  - Fluorescein angiography
- Collect urine and blood specimen for the following examinations:
  - Urinalysis
  - Hematology, chemistry serum sample
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.

- If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
  If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion.
- **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT should not be administered.** The subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the event will be reported as an AE.

- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.
- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU).
  - Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after each IVT injection.
- If the subject has consented to Biomarker aqueous humor sample collection, collect the aqueous humor sample after DE-122 or Sham IVT. If DE-122 or Sham IVT is not administered, the aqueous humor sample should be collected with no time restriction.

- If subject has not been fasting, schedule the subject as soon as possible for fasting blood draw and urine specimen.
- Upload collected images (Fluorescein angiography, Fundus photography and SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 5 (Week 8 (D57±3)).


Baseline IOP ≤21 mmHg
Lucentis® 0.5mg IVT
40 (±10) minutes after Lucentis® IVT
IOP
≤21 mmHg
AND < 10 mmHg increase
from BL?
YES
No
60 (±10) minutes after Lucentis® IVT
IOP
≤21 mmHg
AND < 10 mmHg increase
from BL?
YES
No
> 21 mmHg,
however < 30 mmHg AND
< 10 mmHg increase
from BL?
No
YES
DE-122 or Sham IVT
Yes
per investigator's
discretion
No
Within 30 minutes after DE-122 or Sham IVT
Slit-lamp biomicroscopy and Indirect ophthalmoscopy
40 (±10) minutes after DE-122 or Sham IVT
IOP
≤21 mmHg
AND < 10 mmHg increase
from BL?
YES
No
Study continue
60 (±10) minutes after DE-122 or Sham IVT
IOP
≤21 mmHg
AND < 10 mmHg increase
from BL?
YES
No
Study continue
IOP ≥ 30 mmHg or
≥ 10 mmHg increase
Will be reported as AE
And Should be prescribed IOP
lowering medication
> 21 mmHg and < 30 mmHg
Treatment
per investigator's discretion
DE-122 or Sham IVT Skip
IOP ≥ 30 mmHg or
≥ 10 mmHg increase
Will be reported as AE
And Should be prescribed IOP
lowering medication
> 21 mmHg and < 30 mmHg
Treatment
per investigator's discretion
Study continue
Study continue

7.5.2.5. Visit 5 (Week 8 (D57±3))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
      If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion.
    - **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT should not be administered.** The subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's

discretion (an unscheduled visit may apply), and the event will be reported as an AE.

- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.
- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU)
  - Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after each IVT injection.
- Upload collected images (SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 6 (Week 12 (D85±4)). Remind subjects to fast 8 hours prior to next visit.

7.5.2.6. Visit 6 (Week 12 (D85±4))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy

  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
  - Fundus photography
  - Fluorescein angiography
- Collect urine and blood specimen for the following examinations:
  - Urinalysis
  - Hematology, chemistry serum sample
- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
      If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion.
    - **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT should not be administered.** The subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the event will be reported as an AE.
- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.

- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU).
  - Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after each IVT injection.
- If subject has not been fasting, schedule the subject as soon as possible for fasting blood draw and urine specimen.
- Upload collected images (Fluorescein angiography, Fundus photography and SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 7 (Week 16 (D113±4)).

7.5.2.7. Visit 7 (Week 16 (D113±4))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy

- SD-OCT
- SS-OCT angiography (for selected sites)

- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
      If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion.
    - **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT should not be administered.** The subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the event will be reported as an AE.
- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.
- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU).
  - Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.

- IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.
  - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
  - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.

- AE assessments must be performed after each IVT injection.
- Upload collected images (SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 8 (Week 20 (D141±4)).

7.5.2.8. Visit 8 (Week 20 (D141±4))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
- Collect blood specimen for the following examinations:
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- **Perform Lucentis® administration** as per drug labeling, and then perform the following procedures after Lucentis® administration.
  - IOP will be measured at 40 (±10) minutes post-injection.
    - If post-injection IOP is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.

- If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.

– IOP will be measured at 60 (±10) minutes post-injection, if applicable.

- If post-injection IOP at 60 (±10) minutes is ≤ 21 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered.
- If post-injection IOP at 60 (±10) minutes is > 21 mmHg, however the IOP is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion, DE-122 or Sham IVT will be administered per the Clinical Investigator's discretion.
  If the Clinical Investigator determine that DE-122 or Sham IVT will Not be administered, the subject will be treated according to the Clinical Investigator's discretion. The DE-122 or Sham IVT injection can be performed at the follow up visit (within the time window of Visit 8) per the Clinical Investigator's discretion.
- **If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, DE-122 or Sham IVT should not be administered at the day of the visit.** Per the Clinical Investigator and Medical Monitor, the DE-122 or Sham IVT injection can be performed if IOP at the follow up visit (within the time window of Visit 8) is < 30 mmHg AND increased < 10 mmHg from pre-injection IOP and there is no concern regarding retinal artery perfusion.
  If DE-122 or Sham IVT injection will not be performed, the subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion (an unscheduled visit may apply), and the event will be reported as an AE.

- **Perform DE-122 or Sham administration**, and then perform the following procedures after DE-122 or Sham administration.
- After DE-122 or Sham administration, the following will be performed: (all ophthalmic procedures to be performed OU)
  – Within 30 minutes following DE-122 or Sham IVT
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  – IOP measurement 40 (±10) minutes following DE-122 or Sham IVT injection
    - If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  – IOP will be measured at 60 (±10) minutes following DE-122 or Sham IVT injection, if applicable.

  - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
  - If post-DE-122 or Sham injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.

- AE assessments must be performed after each IVT injection.
- If the subject has consented to Biomarker aqueous humor sample collection, collect the aqueous humor sample after DE-122 or Sham IVT.
- Collect blood specimen for the following examinations at 3 hrs (±10 mins) post DE-122 or Sham injection. If DE-122 or Sham IVT injection is skipped, the blood sampling will be done at 3 hrs (±10 mins) post Lucentis® administration:
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- Upload collected images (SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 9 (Week 20 + 2 days) or Visit 10 (Week 20 + 7 (±1) days).

7.5.2.9. Visit 9 (Week 20 + 2 days)

For only the subjects who have consented under the protocol prior to Version 4.0

- Perform the following assessments:
  - Query for AEs
  - Update medical history and medications
- Collect blood specimen for the following examinations at 48 (±2) hrs post DE-122 or Sham injection. If DE-122 or Sham IVT injection was skipped at Visit 8, blood specimen will be collected at 48 (±2) hrs post Lucentis® IVT injection.
  - PK serum sample
  - Biomarker serum sample
- Schedule the subject to return for Visit 10 (Week 20 + 7 (±1) days).

7.5.2.10. Visit 10 (Week 20 + 7 (±1) days)

- Perform the following assessments:
  - Query for AEs
  - EKG

  - Update medical history and medications
- Collect blood specimen for the following examinations:
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Biomarker serum sample
- Schedule the subject to return for Visit 11 (Week 24 (D169±5)). Remind subjects to fast 8 hours prior to next visit.

7.5.2.11. Visit 11 (Week 24 (D169±5))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)
  - Query for AEs
  - Update medical history and medications
  - Physical examination (if not performed by external internist)
  - Vital signs
  - EKG
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
  - Fundus photography
  - Fluorescein angiography
- Collect urine and blood specimen for the following examinations:
  - Urinalysis
  - Serum pregnancy test (for females of child-bearing potential)
  - Hematology, chemistry serum sample
  - PK serum sample **(for only the subjects who have consented under the protocol prior to Version 4.0)**
  - Immunogenicity serum sample
  - Biomarker serum sample

- Rescue therapy with any anti-VEGF medication may be allowed if the following rescue criteria are met:
  - BCVA decrease of ≥ 5 letters from the last visit score **OR**
  - CST increase from the last visit of ≥ 50µm **OR**
  - The discretion of investigator
- If rescue is performed, the following assessments must be performed after the administration of Rescue treatment: (all ophthalmic procedures to be performed OU)
  - Within 30 minutes following Rescue treatment
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP: 40 (±10) minutes following injection
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after Rescue treatment, if applicable.
- If subject has not been fasting, schedule the subject as soon as possible for fasting blood draw and urine specimen.
- Upload collected images (Fluorescein angiography, Fundus photography and SD-OCT) of the study eye to the central reading center.
- Schedule the subject to return for Visit 12 (Week 28 (D197±5)).

7.5.2.12. Visit 12 (Week 28 (D197±5))

- Perform the following assessments:
  - Query for AEs
  - Update medical history and medications
  - Vital signs
  - BCVA (ETDRS)
  - M-CHARTS™

  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
- Rescue therapy with any anti-VEGF medication may be allowed if the following rescue criteria are met:
  - BCVA decrease of ≥ 5 letters from the last visit score **OR**
  - CST increase from the last visit of ≥ 50μm **OR**
  - The discretion of investigator
- If rescue is performed, the following assessments must be performed after the administration of Rescue treatment: (all ophthalmic procedures to be performed OU)
  - Within 30 minutes following Rescue treatment
    - Slit-lamp biomicroscopy
    - Indirect ophthalmoscopy
  - IOP: 40 (±10) minutes following injection
    - If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection.
  - IOP will be measured at 60 (±10) minutes post-injection, if applicable.
    - If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up (an unscheduled visit may apply).
    - If post-injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be treated according to the Clinical Investigator's discretion.
- AE assessments must be performed after Rescue treatment, if applicable.
- Upload collected images (SD-OCT) of the study eye to Reading center.
- Schedule the subject to return for Visit 13/Exit (Week 32 (D225±5)). Remind subjects to fast 8 hours prior to next visit.

