CLINICAL STUDY PROTOCOL

A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in Comparison with Eylea in Patients with Diabetic Macular Edema

PROTOCOL NUMBER CT-P42 3.1

EudraCT Number: 2020-004278-23

Investigational Product: CT-P42 (proposed Eylea biosimilar)

Sponsor: [redacted]

Sponsor Contact : [redacted]

SAE Reporting : [redacted]

Version and Date of Protocol: Protocol Version 4.0, including country specific A.0, 15 April 2022

Protocol Approval

Study Title	A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in comparison with Eylea in Patients with Diabetic Macular Edema
Protocol Number	CT-P42 3.1
Protocol Date	Protocol Version 4.0, including country specific A.0, 15 April 2022

Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled 'A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in comparison with Eylea in Patients with Diabetic Macular Edema' and the accompanying Investigator's Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 4.0, including country specific A.0, dated 15 April 2022, the International Council for Harmonisation harmonized tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug (mentioned as CT-P42 or Eylea) only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the study drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator	Date
Printed name of Principal Investigator	

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Protocol Synopsis

Protocol Number: CT-P42 3.1
Title: A Randomized, Active-Controlled, Double-Masked, Parallel-Group, Phase 3 Study to Compare Efficacy and Safety of CT-P42 in comparison with Eylea in Patients with Diabetic Macular Edema
Study Phase: Phase 3
Study Centers: [redacted]
Test Drug Formulation, Dose and Regimen: Main Study Period CT-P42, 2 mg/0.05 mL by intravitreal (IVT) injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses Extension Study Period CT-P42, 2 mg/0.05 mL by IVT injection via a single-dose pre-filled syringe (PFS) at Extension Week 0 (1 dose)
Reference Drug, Dose and Regimen: Main Study Period European Union (EU)-approved Eylea, 2 mg/0.05 mL by IVT injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses
Objectives: Primary Objective • To demonstrate that CT-P42 is similar to Eylea in terms of efficacy as determined by clinical response according to the mean change from baseline at Week 8 in Best Corrected Visual Acuity (BCVA) using Early Treatment of Diabetic Retinopathy Study (ETDRS) chart Secondary Objectives • To evaluate additional efficacy, pharmacokinetics (PK), usability, and overall safety including immunogenicity
Main Selection Criteria: Male or female patients aged ≥18 years with diabetic macular edema (DME), secondary to type 1 or type 2 diabetes mellitus (DM) will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.
Inclusion Criteria: Each patient must meet all of the following criteria to be enrolled in this study: 1. Male or female patient aged ≥18 years. 2. Patient who has type 1 or 2 DM. 3. Patient with DME secondary to DM involving the center of the macula (defined as the Optical Coherence Tomography [OCT] central subfield) in the study eye. 4. Patient whose central subfield retinal thickness is ≥350 μm as assessed by OCT based on central results in the study eye at Screening. 5. Patient who has BCVA score of 73 to 34 (approximate Snellen equivalent of 20/40 to 20/200) using ETDRS charts in the study eye at Screening and Day 1 (for more detailed BCVA procedures, see the study procedure manual). 6. Decrease in vision determined to be primarily the result of DME in the study eye. 7. Patient and/or their legally authorized representative are informed and will be given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any specific procedures. 8. Female patient must agree to use highly effective methods of contraception consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug (excluding women who are not of childbearing potential). Examples include the following:

a) Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
b) Intrauterine device or intrauterine hormone-releasing system
c) True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

A woman is considered of childbearing potential, following menarche and until becoming post-menopausal unless surgically sterile. Menopausal female patients must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential. Male patient who is sexually active with a woman of childbearing potential must agree to use highly effective method described as above or 2 acceptable methods of contraception (e.g., Male or female condom AND additional hormonal or barrier contraceptive method other than condom by female partner) consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug. Contraception is not required if either patient or his/her partner who has been surgically sterilized more than 24 weeks prior to the date of informed consent.