7.5.3. Study Exit

7.5.3.1. Visit 13/Exit (Week 32 (D225±5))

- Perform the following assessments: (all ophthalmic procedures to be performed OU)

  - Query for AEs
  - Update medical history and medications
  - Physical examination (if not performed by external internist)
  - Vital signs
  - EKG
  - BCVA (ETDRS)
  - M-CHARTS™
  - Slit-lamp biomicroscopy
  - IOP
  - Indirect ophthalmoscopy
  - SD-OCT
  - SS-OCT angiography (for selected sites)
  - Fundus photography
  - Fluorescein angiography
- Collect urine and blood specimen for the following examinations:
  - Urinalysis
  - Serum pregnancy test (for females of child-bearing potential)
  - Hematology, chemistry serum sample
- If subject has not been fasting, schedule the subject as soon as possible for fasting blood draw and urine specimen.
- Upload collected images (Fluorescein angiography, Fundus photography and SD-OCT) of the study eye to the central reading center.
- Exit subject from study.

7.5.4. Unscheduled Visits

If a subject requires evaluation between scheduled visits, complete all applicable study specified procedures as necessary and record the information on the Unscheduled Visit form(s).

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible subjects must meet all eligibility criteria described in Section 8.1 and Section 8.2.

8.1. Subject Inclusion Criteria

At Screening (Day -14 to Day -1) and Visit 1 (Day 1), subjects must meet all of the following inclusion criteria:

1. Provide signed written informed consent on the IRB/EC approved ICF and provide authorization as appropriate for local privacy regulations.
2. Male or female 50 years of age or older on the date of signing the ICF and able and willing to comply with all treatment and follow-up study procedures.
3. Diagnosis of active choroidal neovascularization (presence of subretinal or intraretinal fluid) secondary to wet AMD as assessed by SD-OCT in the study eye.
4. Diagnosis of active leakage secondary to wet AMD as assessed by FA in the study eye.
5. Diagnosis of wet AMD in the study eye prior to Screening visit (Visit 0) treated with repeated intravitreal anti-VEGF medication (i.e., At least 3 IVT injections of Anti-VEGF for treatment naïve eyes or eyes adequately maintained on continuous intravitreal anti-VEGF therapy).
6. Last treatment with intravitreal injection of anti-VEGF in the study eye > 20 days and < 80 days prior to Screening visit (Visit 0).
7. All lesion types except for RAP, total lesion size of ≤ 12 disc areas, contain ≤ 50% hemorrhage and no fibrosis or atrophy involving the foveal center in the study eye.
8. BCVA of 65 to 25 ETDRS letters (equivalent to 20/50 to 20/320) in the study eye.
9. BCVA of 25 ETDRS letters (equivalent to 20/320) or better in the fellow eye.
10. Reasonably clear media and some fixation in the study eye to allow for good quality SD-OCT and fundus photography.

8.2. Subject Exclusion Criteria

A subject with any of the following conditions is not eligible to participate in the study:

Ocular:

1. Use of any of the following treatments or anticipated use of any of the following treatments to the study eye:
   - Intravitreal or periocular corticosteroid, within 90 days prior to Visit 1 (Day 1) and throughout the study;
   - Fluocinolone acetonide intravitreal implant, within 12 months prior to Visit 1 (Day 1) and throughout the study;

- Visudyne photodynamic therapy, within 90 days prior to Visit 1 (Day 1) and throughout the study;

2. Uncontrolled or advanced glaucoma, evidenced by an IOP of > 21 mmHg or cup/disc ratio > 0.8 while on medical therapy, or chronic hypotony (< 6 mmHg) in the study eye.
3. Evidence of any other ocular disease other than wet AMD in the study eye that may confound the outcome of the study (e.g., active diabetic retinopathy, posterior uveitis, pseudovitelliform macular degeneration, moderate/severe myopia).
4. History of vitrectomy in the study eye.
5. Need for ocular surgery in the study eye during the course of the study.
6. YAG laser capsulotomy within 30 days prior to Visit 1 (Day 1) in the study eye.
7. Intraocular surgery, including lens removal or laser, within 90 days prior to Visit 1 (Day 1) in the study eye.
8. Ocular or periocular infection in either eye.
9. Pupillary dilation inadequate for quality stereoscopic fundus photography in the study eye.
10. Media opacity that would limit clinical visualization, intravenous fluorescein angiography, or SD-OCT evaluation in the study eye.
11. History of herpetic infection in the study eye or adnexa.
12. Presence of known active toxoplasmosis, inactive toxoplasmosis or toxoplasmosis scar in either eye.
13. Presence of any form of ocular malignancy including choroidal melanoma in either eye.

Non-Ocular:

14. Prior treatment with DE-122 injectable solution.
15. Use of any of the following treatments or anticipated use of any of the following treatments during the study:
    - Systemic treatment with anti-VEGF agents (e.g., bevacizumab)
    - Agents targeting the endoglin pathway
16. Allergy or hypersensitivity to study drug product, fluorescein dye, or other study related procedures/medications.
17. Inadequate renal function: e.g., serum creatinine > 1.3 mg/dL and BUN > 2 x the ULN.
18. Inadequate hematologic function: e.g., hemoglobin < 10 g/dL; platelet count < 130 x 10^9 /L; WBC < 3.8 X 10^9 /L or > 10.9 X 10^9 /L.
19. Inadequate liver function: e.g., serum bilirubin > 1.5 mg/dL, GGT, SGOT/ALT, SGPT/AST, and alkaline phosphatase outside 2 x ULN.
20. History of bone marrow suppression.

21. Active bleeding or pathologic condition that carries a high risk of bleeding (e.g., hereditary hemorrhagic telangiectasia).
22. History of hemorrhage, epistaxis, hemoptysis (> ½ teaspoon bright red blood), or treatment with anticoagulants within 90 days prior to Visit 1 (Day 1).
23. Myocardial infarction, stroke or history of transient ischemic attacks within 180 days prior to Visit 1 (Day 1).
24. Major surgery within 90 days prior to Visit 1 (Day 1). Major surgery is defined as any surgery involving a risk to the life of the subject, including any operation upon an organ within the cranium, chest, abdomen, or pelvic cavity.
25. Therapeutic radiation to the head or neck within 90 days prior to Visit 1 (Day 1).
26. Participation in other investigational drug or device clinical trials within 30 days prior to Visit 1 (Day 1) or planning to participate in other investigational drug or device clinical trials for the duration of the study. This includes both ocular and non-ocular clinical trials.
27. Uncontrolled blood pressure (defined as systolic > 180 mmHg and/or diastolic > 110 while subject is sitting). If a subject's initial reading exceeds these values, a second reading may be taken 30 or more minutes later. If a subject's blood pressure needs to be controlled by antihypertensive medication, the subject can be eligible if medication is taken continuously for at least 30 days prior to Visit 1 (Day 1).
28. Atrial fibrillation not controlled by the subject's primary care physician or cardiologist within 30 days prior to Visit 1 (Day 1).
29. Clinically significant concurrent illness, laboratory or EKG abnormality.
30. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
31. Any systemic infection within 30 days prior to Visit 1 (Day 1).
32. Females who are pregnant or lactating and females of child-bearing potential who are not using adequate contraceptive precautions (i.e., IUD, oral contraceptives, barrier method, or other contraception deemed adequate by the Clinical Investigator). Men who do not agree to practice an acceptable method of contraception throughout the course of the study.
33. Use of marijuana or illegal medication within 30 days prior to Visit 1 (Day 1) and throughout the study.
34. Unable to comply with study procedures or follow-up visits.

In addition, the Clinical Investigator or Santen Medical Monitor may declare a subject ineligible for any sound reason.

8.3. Subject Withdrawal Criteria

An early termination occurs when a subject who provides written informed consent ceases participation in the study, regardless of circumstances, before the completion of the study. Subjects may voluntarily withdraw from the study at any time for any reason. In addition, the Clinical Investigator or the Medical Monitor may terminate a subject's study participation for reasons related to the best interest of the subject. Subjects who terminate from the study may be replaced. Subjects may be terminated from the study due to any of the following reasons:

- Non-compliance
- Lost to follow-up
- Protocol violation
- Withdrawal by subject
- AEs
- Death
- Other

If a subject is discontinued from the study before completing Visit 13/Exit (Week 32 (Day 225±5)), then to the extent possible, all assessments, including safety, that are scheduled to be performed at Visit 13/Exit should be performed on the day of discontinuation.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

DE-122 is a chimeric anti-CD105 IgG1 antibody consisting of human Cκ and Cγ1 constant regions with murine Vκ and V_H regions. DE-122 is composed of two light chains of 213 amino acids and two heavy chains of 448 amino acids and has an approximate molecular weight of 148 kDa. DE-122 is utilized in this clinical study in a formulation designed for IVT injection.

9.2. Concomitant Medications

The use of any concomitant prescription or over-the-counter medication will be recorded during the study. Therapy considered necessary for the subject's welfare may be given at the discretion of the Clinical Investigator during the study. Whenever possible, concomitant medications should be administered in dosages that remain constant throughout the study. The generic name, indication, route of administration, frequency, dose, start date and stop date (if applicable) will be recorded for each medication.

9.2.1. Prohibited Medications or Treatments

Any treatments for wet AMD in the study eye other than DE-122 and Lucentis® are prohibited during the study.

Any systemic treatments with anti-VEGF agents (e.g., bevacizumab) are prohibited during the study.

The decision to administer a prohibited concomitant medication or treatment during the study should be made with the safety of the subject as the primary consideration. Whenever possible, Santen should be notified before any prohibited medication or treatment is administered or if the permissibility of a specific medication or treatment is in question.

9.2.2. Rescue Therapy

Rescue therapy is defined as IVT injection of Anti-VEGF medication in the study eye. Eligibility for Rescue therapy to be determined as per rescue criteria in Section 7.1.

9.3. Treatment Compliance

In order to obtain efficacy and safety data, it is critical that the treatment regimen and visit schedule specified in this protocol are followed. The Clinical Investigator is required to administer the DE-122 injection and Lucentis®, and is responsible for scheduling the subject for follow-up visits as specified in the protocol. Study monitors will verify pertinent data to confirm the study is conducted according to the protocol.

9.4. Randomization and Masking

The first 6 subjects will be randomized in a 1:1 ratio to Arm 1 or Arm 2 at Visit 1 in Stage 1. If the safety and tolerability at Week 4 for the 6 subjects are acceptable, randomization will be

continued in a 1:2:2 ratio in the three arms for the remaining approximately 70 subjects in Stage 2.

To balance the randomization, subjects will be stratified by subgroups on the reading center's assessment of lesion type, up to approximately one third (1/3) of the subjects in each arm should have PCV in Stage 2.

One of arms will have sham injection which is a mimic procedure of a real intravitreal injection but does not penetrate the eye. To keep masking of the clinical trial, investigator and authorized study staffs must follow the points below.

- The designated unmasked injecting physician and the designated unmasked injection staff must ensure any information regarding clinical study drugs injection during the study is inaccessible to other study staff.
- The designated unmasked injecting physician and the designated unmasked injection staff cannot perform any assessments or examinations for the study other than clinical study drug injection procedures and examinations post drug injections.
- Masked study staff not designated to study drug injections, including investigators, examiner and other clinical site staff, cannot participate in any procedures for clinical study drug injections and examinations post drug injections.

In case of a medical emergency, the Principal Investigator or site staff may reveal the treatment information by unmasking in IWRS to know which treatment the subject has received. The Principal Investigator should contact Santen, or Santen's designee, before taking this measure, if there is sufficient time. Santen, or Santen's designee, must be informed of all instances where the code is broken and of the reasons for such instances.

Additionally, the adverse event or serious adverse event for which study treatment was unmasked should be reported to Santen Drug Safety (see Section 12.1).

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Investigational Drug

DE-122 for IVT injection is formulated in a proprietary, clear, aqueous solution. The 2 dose levels of DE-122 to be administered in the study eye are shown in Table 4.

Table 4: DE-122 Dosing

Injection Volume of:	Will deliver approximately:
20 microliters of 100 mg/mL DE-122	2.0 mg DE-122
40 microliters of 100 mg/mL DE-122	4.0 mg DE-122

The Clinical Investigator will use syringes and needles supplied by Santen/Representative.

10.1.2. Concomitant drug

Lucentis® 0.5 mg (50 µL) is administered in all groups.

10.1.3. Study Drug Complaint Reporting

Complaints regarding the DE-122 for IVT injection should be reported to Santen/Representative Product Complaint at clinicalsupplies@santen.com or +1-415-268-9100.

10.1.4. Other Study Supplies

Santen/Representative will supply a fluoroquinolone equivalent antibiotic eye drop, needles and syringes, and would supply 10 % povidone iodine and sharps container.

10.2. Study Drug Packaging and Labeling

DE-122 injectable solutions are filled (0.3 mL fill) in 2-mL Type 1 Glass (borosilicate) clear vials, capped with 13 mm Gray Butyl stoppers with B2-40 coating, and sealed with a 13 mm colored Flip-Off Truedge. Each single use vial will be placed in a unit carton, and the labeling will include protocol number, kit number, and storage conditions.

The vial packaging and carton labeling for Sham is the same as DE-122 injectable solutions, but no DE-122 is filled in the Sham vial.

Commercially available Lucentis® will be provided by Santen/Representative for use as concomitant therapy in all groups and will be labeled for the study.

10.3. Study Drug Storage

Investigational drug (DE-122 injectable solutions and Sham) will be provided by Santen/Representative and will be stored in an appropriate secure area at the investigational site. DE-122 and Sham vials should be protected from light, stored upright, and kept refrigerated at 2° to 8°C (36° to 46°F).

Lucentis® storage will be as per Lucentis® drug labeling.

10.4. Study Drug Preparation

<Concomitant drug: Lucentis® >

Lucentis® preparation to be done as per Lucentis® drug labeling.

<Investigational drug: DE-122>

Once an investigational drug vial number has been assigned to the subject, the vial of investigational drug with the assigned vial number will be removed from the refrigerator. Care should be taken to protect the product from light. Investigational drug should be drawn into the provided sterile single-use custom marked syringe (see Section 10.5) within 30 minutes after removing the vial from the refrigerator. Investigational drug should be injected within 1 hour of being drawn up into the single-use syringe. Study drug preparation should be performed by the designated injecting physician.

Each vial contains enough DE-122 to inject one subject. Each vial will be used one time only. Write the subject number on the carton label. After use, return the vial in the unit carton, seal and initial the carton.

<Investigational drug: Sham>

The study drug preparation for Sham injection is same as DE-122.

10.5. Loading the Syringe

<Concomitant drug: Lucentis®>

Lucentis® administration to be done as per Lucentis® drug labeling.

<Investigational drug: DE-122>

A sterile, single-use 250 µL syringe custom marked at 20 µL or 40 µL will be provided separately for IVT injection of DE-122. Instructions for filling the syringe are as follows:

1. Remove the sterile, single-use 250 µL syringe, custom marked at 20 µL or 40 µL, from the packaging.
2. Attach a 19-gauge x 1 ½ inch filter needle to the syringe. DE-122 is dispensed in a 0.3 ml fill in a 2 mL vial. See Figure 2.
3. Using sterile technique, carefully draw up approximately 200 µL of DE-122 into the syringe. (Sufficiently larger volume than 20 or 40 µL is needed to allow for dead space in syringe and needles prior to IVT injection).
4. Remove the 19-gauge x 1½ inch filter needle from the syringe and replace with a 30-gauge x 0.5-inch needle for the IVT injection.
    a. Ensure that the 30-gauge x 0.5-inch needle is affixed tightly to the syringe.
    b. Align the top edge of the red O-ring of the plunger with the 20 µL or 40 µL black mark on the syringe, expelling the excess fluid drawn up. See Figure 3.

c. Ensure there are no air bubbles within the syringe or the needle hub prior to injection, and prior to expelling the excess fluid drawn up.

Figure 2: 0.3 mL fill in a 2 mL vial

Figure 3: Alignment of the syringe (20 µL example)

<Investigational drug: Sham>

Loading syringe procedure for Sham injection is similar to DE-122; no drug product will be drawn up into the syringe.

10.6. Eye Preparation

<Concomitant drug: Lucentis®>

Eye preparation for Lucentis® administration to be done as per Lucentis® drug labeling.

<Investigational drug: DE-122>

Prior to DE-122 administration, the study eye should be prepared as follows:

1. Dilate pupil (1 % mydriacyl and 2.5 % phenylephrine or equivalent applied topically) approximately 10 minutes prior to injection.
2. Administer 1 eye drop of topical anesthetic (0.5 % proparacaine hydrochloride ophthalmic solution or an equivalent topical ophthalmic anesthetic).
3. Administer 10 % povidone iodine.

4. Use a sterile cotton-tipped applicator to remove excess fluid from the lower conjunctival sac.
5. Take 2 sterile cotton tipped applicators and thoroughly soak with 0.5 % proparacaine topical anesthetic eye drops or an equivalent topical ophthalmic anesthetic. Place the soaked applicators, side by side, gently but firmly on the conjunctival surface at the area of the entry site described below in Step 2 (Section 10.7) and hold in place for approximately 1 minute.
6. Insert sterile eyelid speculum.
7. Place sterile eye drape over study eye.

<Investigational drug: Sham>

Eye preparation for Sham injection is the same as DE-122.

10.7. Study Drug Administration

<Concomitant drug: Lucentis®>

Lucentis® administration to be done as per Lucentis® drug labeling.

<Investigational drug: DE-122>

1. Prior to starting the injection procedure, DE-122 should have been prepared as described in Section 10.4 and Section 10.5, and the study eye should have been prepared as described in Section 10.6.
2. If the subject is phakic, the entry site is 4.0 mm from the limbus. If the subject is pseudophakic or aphakic, the entry site is 3.5 mm from the limbus. A caliper may be used to identify the needle entry site. The entry site location for the investigational drug should be the same quadrant as the concomitant drug, but not at the same entry point.
3. Insert the needle perpendicular to the eye wall at the location specified in Step 2 (Section 10.7). The needle should be inserted until the tip is just visible through the dilated pupil. Note: If paracentesis is considered necessary, it should be performed after injection of the DE-122 and noted in the source documents.
4. Very slowly, inject the entire DE-122 dose volume (20 µL or 40 µL) and slowly withdraw the needle. Do not pull back on the plunger at any time prior to withdrawing the needle.
5. Briefly apply pressure for approximately 1 minute to the needle entry site with sterile cotton tipped applicator (may be skipped per Clinical Investigator's discretion).
6. Remove the eyelid speculum.
7. Patch the study eye at the Clinical Investigator's discretion.
8. Prescribe fluoroquinolone equivalent antibiotic eye drops three times/day for two days following injection, to be initiated as soon as possible.

<Investigational drug: Sham>

Sham is injection that simulates DE-122 drug administration. Sham intravitreal injections will be administered to subjects according to the same dosing schedule and procedure as DE-122 injections. However, the Sham intravitreal injection procedure will only mimic DE-122 intravitreal injection in that the blunt end of an empty syringe is pressed against an anesthetized eye, instead of a needle attached to DE-122 syringe injected into the anesthetized eye. Therefore, Step #3 and #4 of above DE-122 administration procedure will be skipped for the Sham injection.

To keep masking of the study, investigator and authorized staff must follow the points described in Section 9.4.

10.8. Study Drug Accountability

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The temperature recorder from the shipment will be deactivated and authorized study staff will verify that the temperature was maintained at 2° to 8°C (36° to 46°F) during transit.

The Principal Investigator will keep a current record of the inventory, storage conditions and dispensing of all study drugs. This record will be made available to Santen (or designee) for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the Principal Investigator must be accounted for and in no case will study drugs be used in any unauthorized situation. It is the responsibility of the Principal Investigator to ensure that any used and unused supplies are available to Santen (or designee) throughout the study.