Exclusion Criteria:

A patient meeting any of the following criteria are not eligible for inclusion in this study:

1. Patient who has only one functional eye, even if the eye met all other study requirements, or has and/or is likely to have amblyopia, amaurosis or ocular disorder with BCVA $\leq$ 34 ETDRS letter score (approximate Snellen equivalent of $\leq$ 20/200) in the fellow eye
2. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in the study eye:
   a) Active proliferative diabetic retinopathy, or pre-retinal fibrosis involving the macula
   b) Aphakia
   c) Vitreomacular traction or epiretinal membrane that is expected to affect central vision
   d) Iris neovascularization, vitreous hemorrhage, or tractional retinal detachment
   e) Ocular inflammation (including trace or above)
   f) Uncontrolled glaucoma or filtration surgery for glaucoma in the past or likely to be needed in the future
   g) Intraocular pressure (IOP) ≥25 mmHg
   h) Spherical equivalent of the refractive error of worse than -6 diopters myopia
   i) Structural damage to the center of the macula that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates
   j) Concurrent and/or history of disease, other than DME, that could compromise visual acuity, require medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause) as assessed by the investigator
   k) Inability to obtain fundus and OCT images due to, but not limited to, insufficient media clarity or inadequate pupil dilation
3. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in either eye:
   a) Concurrent and/or history of idiopathic or autoimmune uveitis
   b) Evidence or suspicion of infection including blepharitis, keratitis, scleritis, or conjunctivitis
   However, a patient who has completely recovered from the infection at Day 1 is allowed to be enrolled at the investigator's discretion.
4. Patient who currently has, or has a history of (where indicated) systemic condition including one or more of the following:
   a) Uncontrolled DM as defined by hemoglobin A1c >10%
   b) Uncontrolled blood pressure defined as systolic ≥160 mmHg or diastolic ≥100 mmHg measured after 5 minutes of rest while sitting
   c) History of vascular disease such as cerebrovascular accident, myocardial infarction, transient ischemic