10.9. Study Drug Handling and Return

All investigational products including used/unused vials of DE-122/Lucentis® and syringes supplied by Santen/Representative will be fully accounted for by the monitor with the help of the unmasked person responsible for dispensing the DE-122 and will be returned to Santen/Representative or designee. Accountability will be documented by use of drug accountability forms.

Refer to Study Drug Manual for study drug handling.

11. ASSESSMENT OF EFFICACY

11.1. Best Corrected Visual Acuity (BCVA)

BCVA is the primary efficacy variable for this study, and mean change from baseline in BCVA at Week 24 is the primary efficacy endpoint. Proportion of subjects with BCVA Improvement of ≥ 15 letters, <15 letters change (stable) and loss of ≥ 15 letters from baseline at Week 24 are secondary endpoints.

The visual acuity will be recorded using the ETDRS chart and total number of letters at 4 meter and 1 meter will be recorded. If a subject could not read ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded.

11.2. Central Subfield Thickness (CST), Macular Volume (MV), Central Retinal Lesion Thickness (CRLT)

CST, MV, and CRLT measured by SD-OCT are secondary efficacy variables, and change in CST, MV, and CRLT from baseline at Week 24 are secondary endpoints. All 3 parameters will be measured by the central reading center.

11.3. Lesion area

Change in total lesion area, total area of CNV, greatest linear dimension of the total lesion area by FA from baseline at Week 24 are secondary efficacy endpoints. Lesion areas will be measured by the central reading center.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events

12.1.1. Definition of Adverse Events

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 AE, therefore, can be an unintended sign (including an abnormal laboratory finding), symptom, or disease that has clinical significance and is temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In clinical studies, an undesirable medical condition occurring at any time, including baseline or pre-treatment period, may be recorded as an AE even if no study drug has been administered.

Any significant adverse change in a subject's condition from baseline, regardless of causality, is to be considered an AE, unless the change is determined to be a continuation of a pre-existing condition that is documented in the subject's medical history. However, a clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE. In addition, all conditions that lead to hospitalizations, defined as an overnight hospital stay, are considered as AEs. This includes planned elective surgeries.

Lack of efficacy of the study drug(s) for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Clinical Investigator. An elective surgical procedure scheduled or planned prior to study entry is not considered an AE if an overnight hospital stay is not required, and the underlying diagnosis for which surgery is to be performed should be captured in the medical history as a pre-existing condition. The surgical procedure should also include the term "elective" in all reports.

12.1.1.1. Assessment of Adverse Events

Clinical Investigators will seek information on AEs at each subject contact. Subjects should be asked, using a general, non-direct question, if there has been any change in their general health. Direct questioning and examination should then be performed as appropriate.

Severity of the AE should be assessed according to the following criteria:

> **Mild:** No interference with the subject's daily activities; no medical intervention/therapy required
>
> **Moderate:** Possible interference with the subject's daily activities; no or minimal medical intervention/therapy required
>
> **Severe:** Considerable interference with the subject's daily activities; medical intervention/therapy required

Regardless of severity, some AEs may also meet regulatory serious criteria. Refer to definitions and reporting of serious adverse events (SAEs) in Section 12.1.2.

A Clinical Investigator who is qualified in medicine must make the determination of the relationship of the study drug(s) to each AE (related or not related). The Clinical Investigator

should decide whether, in his or her medical judgment, there is a reasonable possibility that the DE-122, Lucentis® or the Sham injection could have caused the AE/SAE based on facts, evidence, scientific rationales, and clinical judgment. When assessing causality, the Clinical Investigator may consider the following information when determining the relationship to the study drug(s) for each AE: mechanism of action, biologic plausibility, confounding risk factors (i.e., medical history, concomitant medications), temporal relationship, dechallenge/rechallenge, and lack of alternative explanation. It should be specified if the AE is related to the injection procedure and not the study drug.

- The AE may be recorded as **Related** to the study drug(s) if there is a plausible temporal relationship between the onset of the AE and administration of the study drug(s), and the AE cannot be readily explained by the subject's clinical state, concurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug(s),; and/or the AE abates or resolves upon discontinuation of the study drug(s).
- Reporting the AE as **Not Related** to study drug(s), may be considered if, for example, there is good evidence that the AE has an etiology other than the study drug(s) (e.g., pre-existing medical condition, underlying disease, concurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug(s) (e.g., cancer diagnosed 2 days after dose of study drug(s)).

12.1.1.2. Reporting Adverse Events

AEs, whether spontaneously reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE eCRF. Each recorded AE will be described by its duration (i.e., start and end dates), frequency, severity, regulatory seriousness criteria if applicable, suspected relationship to the study drug(s), relation to injection procedure, location, actions taken and outcome.

AEs that occur after any subject has provided written informed consent, before treatment, during treatment, or until study exit visit, whether or not they are related to the study, must be recorded. To improve the quality and precision of acquired AE data, Clinical Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms and /or laboratory or test findings (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis, and enlarged heart on chest x-ray). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).

  If the diagnosis is not known, then record the leading component sign, symptom or test finding and describe the other clinically related findings in the narrative description of the case. A suspected diagnosis can be used and described as such

(e.g., record suspected or probable myocardial infarction); this has to be updated in the clinical database once the diagnosis is confirmed.

AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term. If a primary AE is recorded, events occurring secondary to the primary event should be described in the narrative description of the case. For example:

The subject developed orthostatic hypotension and subsequently fainted and fell to the floor wherein she experienced a head trauma and neck pain.

The primary AE in this example is orthostatic hypotension. The fall, head trauma and neck pain should be described in the narrative description of the case.

- For intermittent events (e.g., intermittent headache), the event onset date should be recorded as the date the subject first started to experience the event and resolution date should reflect when the last occurrence resolved or stopped. Separate AEs for each event should not be recorded. For example, if a subject experienced headache on 14SEP2015 lasting for three hours, then subsequently experienced intermittent episodes of headache every day for approximately 3 hours until 21SEP2015, then the AE date of onset is 14SEP2015 and the resolution date is 21SEP2015.
- For intermittent events, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate.
- For intermittent hospitalizations occurring for a primary AE (e.g., in a subject with multiple sclerosis, commonly known for its relapsing and remitting course, in some cases leading to multiple hospital confinements), the subsequent hospitalizations should be described in the narrative description of the case.
- If treatment was initiated, include the treatment and duration of the medication(s) in the eCRF.

12.1.2. Serious Adverse Events

SAEs are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. Any adverse event is considered a serious adverse event if it results in any of the following outcomes:

- Death
- Life threatening:

  A life-threatening event is any event that places the subject at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Hospitalization, at the minimum an overnight stay
- A persistent or significant disability/incapacity

- A congenital anomaly/birth defect
- Other medically significant events:

  Other medically significant events are events that may not result in death, be life-threatening, or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

- Sight threatening event:

  A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event. It is defined as a loss of ≥ 30 letters or 6 lines of vision from Baseline.

12.1.2.1. Reporting Serious Adverse Events

A SAE eCRF must be completed with as much information available within 24 hours of knowledge of the event.

To improve the quality and precision of acquired SAE data, Clinical Investigators should observe the following guidelines:

- **Death** - Death is an outcome of an event. The event that resulted in the death should be recorded and reported as a SAE.
- **Hospitalizations for Surgical or Diagnostic Procedures** - The illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

When new significant information (including the outcome of the event) is obtained, the Clinical Investigator should enter the information directly into the eCRF within 24 hours or as soon as possible after knowledge of the information.

Depending on the nature and seriousness of the AE, Santen may request additional documentation, for example, copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, the site should summarize the hospital discharge summary and provide to Santen upon request.

12.1.2.2. Expedited Reporting of Serious Adverse Events

Santen (or designee) will provide the Principal Investigator with a reporting cover letter and an anonymized MedWatch 3500A or CIOMs form as appropriate for expedited reporting of SAEs to the IRB or IEC and the Philippines or the US regulatory agency. The Principal Investigator is responsible for receiving and reviewing expedited safety reports, submitting expedited safety reports to the IRB or IEC, and maintaining copies of expedited safety reports in the study records.

12.1.3. Events of Special Interest

Events of Special Interest (ESIs) are events that may require special attention for the purposes of on-going patient safety review during this study. The following are considered ESIs and should be reported on the appropriate eCRF with as much information as available within 24 hours of knowledge of the event:

- **Study medication administration error** – Study medication administration errors determined to be significant by the Clinical Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: overdose of study medication and administration of study medication from an incorrect kit.
- **Pregnancy** - There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 12 weeks after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject removed from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.
- **Ocular telangiectasia and bleeding events** – There is no data showing that the investigational product is related to these events. However, these are seen in the Osler-Weber-Rendu (OWR) syndrome, a genetic condition that causes endoglin dysfunction. DE-122 binds to and suppresses human endoglin, thus information about the ocular manifestations of OWR are of value in predicting possible ocular adverse events following IVT injection of DE-122. The following events will be considered ESIs and the subject followed until the end of the study or resolution of the event.
  - Ocular telangiectasia (Conjunctival and intraocular)
  - Intra- and extra-ocular bleeding (hemorrhage) not attributed to the injection procedure and/or AMD
  - Common systemic OWR signs: Epistaxis, gingival bleeding and mucocutaneous telangiectasia

12.1.4. Follow-up of Adverse Events

All reported AEs should be followed until resolution or until the subject's participation in the study ends. Subjects with the following types of events should be followed by the Investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained.

- On-going SAEs
- On-going ESIs (excluding medication errors not resulting in AEs)
- Early termination and withdrawal from the study due to study drug related AEs

In addition, on a case by case basis, Santen (or designee) may request follow up beyond the scheduled exit visit.