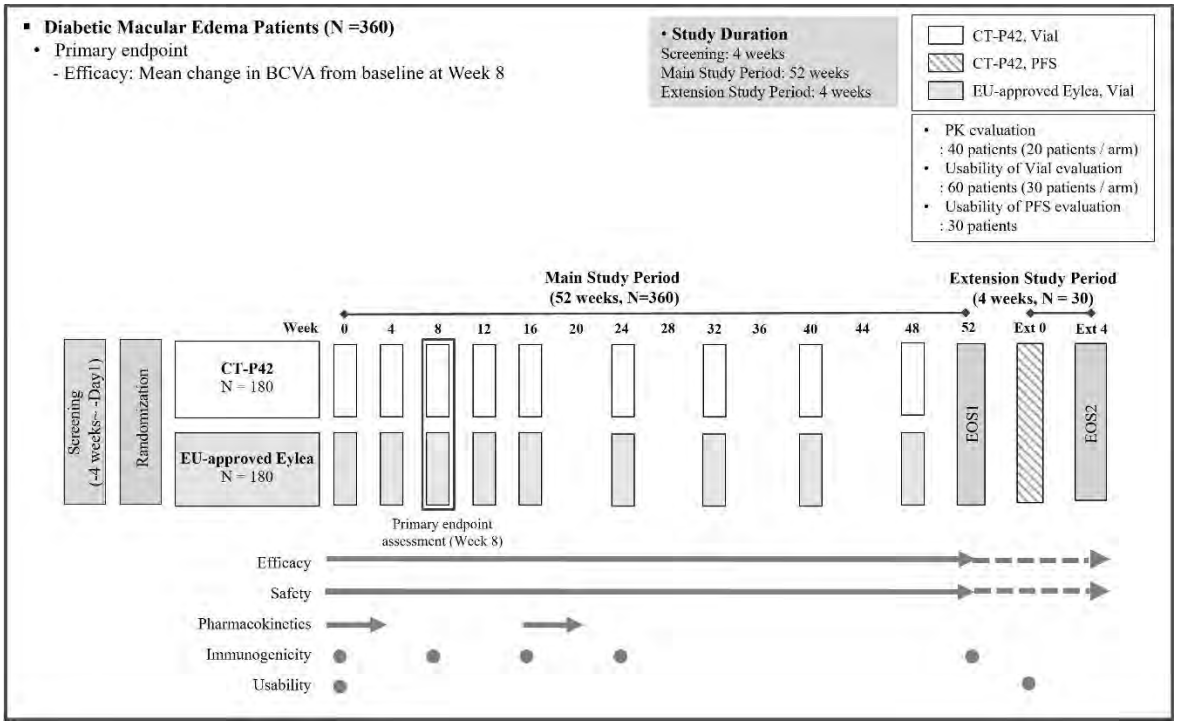
attack, or thromboembolic reaction including pulmonary embolism within 180 days prior to the first study drug administration
   d) New York Heart Association Functional Classification Class III or IV heart failure, or severe uncontrolled cardiac disease (i.e., unstable angina)
   e) Current treatment for serious systemic infection
   f) History of recurrent significant infections in the opinion of the investigator
   g) Renal failure requiring dialysis or renal transplant
   h) History of malignancies within 5 years prior to the first study drug administration, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma *in situ*
   i) History of other disease, metabolic dysfunction, physical examination finding, electrocardiogram (ECG) finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that, in the opinion of the investigator, contraindicates the use of the study drug or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications
   j) Evidence of significant uncontrolled concomitant diseases including cardiovascular system, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disorders, or psychiatric condition as assessed by the investigator.
5. Patient who has one or more previous/concomitant treatments of the following:
   a) Previous systemic or ocular treatment with aflibercept including potential biosimilars
   b) Previous treatment with ocular anti-angiogenic agents (pegaptanib sodium, bevacizumab, ranibizumab etc.) in the study eye
   c) Administration of systemic anti-angiogenic agents and/or ocular anti-angiogenic agents in fellow (non-study) eye within 180 days prior to the first study drug administration
   d) Previous use of intraocular or periocular corticosteroids including dexamethasone implant (e.g., Ozurdex) within 180 days, or fluocinolone acetonide implant (e.g., Iluvien) within 36 months prior to the first study drug administration in the study eye
   e) Laser photocoagulation (panretinal or macular) in the study eye within 90 days prior to the first study drug administration
   f) More than two previous macular laser treatments, and/or focal laser scars in the fovea that could limit BCVA improvement in the study eye
   g) History of vitreoretinal surgery including scleral buckling in the study eye
   h) Any intraocular surgery including cataract surgery in the study eye within 90 days prior to the first study drug administration or planned or expected during the study
   i) Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days prior to the first study drug administration
   j) Treatment with any investigational medicinal product and/or device within 30 days or 5 half-lives, whichever is longer, prior to the first study drug administration.
6. Patient with a hypersensitivity to immunoglobulin products, or patient who has allergies to any of the excipients or components of study drug, any other human proteins, or diagnostic process (e.g., anesthetics, topical broad–spectrum microbicides, fluorescein).
7. Female patient who is currently pregnant or breastfeeding.
8. Patient who, in the opinion of the investigator, should not participate in the study.

Study Design:

This study is a randomized, active-controlled, double-masked, parallel-group, multicenter, Phase 3 study designed to evaluate the efficacy, PK, usability, and overall safety including immunogenicity of CT-P42 and Eylea via IVT injection using a single-dose vial kit in the Main Study Period. An open-label, single-arm, single dose extension study can be followed to evaluate usability, efficacy, and safety of CT-P42 via IVT injection using a single-dose PFS.

During the Main Study Period, approximately 360 patients will be administered CT-P42 or Eylea via IVT injection (in 1:1 ratio) using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses. After the completion of the Main Study Period, approximately 30 patients can enter Extension Study Period to receive one additional dose of CT-P42 via IVT injection using a single-dose PFS at Extension Week 0 regardless of the treatment group in the Main Study Period. The study design and patient assessment overview are presented in the figure below.

Study Design Overview



Abbreviations: BCVA=Best Corrected Visual Acuity; EOS=End-of-Study; Ext 0=Extension Week 0; Ext 4=Extension Week 4; PFS=Pre-filled syringe; PK=Pharmacokinetics; EU=European Union

* The first EOS (EOS1) assessments will be performed at Week 52 for all patients who complete the Main Study Period. Patients who discontinue early from the study will visit the study center for the EOS1 evaluations at least 4 weeks after the last dose of study drug administration. For the patients who discontinued the study drug prior to the completion of Week 8 visit, the patients will be asked to return to the site at Week 8 to complete all planned assessments for the EOS1 visit.

* Blood samples for PK assessment will be collected for approximately 40 patients (20 patients per treatment group).

* Usability assessments of CT-P42 and Eylea vial kit will be performed at Week 0 for approximately 60 patients (30 patients per treatment group).

* Approximately 30 patients who complete the Main Study Period up to Week 52 can receive a single dose of CT-P42 PFS at Extension Week 0 to evaluate usability in the Extension Study Period.

Screening Period (Day -28 to Day -1):

Screening will take place between Day –28 and Day –1 (4 weeks), prior to the first study drug administration.

Main Study Period (Week 0 to Week 52):

On Day 1 (Week 0), patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. Only 1 eye per patient will be considered in this study and called as the 'study eye'. For patients who met criteria in both eyes, the eye with the worst BCVA will be selected as the study eye. If a patient has DME with similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. If neither eye is dominant, the right eye will be designated as the study eye. Eligible patients will be randomly assigned to either the CT-P42 or Eylea treatment group in a 1:1 ratio. The randomization to treatment assignment will be stratified as follows:

- BCVA score (<55 letters versus ≥55 letters) using the ETDRS chart on Day 1
- Country
- PK subgroup (Yes versus No)

<u>The First End-of-Study (EOS1) Visit (Week 52):</u>

The first EOS visit will occur at Week 52, 4 weeks after the last dose at Week 48. Patients who discontinue early from the study will visit the study center at least 4 weeks after the last dose of study drug administration for EOS1 evaluations. For the patients who discontinued the study drug prior to the completion of Week 8 visit, the patients will be asked to return to the site at Week 8 to complete all planned assessments for the EOS1 visit.

Extension Study Period (Extension Week 0 to Extension Week 4):

Approximately 30 patients who complete the Main Study Period up to Week 52, regardless of the treatment groups that they were randomized to, can participate in the open-label Extension Study Period. The patients must sign the ICF before participation in Extension Study Period. At Extension Week 0, patients will receive a single dose of CT-P42 PFS. CT-P42 PFS on Extension Week 0 is recommended 8 weeks after the last study drug administration in Main Study Period (Week 48). However, the actual dosing interval from the last administration of study drug in Main Study Period (Week 48) can be determined based on investigator's discretion considering the approved regimen of Eylea where treatment interval after first 12 months of treatment with Eylea may be extended based on investigator's judgement of visual and/or anatomic outcomes, and there are limited data for treatment interval longer than 4 months.

The Second End-of-Study (EOS2) Visit (Extension Week 4):

The second EOS visit will occur at Extension Week 4, 4 weeks after the dose of Extension Study Period.

During the whole study, patients will be asked to comply with all appropriate visits and assessments. All patients will return to the study center at specified visits in schedule of assessments for study drug administration, clinical assessments, and blood samplings. To minimize the risk of potential adverse events (AEs) associated with serial IVT injections, aseptic techniques will be performed. At each visit, the patients will be monitored for AEs and questioned about concomitant treatments until the last EOS visit.

Efficacy Assessments:

Primary Endpoint:

- Mean change from baseline in BCVA using the ETDRS chart at Week 8

Secondary Endpoints:

The following secondary efficacy endpoints will be assessed at each applicable visit up to Week 52, Extension Week 0 and 4:

- Mean change in BCVA using the ETDRS chart from baseline
- Proportion of patients who gained ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Proportion of patients who lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Mean change in central subfield thickness from baseline as determined by spectral-domain OCT
- Percentage of patients with a ≥2-step improvement from baseline in the ETDRS Diabetic Retinopathy Severity Scale (DRSS) score as assessed by fundus photography

Pharmacokinetic Assessment: Blood samples for assessment of C_{max} and T_{max} of free (VEGF-unbound) study drug concentrations in plasma will be collected at pre-dose within 60 minutes, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 6 hours after the first and the fifth study drug administration, respectively.