The follow-up information on an individual SAE, AE, or ESI will be entered into the eCRF prior to database lock. If the information requested by Santen is not part of the eCRF, or when database lock has already been completed, the site's response to follow-up requests should be emailed, faxed or reported to Santen Pharmacovigilance: globalPVAmericas@santen.com or +63-2-857-2111 (fax for the Philippines sites) or +1-415-276-5882 (fax for the US sites).

12.1.5. Manual Back-Up Reporting Procedures

This study is utilizing an electronic data capture (EDC) system for data collection. In the event that the EDC system is unavailable for electronic reporting, the manual back-up reporting procedures below should be followed.

- Complete an AE and SAE form manually
- Attach a cover sheet with your contact information, including site number.
- Email (preferred) or Fax the cover sheet and the AE and SAE form to Santen Pharmacovigilance at globalPVAmericas@santen.com or +63-2-857-2111 (for the Philippines sites) or +1-415-276-5882 (for the US sites).

When the EDC system becomes available, update the EDC system with all previously reported information.

12.2. Safety Parameters

The safety assessments will include AEs, slit lamp biomicroscopy, indirect ophthalmoscopy, BCVA, IOP, fundus photography, fluorescein angiography, serum chemistry, hematology, urinalysis, vital signs, physical examination, EKG, and pregnancy.

12.2.1. Physical Examination

A full body systematic physical examination will be conducted by the Clinical Investigator or an external internist.

12.2.2. Electrocardiogram (EKG)

The Clinical Investigator will review the EKG report for abnormalities.

12.2.3. Vital Signs

Blood pressure and heart rate will be measured using an automated or manual blood pressure monitor. Systolic and diastolic blood pressures will be recorded in millimeters of mercury (mmHg), and heart rate will be recorded in beats per minute (bpm).

12.2.4. Best Corrected Visual Acuity

The BCVA will be recorded using the ETDRS chart and total number of letters at 4 meters and 1 meter will be recorded. If a subject could not read ETDRS chart, Finger Counts, Hand Motion, Light Perception, or No Light Perception will be recorded.

12.2.5. Slit-lamp Biomicroscopy

The Clinical Investigator will assess Slit-lamp biomicroscopy examination using Slit-lamp microscope. On the visit of any IVT treatment, a biomicroscopy examination will be performed prior to Lucentis® injection and a second one within 30 minutes after DE-122 or Sham injection. This will be also applied for the post IVT injection of Rescue treatment.

12.2.6. Intraocular Pressure

IOP will be measured by applanation tonometry and reported in millimeters of mercury (mmHg). On the visit of any IVT injection, IOP will be measured before Lucentis® and 40 (±10) minutes after Lucentis® injection. If post-injection IOP is > 21 mmHg or increased ≥ 10 mmHg from pre-injection IOP, the IOP will be measured again 60 (±10) minutes following Lucentis® injection. If there is an increase of ≥ 10 mmHg at 60 (±10) minutes post-injection, the IOP increase of ≥ 10 mmHg will be reported as an AE.

Moreover, IOP will be measured after DE-122 or Sham injection. If post-DE-122 or Sham injection IOP is > 21 mmHg or increased ≥ 10 mmHg from pre-injection IOP, the IOP will be measured again 60 (±10) minutes following injection. If there is an increase of ≥ 10 mmHg at 60 (±10) minutes post-injection compared to pre-injection IOP, the IOP increase of ≥ 10 mmHg will be reported as an AE. This will be also applied for the post IVT injection of Rescue treatment.

12.2.7. Indirect Ophthalmoscopy

The Clinical Investigator will assess Indirect ophthalmoscopy using indirect ophthalmoscope. On the visit of any IVT treatment, an ophthalmoscopy examination will be performed prior to Lucentis® injection and a second one within 30 minutes after DE-122 or Sham injection. This will be also applied for the post IVT injection of Rescue treatment.

12.2.8. Urine Pregnancy Test

A urine pregnancy test will be conducted for all females of childbearing potential.

12.2.9. Serum Pregnancy Test

A serum pregnancy test will be conducted for all females of childbearing potential.

12.2.10. Serum Chemistry, Hematology and Urinalysis

Serum Chemistry, Hematology and Urinalysis will be measured by laboratory test company. The blood sample should be fasted for a minimum of 8 hours prior to blood draw for serum chemistry tests.

12.2.11. Fundus Photography

Digital color fundus photography will be taken following the procedure provided by the central reading center.

12.2.12. Fluorescein Angiography

Fundus fluorescein angiography will be taken following the procedure provided by the central reading center.

12.2.13. Adverse Events

AEs will be elicited from the subjects starting at the Screening through study exit. The information will include at least a description of the event, whether or not it is serious, onset and duration, frequency, severity, relation to masked study therapy, relation to injection procedure, location (OD, OS, OU or NA), action taken and outcome. Prior to evaluating the incidences, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDra, 2013). Ocular and non-ocular AEs will be summarized separately. See Section 12.1 for complete information regarding AE reporting.

13. PHARMACOKINETIC ASSESSMENTS

The DE-122 concentration in serum will be measured before and after Visit 1 (Day 1) and Visit 8 (Week 20) IVT administrations of DE-122 (2.0 mg and 4.0 mg) or Sham.

13.1. Serum Sample Collection

Serum samples will be collected according to the examination schedule. On days when Visit 1 (Day 1) and Visit 8 (Week 20) DE-122 IVT or Sham injections are administered, serum samples will be collected pre-Lucentis® injection and 3 hours (±10 min) post DE-122 IVT or Sham injections. On day of the Visit 4 (Week 4) DE-122 IVT or Sham injection, serum samples will be collected prior to Lucentis® injection. See Section 23.4.16 and/or separate procedure manual for the pharmacokinetic serum sample collection, storage and shipment.

13.2. Sample Analysis

Serum concentrations of DE-122 will be determined by ELISA (enzyme-linked immunosorbent assay) method at inVentiv Health Clinical, Inc.

14. OTHER ASSESSMENTS

14.1. Demographics and Baseline Characteristics

Subject demographics include age, race, sex, and ethnicity. Baseline characteristics include medical history, prior medications, and baseline results of physical examination, EKG, vital signs, BCVA, slit-lamp biomicroscopy, IOP, indirect ophthalmoscopy, SD-OCT, pregnancy test, laboratory tests (hematology, chemistry, and urinalysis), fundus photography, and fluorescein angiography. For assessments performed multiple times before the IVT injection of DE-122, the last pre-injection value will be used as the baseline value.

14.2. Immunogenicity

ADA titers will be measured in serum samples collected according to the examination schedule.

15. OTHERS

15.1. Biomarker

15.1.1. Serum Sample Collection

For the biomarker finding, serum samples will be collected according to the examination schedule and measured for levels of angiogenesis-related proteins. The serum samples will be also stored for future exploratory research to identify possible biomarkers associated with the study drug(s) and/or ophthalmologic disease conditions. See Section 23.4.19, Appendix D for procedures for the serum sample collection, storage and shipment.

15.1.2. Aqueous Humor Sample Collection

For the biomarker finding, aqueous humor samples from the study eye will be collected according examination schedule only from subjects who has consented and measured for levels of angiogenesis-related proteins. Aqueous humor samples will be also stored for future exploratory research to identify possible biomarkers associated with the study drug(s) and/or ophthalmologic disease conditions. See Section 23.4.20, Appendix D for procedures for the aqueous humor sample collection, storage and shipment.

15.2. SS-OCT Angiography

SS-OCT angiography will be taken following examination schedule at selected sites.

15.3. M-CHARTS™

The degree of metamorphopsia will be recorded using the M-CHARTS™, and vertical metamorphopsia score (MV) and horizontal metamorphopsia score (MH) will be recorded.

16. STATISTICAL METHODS

16.1. Analysis Time Points

One primary analysis (Week 24) and follow-up analysis (Week 32) will be performed.

16.1.1. Primary Analysis

Descriptive summaries of the following efficacy and safety measures will be provided by treatment arms at the Week 24:

- Mean change in BCVA from baseline
- Change in CST and macular volume from baseline
- Change in central retinal lesion thickness from baseline
- Proportion of subjects with BCVA Improvement of ≥ 15 letters, < 15 letters change (stable) and loss of ≥ 15 letters from baseline
- Change in total lesion area and total area of CNV from baseline
- Change in greatest linear dimension of the total lesion area from baseline
- Safety assessment include AEs, BCVA, slit lamp biomicroscopy, IOP, indirect ophthalmoscopy, serum chemistry, hematology, urinalysis, vital signs, physical examination, fundus photography, fluorescein angiography, EKG, and pregnancy

Additional variables of interest will also be provided.

16.2. General Considerations

All study parameters will be listed and a selected list of parameters will be summarized descriptively by treatment arm. The descriptive statistics will include number of observations (n), mean, standard deviation, minimum, and maximum for continuous parameter and frequency (n) and percent (%) for categorical parameters.

Details about the statistical analyses for this study will be provided in the statistical analysis plan (SAP).

All data manipulations and descriptive summaries will be implemented using SAS®, Version 9.1.3 or later.

16.2.1. Sample Size

Approximately 76 subjects (Arm 1: 17, Arm 2: 31, Arm 3: 28) with wet AMD will be enrolled at approximately 14 sites. The final number of subjects enrolled may be adjusted based on the judgments from Safety Review Team. This sample size is not planned based on statistical considerations.

16.2.2. Statistical Hypotheses and Level of Significance

No statistical hypothesis is defined for this study.

16.2.3. Randomization

The first 6 subjects will be randomized to Arm 1 and Arm 2 in a 1:1 ratio in Stage 1. If the safety and tolerability at Week 4 are acceptable, remaining approximately 70 subjects will be randomized to all Arms in a 1:2:2 ratio in Stage 2. To balance the randomization, subjects will be stratified by subgroups on the central reading center's assessment of lesion type, up to approximately one third (1/3) of the subjects in each arm should have PCV in Stage 2.

16.2.4. Study Eye

The study eye must meet all inclusion and exclusion criteria, including confirmation by the central reading center. If both eyes are eligible based on inclusion and exclusion criteria, the study eye is defined as the eye with worse vision. If both eyes have the same vision, the right eye (OD) should be determined as the study eye.

16.3. Study Populations

The following study populations are defined for analysis: Intention-to-treat (ITT) and Safety.

ITT Population: The ITT population will include all randomized subjects in the study.

Safety Population: The Safety population will include all randomized subjects who received at least one study medication. It will be the study population for safety analyses.

PK Population: The PK population will include all subjects who received at least one DE-122 and have at least one post-injection PK assessment. It will be the study population for PK analyses performed with subjects as treated.

Full Analysis Set: The Full Analysis Set (FAS) will include all randomized subjects who received at least one study medication and provided at least one post-baseline BCVA measurement. The efficacy analysis will be performed on the FAS or a subset of the FAS.

Per-Protocol Set: The Per-Protocol Set (PPS) Population is a subset of the FAS. It includes all FAS subjects without major protocol violations that could affect the primary efficacy endpoint.

16.4. Handling of Missing Values

Primary analysis of the primary efficacy endpoint will be based on the observed cases. Missing BCVA measurements will be imputed using the Last-Observation-Carried-Forward (LOCF) approach as a sensitivity analysis. For safety measures, missing scores will not be imputed for data summaries.

Completely or partially missing onset and resolution dates for AEs and completely or partially missing start and end dates of concomitant medications will be imputed in a conservative fashion that will be detailed in the SAP.

16.5. Demographics and Baseline Characteristics

Age, sex, race, ethnicity, and baseline assessments will be summarized descriptively by treatment arms.

Subjects with abnormal medical history will be tabulated by treatment arm and body system.

Subjects using any prior medications will be tabulated by treatment arms, Anatomical Therapeutic Chemical levelbyrs, and preferred term specified in the World Health Organization Drug Dictionary Enhanced (World Health Organization Drug Dictionary, 2011).

16.6. Efficacy Analyses

16.6.1. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoint, BCVA mean change from baseline at Week 24 will be analyzed based on observed cases using descriptive statistics. Observed BCVA in the study eye as well as imputed data using LOCF approach will be presented descriptively and graphically by study visit.

The primary analysis will be based on the FAS and repeated analysis will be performed on the PP Population.

16.6.2. Analysis of Secondary Efficacy Endpoints

Change from baseline in CST, MV, CRLT, total lesion area and total CNV by SD-OCT, greatest linear dimension of the total lesion area by FA at Week 24 will be calculated and analyzed. Percentage/Proportion of subjects with BCVA :1) gain of ≥ 15 ETDRS letters (3-line gainers); 2) < 15 letters change (stable); and 3) ≥ 15 letter loss will be summarized and tabulated.

16.7. Safety Analysis

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include adverse events (AEs), BCVA, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP), serum chemistry, hematology, urinalysis, vital signs, physical examination, fundus photography, fluorescein angiography, EKG and pregnancy.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Subjects with any AEs will be tabulated by system organ classification and preferred term specified in the MedDRA. Similarly, subjects with any ocular and non-ocular AEs and ESIs will be tabulated separately. AEs, ocular and non-ocular, as well as ESIs will also be summarized by relationship to treatment and maximum severity. In addition, SAEs and discontinuations due to AEs will be summarized.

Ocular safety outcome measures will be summarized using descriptive statistics.

16.8. Pharmacokinetics Analysis

To assess pharmacokinetic profile, pharmacokinetic parameters (C_{max}, AUC, T_{max}, $t_{1/2}$) will be summarized for after the Visit 1 (Day 1) and Visit 8 (Week 20) DE-122 IVT injections.

16.9. Immunogenicity Analysis

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

16.10. Other Analysis

16.10.1. Biomarker Analysis

To explore the biomarkers, serum and aqueous humor samples will be collected at specified time points and measured for levels of angiogenesis-related proteins. Changes from baseline in levels of biomarkers will be summarized descriptively by treatment arms.

16.10.2. M-CHARTS™

To explore the degree of metamorphopsia change in vertical metamorphopsia score (MV) and horizontal metamorphopsia score (MH) from baseline will be analyzed.

17. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Principal Investigator will allow representatives of Santen's monitoring team (or designee), the governing institutional review board (IRB), the Philippines FDA, the FDA in the US and other applicable regulatory agencies to inspect all study records, eCRFs, recruitment materials and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the eCRF, and compliance with the Philippines FDA, the FDA in the US or other regulatory agency regulations.

17.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Santen (or designee) will evaluate the investigational study site to:

- Determine the adequacy of the study facilities.
- Review with the Principal Investigator(s) and authorized study staff their responsibilities with regard to protocol procedures adherence, and the responsibilities of Santen (or designee).

During the study, Santen (or designee) will have regular contact with the investigational site, for the following:

- Provide information and support to the Principal Investigator(s).
- Confirm that facilities remain acceptable.
- Assess adherence to the protocol and GCP.
- Perform investigational product accountability checks and quality control procedures.
- Ensure the on-going implementation of accurate data entry in the eCRF.
- Perform source data verification, including a comparison of the data in the eCRFs with the subject's medical records and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Santen.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the IRB or Independent Ethics Committee (IEC).

Santen (or designee) may remotely access the eCRFs at any time during the study for centralized monitoring. Santen (or designee) will be available between visits if authorized study staff needs study related information or support.

17.2. Audits and Inspections

The Principal Investigator will allow Santen (or designee), the governing IRB or IEC, and applicable regulatory agencies to audit and inspect any aspect of the study, including all study

records, eCRFs, recruitment materials, and corresponding portions of the subject's charts and medical records at any time during the study. These study records must be retained at the study site and made available for audits and inspections. The purpose of these audits and inspections is to verify adherence to the protocol, completeness and accuracy of the eCRF data, and compliance with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

The Principal Investigator or authorized study staff will notify Santen (or designee) should the site be audited or inspected by the governing IRB or IEC, and applicable regulatory agencies. Santen (or designee) will also notify the investigational site of any known pending site audits or inspections planned by Santen (or designee), governing IRB or IEC and regulatory agencies.

17.3. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Principal Investigator and made available for inspection.

18. QUALITY CONTROL AND QUALITY ASSURANCE

18.1. Quality Control

Santen (or designee) will provide instructional material to the study sites, as appropriate; including but not limited to instruction on the protocol, the completion of eCRFs, and study procedures. Santen (or designee) will communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic visits to the study site. During those visits, Santen (or designee) will perform source data verification with the subject's medical records and other records relevant to the study. Upon receiving the eCRFs, Santen (or designee) will review and evaluate eCRF data and use standard system edits and may use centralized monitoring to detect errors in data collection.

18.2. Quality Assurance

Santen (or designee) may conduct a quality assurance audit at any time.

19. ETHICS

19.1. Ethics Review

The final study protocol and the final version of the ICF, and other study related material, as appropriate, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Principal Investigator must submit written approval to Santen (or designee) before study initiation. See Section 23.1 Appendix A for a list of obligations of Investigators.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local regulations and guidelines. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and at least annually.

The Principal Investigator is also responsible for providing the IRB or IEC with progress reports and notifications of any reportable serious adverse drug reactions from the investigational product.

19.2. Ethical Conduct of the Study

This study will be conducted in compliance with IRB or IEC, and regulatory requirements. This study will also be conducted in compliance with the protocol, GCP guidelines, International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki.

19.3. Written Informed Consent

The Principal Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and possible benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time. Subjects should be given the opportunity to ask questions and allowed time to consider the information provided. Before participating in any study-related activity, voluntary informed consent must be documented by the use of a written ICF approved by the IRB or IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The original signed and dated ICF will be retained with the study records, and a copy of the signed ICF will be given to the subject or the subject's legally authorized representative.

20. DATA HANDLING AND RECORDKEEPING

20.1. Inspection of Records

The Principal Investigator will allow Santen (or designee), the governing IRB or IEC and applicable regulatory agencies to inspect any aspect of the study, including all study records, eCRFs, recruitment materials and corresponding portions of the subject's charts and medical records at any time during the study. The purpose of these inspections is to verify adherence to the protocol, completeness and accuracy of the eCRF data, and compliance with GCP guidelines and applicable regulatory requirements.

20.2. Retention of Records

All records relating to the conduct of this study are to be retained by the Principal Investigator until notified by Santen (or designee) that the records may be destroyed.

20.2.1. Source Documents

The Principal Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents include subject medical records, hospital charts, study files, as well as the results of diagnostic tests (e.g., laboratory tests).

The following minimum information should be entered into the subject's medical record:

- The date the subject was enrolled and the subject number
- The study protocol number and the name of Santen Inc.
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study-related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study drug accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination

20.2.2. Data Collection

The Principal Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened and enrolled subjects will be entered into eCRFs. Review of the eCRFs will be completed remotely by Santen (or designee). At designated intervals, a study monitor will perform source data verification on site. During those visits, Santen (or designee) will monitor the subject data recorded in the eCRF against source documents at the study site. Santen (or designee) will review and evaluate eCRF data and use standard system edits, and may use centralized monitoring evaluations, to detect errors in data collection. At the end of the study, a copy of the completed eCRFs will be sent to the site to be maintained as study records.

21. PUBLICATION POLICY

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied that is indicated as confidential. Information pertaining to this study will be published on www.clinicaltrials.gov and http://registry.healthresearch.ph/.

The data generated by this clinical study are the property of Santen and should not be disclosed without the prior written permission of Santen. These data may be used by Santen now and in the future for presentation or publication at Santen's discretion or for submission to governmental regulatory agencies. Santen reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the Principal Investigator agrees to the release of the data from this study and acknowledges the above publication policy.

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23. APPENDICES

23.1. Appendix A - Obligations of Investigators

In summary, the Clinical Investigator has agreed to the following obligations:

- Obtaining informed consent from every subject prior to the subject's participation in any study related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the IRB before involving any subject in any study related activity; submitting verification of the approval to the Sponsor; submitting periodic progress reports (at least annually) and final report to IRB and to the Sponsor.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing the Sponsor of all deviations from the protocol.
- Informing the IRB of all protocol amendments/modifications; sending the Sponsor a copy of the letter from the IRB approving the amendment/modification.
- Reporting to the Sponsor and the IRB any adverse experiences that occur in the course of the investigation, this includes Serious Adverse Events within 24 hours.
- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB and of all action by the IRB regarding the study.
- Making study records available for inspection by the Sponsor and representatives of the Food and Drug Administration and other regulatory agencies; keeping records until notified by the Sponsor that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to the Sponsor (Section 23.1).

I. Prior to the Beginning of the Study

- A current curriculum vitae (CV) if not submitted to Santen previously or if updated.
- CVs for all sub-Investigators.
- A letter from the IRB indicating that the protocol was approved, including the name and address of the IRB.
- A copy of the consent form approved by IRB.
- A list of current members of the IRB.

II. While the Study Is in Progress

- Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
- Original Case Report Forms for each subject enrolled in the study.

- Information regarding all deviations from the protocol.
- Information regarding all adverse medical events occurring to a subject while enrolled in the study.
- Annual progress report (if study is ongoing for more than one year). Letter from the IRB indicating approval of the annual progress report.

III. Once the Study Is Completed

- Disposition of all used and/or unused test and control articles, as well as documentation of all drug accountability.
- A final study report.

23.2. Appendix B - Elements of Informed Consent

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written ICF.

1. State that the study involves RESEARCH.
   A. Explain the PURPOSE of the research.
   B. Trial treatments and the probability for random assignment to each treatment.
   C. State the expected DURATION of the subject's participation.
   D. Describe the PROCEDURES to be followed.
   E. Identify any EXPERIMENTAL procedures.
2. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
3. Describe any BENEFITS to the subject and responsibility for the subject or to others that may reasonably be expected from the research.
4. Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
5. A. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained.
   B. Note that the FDA MAY INSPECT the records.
6. For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain (a) what they consist of, OR (b) where further information may be obtained.
7. A. Tell whom to contact for ANSWERS to pertinent questions about (a) the research, and (b) research subjects' rights.
   B. Tell whom to contact in the event of a research-related INJURY to the subject.
8. State that:
   A. Participation is VOLUNTARY,
   B. Refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled
   C. The subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

II. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in this protocol are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in this protocol is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

REFERENCE: 21 CFR Part 50.25 – PROTECTION OF HUMAN SUBJECTS, Elements of Informed Consent.

23.3. Appendix C - Declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any

serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.
31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.
32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

23.4. Appendix D - Procedures for Examinations

23.4.1. Demographics/Eligibility, Medical/Surgical History and Concomitant Medication

Demographics/Eligibility, medical/surgical history and concomitant medication will be obtained through subject interviews at Screening (Day -14 to Day -1). Medical history and concomitant medications will be obtained through subject interviews at each visit.

23.4.2. Physical Examination

A full body systematic physical examination will be conducted during Visit 0/Screening (Day -14 to Day -1), Visit 11 (Week 24) and Visit 13 (Week 32). Clinical Investigator or an external internist will confirm subject's overall condition noting any abnormalities by a review of the following systems: e.g., head, eyes, ears, nose and throat (HEENT), cardiopulmonary, endocrine, gastrointestinal, musculoskeletal/rheumatic, neurologic/psychiatric, dermatologic, hepatic/renal systems, and other.

The Clinical Investigator will assess subject's overall condition to determine qualification for study entry considering possible class effects of DE-122. Newly noted abnormalities or worsening of previously noted abnormalities found at Study Exit, or at any safety assessment visit, will be assessed as an AE. The Clinical Investigator should use his or her clinical judgment for appropriate treatment and/or medical referral.

23.4.3. Vital Signs

Blood pressure and heart rate will be measured at each visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit10 (Week 20 + 7 days) using an automated or manual blood pressure monitor. Systolic and diastolic blood pressures will be recorded in millimeters of mercury (mmHg) and heart rate will be recorded in beats per minute (bpm).

In accordance with the recommendations of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (US_Dept_Health_And_Human_Services, 2004), the following measurement procedure will be used to measure vital signs:

- Subject should not smoke or ingest caffeine within the 30-minute period immediately before the measurement.
- Subject should be seated quietly in a chair with the back supported, feet on the floor, arm bared, and arm supported at heart level.
- Begin the measurement after at least 5 minutes of rest.
- To ensure an accurate measurement, use an appropriately sized cuff. The cuff bladder should encircle at least 80 % of the arm. Many adults need a large cuff.
- Take two (2) systolic/diastolic pressure and heart rate measurements separated by at least 30 seconds. Record each measurement in the subject's source document.

- If the two pressure measurements differ by 5 mmHg or less, then the average of the two becomes the recorded pressure. For example, if the two measurements are 120/90 and 125/95, then 122.5/92.5 is the recorded systolic/diastolic pressure.
- If the two pressure measurements differ by more than 5 mmHg, then a third reading measurement is made, and the average of the three becomes the recorded pressure. For example, if the three measurements are 115/90, 124/96, and 120/92, then 119.7/92.7 is the recorded systolic/diastolic pressure. The recorded blood pressure will be the average of the measurements.
- Record the heart rate. For heart rate, the average of the two (or three, if performed) measurements obtained becomes the recorded heart rate.

23.4.4. EKG

EKGs will be recorded at Visit 0/Screening (Day -14 to Day -1) and reviewed for abnormalities by the Clinical Investigator prior to enrollment. EKGs will also be performed at Visit 3 (Week 1), Visit 10 (Week 20 + 7 days), Visit 11 (Week 24) and Visit 13 (Week 32).

23.4.5. Best Corrected Visual Acuity

ETDRS chart will be used to examine BCVA at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit10 (Week 20 + 7 days). See Study Procedures manual for the detailed procedure for measuring visual acuity.

23.4.6. M-CHARTS™

M-CHARTS™ will be used to examine metamorphopsia at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit10 (Week 20 + 7 days). Two types of values which are vertical metamorphopsia score (MV) and horizontal metamorphopsia score (MH) will be assessed. See instruction for measuring metamorphopsia.

23.4.7. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be used to examine eye structures at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit 10 (Week 20 + 7 days). Slit-lamp biomicroscopy will be performed prior to injection and then again within 30 minutes after injection on the visit of DE-122. This will be also applied for the post IVT injection of Rescue treatment.

The lid, conjunctiva, cornea, and lens will be observed with the slit-lamp beam approximately 0.3 mm in width and 1.0 mm in length and graded on a 4-point scale (0-3 scale) as described below:

Lid Redness

None	(0) =	Normal
Mild	(1) =	Redness of most or all the lid(s) margin OR skin
Moderate	(2) =	Redness of most or all the lid(s) margin AND skin
Severe	(3) =	Marked diffuse redness of both lid(s) margin AND skin

Lid Edema

None (0) = Normal

Mild (1) = Localized to a small region of the lid(s)

Moderate (2) = Diffuse, most or all the lid(s) but not prominent/protruding

Severe (3) = Diffuse, most or all the lid(s) AND prominent/protruding

Conjunctival (Palpebral and Bulbar) Hyperemia

None (0) = Normal

Mild (1) = Slight localized injection

Moderate (2) = Pink color, confined to palpebral OR bulbar conjunctiva

Severe (3) = Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Edema

None (0) = Normal

Mild (1) = Slight localized swelling

Moderate (2) = Mild/medium localized swelling or mild diffuse swelling

Severe (3) = Moderate diffuse swelling

Corneal Edema

None (0) = Normal

Mild (1) = Mild, diffuse stromal haze

Moderate (2) = Dense, diffuse stromal haze or bullae

Severe (3) = Dense, diffuse bullae or stromal haze AND stromal edema

Lens

The lens will be noted as phakic, aphakic, or pseudophakic. Phakic lens will be graded as described below:

None (0) = No lens discoloration nor opacification

Mild (1) = Yellow lens discoloration or small lens opacity (axial or peripheral)

Moderate (2) = Amber lens discoloration or medium lens opacity (axial or peripheral)

Severe (3) = Brunescent lens discoloration or complete lens opacification (no red reflex)

Anterior chamber cells and flare will be observed with a 1.0 mm in width and 1.0 mm in length slit beam and graded using the Standardization of Uveitis Nomenclature (SUN) scale (Sun Working, 2005). The iris and the pupil will be evaluated for the presence of clinically significant abnormalities.

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) = None

(1) = Faint

(2) = Moderate (iris/lens details clear)

(3) = Marked (iris/lens details hazy)

(4) = Intense (fibrin/plastic aqueous)

Iris

The iris will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any clinically significant abnormalities will be noted.

Pupil

The pupil will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any clinically significant abnormalities will be noted.

23.4.8. Intraocular Pressure

IOP will be measured by applanation tonometry at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit 10 (Week 20 + 7 days).

At visits with IVT injection, IOP will be measured before Lucentis® injection and 40 (±10) minutes after injection. If post-Lucentis® injection IOP is > 21 mmHg or increased ≥ 10 mmHg from pre-injection IOP, the IOP measurement will be repeated at 60 (±10) minutes following Lucentis® injection.

If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, the subject should be prescribed a topical IOP-lowering medication until he or she returns for follow-up per the Clinical Investigator's discretion, and the event will be reported as an AE.

IOP will be also measured after DE-122 or Sham injection. If post-DE-122 or Sham injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-Lucentis® injection at 40 (±10) minutes after injection, the IOP measurement will be repeated at 60 (±10) minutes after the injection. If post-DE-122 or Sham injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased

≥ 10 mmHg from pre-Lucentis® injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. If post-injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be managed according to the Clinical Investigator's discretion.

If rescue IVT injection is performed, IOP will be measured 40 (±10) minutes after the injection. If post-injection IOP is > 21 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, IOP measurement will be repeated at 60 (±10) minutes post-injection. If post-injection IOP at 60 (±10) minutes is ≥ 30 mmHg OR increased ≥ 10 mmHg from pre-injection IOP, the subject should be prescribed a topical IOP-lowering medication, and the IOP elevation will be reported as an AE. Per the Clinical Investigator's discretion, the subject can return for follow-up. If post-injection IOP at 60 (±10) minutes is > 21 mmHg AND < 30 mmHg, the subject will be managed according to the Clinical Investigator's discretion.

The applanation tonometer must be calibrated for accuracy before the first subject undergoes screening, and periodically until the last subject has exited the study. For checking calibration, follow the manufacturer's instructions.

The following IOP measurement procedure is in accordance with the procedure used in the Ocular Hypertension Treatment Study (Gordon et al., 2001) at each visit:

At least two, and sometimes three, consecutive measurements are made to obtain a determination of intraocular pressure. Each IOP measurement should be recorded in the subject's source document and in the eCRFs.

- If the first 2 measurements differ by less than 3 mmHg, report the mean of the first 2 measurements. For example, if the two measurements are 22 and 23, then 22.5 is the final recorded IOP.
- However, if the first 2 measurements differ by greater than or equal to 3 mmHg, take a third measurement and report the median IOP (the median is the middle measurement after arraying the measurements from low to high). For example, if the three measurements are 15, 19, and 16, then 16 is the final recorded IOP.

23.4.9. Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed for each eye at each visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit10 (Week 20 + 7 days) with pupil dilation.

Indirect ophthalmoscopy will be used to examine the retina at each study visit. Indirect ophthalmoscopy will be performed prior to and within 30 minutes after each DE-122 or Sham injection. Areas to be assessed include cup to disc ratio, retina, macula and choroid, and vitreous. This will be also applied for the post IVT injection of Rescue treatment.

Cup/Disc Ratio

The cup/disc ratio will be determined by the examiner and recorded using two decimal places (e.g., 0.80).

Retina, Macula and Choroid

The retina, macula and choroid will be evaluated for the presence of any clinically significant abnormalities, and graded as either normal (within normal limits) or abnormal (clinically significant abnormality present). A description of any abnormalities will be noted.

Vitreous

The following National Eye Institute Grading Scheme will be used to measure vitreous haze and opacification (Nussenblatt et al., 1985).

Vitreous Haze Scale

Step	Description
(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

23.4.10. Spectral Domain Optical Coherence Tomography

Spectralis, Cirrus or 3D OCT will be utilized to take optical images at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit 10 (Week 20 + 7 days). The images will be sent to the central reading center.

23.4.11. Swept Source Optical Coherence Tomography Angiography

Swept Source OCT angiography will be taken at each study visit except Visit 2 (Day 3), Visit 9 (Week 20 + 2 days) and Visit 10 (Week 20 + 7 days).

23.4.12. Fundus Photography

Digital color fundus photography will be taken at Visit 0/Screening (Day -14 to Day -1), Visit 4 (Week 4), Visit 6 (Week 12), Visit 11 (Week 24) and Visit 13/Exit (Week 32). The images will be sent to the central reading center.

23.4.13. Fluorescein Angiography

Fundus fluorescein angiography will be taken at Visit 0/Screening (Day -14 to Day -1), Visit 4 (Week 4), Visit 6 (Week 12), Visit 11 (Week 24) and Visit 13/Exit (Week 32). The images will be sent to the central reading center.

23.4.14. Urine Pregnancy Test

A urine pregnancy test will be conducted before IVT injection at Visit 1 (Day 1) for all females of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 24 months since last menses occurred), has had her uterus and/or both

ovaries removed, or has had a bilateral tubal ligation. To obtain the pregnancy test, the subject should follow instructions provided by the manufacturer of the urine pregnancy test kit.

23.4.15. Serum Pregnancy Test

A serum pregnancy test will be conducted at Screening (Day -14 to Day -1), Visit 11 (Week 24) and Visit 13/Exit (Week 32) for all females of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 24 months since last menses occurred), has had her uterus and/or both ovaries removed, or has had a bilateral tubal ligation. To perform the pregnancy test, Human chorionic gonadotropin (hCG) will be contained into serum parameters that will be measured.

23.4.16. Hematology, Chemistry and Urinalysis

Approximately 10 mL of fasting blood and urine samples will be obtained at Visit 0/Screening (Day -14 to Day -1), Visit 4 (Week 4), Visit 6 (Week 12), Visit 11 (Week 24) and Visit 13/Exit (Week 32). The subjects will be asked to fast for a minimum of 8 hours prior to each blood and urine collection. Samples will be sent to a central laboratory for analysis.

There will be up to approximately 5 blood draws for immunogenicity. Approximately 10 mL or 2 teaspoons will be collected for each blood draw. The total amount of blood collected from each subject during this study will be up to approximately 50 mL

Serum Chemistry, Hematology

The following is a list of the minimum parameters that will be measured. Other additional parameters may also be reported.

Chemistry	**Hematology**
Albumin	red blood cells (RBC)
Creatinine	white blood cells (WBC)
lactate dehydrogenase (LDH)	differential WBC
glucose	platelets (PLT)
calcium	hemoglobin (HGB)
potassium	hematocrit (HCT)
sodium	mean corpuscular volume (MCV)
cholesterol (total, HDL and LDL)	mean corpuscular hemoglobin (MCH)
triglycerides	mean corpuscular hemoglobin conc. (MCHC)
urea nitrogen	
bilirubin (total, direct, indirect)	
alkaline phosphatase (ALP)	
alanine aminotransferase (ALT)	
aspartate aminotransferase (AST)	
gamma glutamyl transferase (GGT)	
Human chorionic gonadotropin (hCG)*	

Prior to enrolling a subject, the Clinical Investigator will indicate on the source document if any screening laboratory values exclude the subject from participating in the study (e.g., serum creatinine > 1.3 mg/dL).

*Conduct only at Visit 0/Screening (Day -14 to Day -1), Visit 11 (Week 24) and Visit 13/Exit (Week 32).

Urinalysis

The following is a list of the minimum urine parameters that will be measured. Other additional urine parameters may also be reported.

Urinalysis
PH
Protein
Erythrocytes
Ketones
Glucose

Prior to enrolling a subject, the Clinical Investigator will indicate on the source document if any screening laboratory values exclude the subject from participating in the study.

23.4.17. Procedures for Pharmacokinetic Serum Sample Collection, Storage and Shipment

Approximately 5 mL of blood sample for assessment of DE-122 levels in serum will be collected pre Lucentis® injection at Visit 1 (Day 1), 3 hrs (±10 mins) post DE-122 or Sham injection at Visit 1 (Day 1), Visit 2 (Day 3), Visit 3 (Week 1), Visit 4 (Week 4), pre Lucentis® injection at Visit 8 (Week 20), 3 hrs (±10 mins) post DE-122 or Sham injection at Visit 8 (Week 20), Visit 9 (Week 20 + 2 days), Visit10 (Week 20 + 7 days) and Visit11 (Week 24) for all subjects. The actual time of dosing and sampling will be recorded on the eCRF. After each serum sample is taken from the subject, the sample is to be stored on ice until processed for the collection of the serum fraction. The blood sample should be processed for serum within approximately **1 hour** after blood collection from the subject.

There will be up to approximately 10 blood draws for PK. Approximately 5 mL or 1 teaspoon will be collected for each blood draw. The total amount of blood collected from each subject during this study will be up to approximately 50 mL.

Please refer to the separate procedure manual for sample handling, storage, and shipment.

This procedure is applicable for the subjects who have consented under the protocol prior to Version 4.0.

23.4.18. Procedure for Immunogenicity Serum Sample

Approximately 2 mL of blood sample will be collected for immunogenicity analysis from the subject at Visit 1 (Day 1) and Visit 11 (Week 24).

There will be up to approximately 2 blood draws for immunogenicity. The total amount of blood collected from each subject during this study will be up to approximately 4 mL.

Refer to the separate procedure manual for sample handling, storage, and shipment.

23.4.19. Procedures for Pharmacogenomics/genomics Blood Sample Collection, Storage and Shipment

Approximately 10 mL of blood will be collected for future genetic analysis from the subject and stored in a refrigerator until shipment. It can be drawn once at any visit during the study after Visit 1(Day 1). Please refer to the separate procedure manual for sample handling, storage, and shipment. The samples will be coded to protect the participant's private information. Individual subjects' results from the research testing on their samples will not be communicated to them.

23.4.20. Procedure for Biomarker Serum Sample

Approximately 10 mL of blood sample will be collected for biomarker analysis from the subject pre Lucentis® injection at Visit 1 (Day 1), 3 hrs (±10 mins) post DE-122 or Sham injection at Visit 1 (Day 1), Visit 2 (Day 3) if applicable, Visit 3 (Week 1), Visit 4 (Week 4), pre Lucentis® injection at Visit 8 (Week 20), 3 hrs (±10 mins) post DE-122 or Sham injection at Visit 8 (Week 20), Visit 9 (Week 20 + 2 days) if applicable, Visit 10 (Week 20 + 7 days) and Visit 11 (Week 24).

There will be up to approximately 10 blood draws for Biomarker. The total amount of blood collected from each subject during this study will be up to approximately 100 mL.

Refer to the separate procedure manual for sample handling, storage, and shipment.

23.4.21. Procedure for Biomarker Aqueous Humor Sample

Approximately 50~120 µL of aqueous humor sample will be collected for biomarker analysis from the subject at Visit 1 (Day 1), Visit 4 (Week 4) and Visit 8 (Week 20).

Refer to the separate procedure manual for sample handling, storage, and shipment.