Secondary Endpoints:

- C_{max1}: Maximum plasma concentration after the first study drug administration
- C_{max2}: Maximum plasma concentration after the fifth study drug administration
- T_{max1}: Time of observed maximum plasma concentration after the first study drug administration
- T_{max2}: Time of observed maximum plasma concentration after the fifth study drug administration

Usability Assessment:

Secondary Endpoints:

The following usability endpoint will be assessed:

- Number of injections with vial kit successfully administered by healthcare professionals at Week 0
- Number of injections with PFS successfully administered by healthcare professionals at Extension Week 0

Safety Assessments:

Secondary Endpoints:
Safety assessments will be performed in both groups on AEs (ocular and non-ocular) including serious adverse events (SAEs), AEs of special interest (AESIs; arterial thromboembolic events and AEs related to IVT injection procedure), IOP test, slit lamp examination, indirect ophthalmoscopy, finger count/hand motion/light perception, immunogenicity assessments including anti-drug antibody and neutralizing antibody, hypersensitivity monitoring, vital signs and weight measurements, ECGs, New York Heart Association Functional Classification assessment, physical examination findings, pregnancy testing, clinical laboratory analyses including hemoglobin A1c, and prior and concomitant treatments monitored throughout the study. Adverse events will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

Sample Size:
Assuming an equivalence margin of ±3 letters with two one-sided significance level of 0.05, a sample size of 316 patients (158 patients in each treatment group) provides an 89% statistical power to demonstrate therapeutic equivalence of CT-P42 to Eylea based on the mean change from baseline in BCVA at Week 8. In the sample size calculation, the common standard deviation (SD) of the mean change from baseline in BCVA was assumed as 8.2 and expected mean difference was assumed to be 0. The dropout rate has been hypothesized at 12%; therefore, approximately 360 patients (180 patients in each treatment group of CT-P42 and Eylea) will be required to be enrolled in this study. [redacted]

Statistical Methods:
Data analysis:
This study will be unmasked for the reporting purposes. The first code break will occur after database lock for data up to Week 24 for all patients and the study results up to Week 24 will be reported in a first Clinical Study Report. The unmasked personnel will be predefined and documented before performing the analyses. The randomization codes for the Main Study Period will not be revealed to patients, investigators, and predefined masked study center personnel until the final Clinical Study Report has been generated except for predefined unmasked personnel from Sponsor and Contract Research Organization.
Statistical Analysis:
[redacted] The statistical methods for this study will be described in a detailed Statistical Analysis Plan (SAP), which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Continuous variables will be summarized by reporting descriptive statistics: the number of observations (n), mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.
Definition of Analysis Set:
All data collected during the Main Study Period will be analyzed in the following analysis sets.

- Intent-to-Treat (ITT) set is defined as all patients who are randomly assigned to receive either of the study drugs, regardless of whether or not any study drug was administered
- Full analysis set (FAS) is defined as all randomly assigned patients who receive at least one full dose of study drug
- Per-Protocol (PP) set is defined as all randomly assigned patients who receive all full doses of study drug up to Week 4 (total 2 injections) and have a BCVA assessment at Week 8. A major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will lead to the exclusion from PP set. Final determinations of the PP set will be made at the masked data review meeting before unmasking
- Safety set for Main Study Period is defined as all randomized patients who receive at least one full or partial dose of study drug
- Pharmacokinetic set is defined as patients who receive at least one full dose of study drug and have at least one post-treatment PK concentration data. A major protocol deviation that may affect the interpretation of study results of PK endpoints will lead to exclusion from PK set. Final determinations of the PK set will be made at the masked data review meeting for the PK endpoints before unmasking.
- Usability set for vial kit is defined as all patients in the Safety set for Main Study Period who have

evaluable usability measurements.

All data collected from the Extension Study Period will be analyzed in the following analysis sets.

- Safety set for Extension Study Period is defined as all patients who receive full or partial dose of study drug via PFS in the Extension Study Period.
- Usability set for PFS is defined as all patients in the Safety set for Extension Study Period who have evaluable usability measurements.

Efficacy Analysis:

The primary efficacy analysis (mean change from baseline in BCVA at Week 8) will be performed for the FAS using an analysis of covariance (ANCOVA) model with the baseline BCVA and country as covariates and treatment group as a factor. Therapeutic equivalence of CT-P42 with respect to Eylea will be concluded if two-sided 90% confidence interval of difference falls entirely within an equivalence margin (±3 letters). The primary endpoint will also be analyzed using the PP set. The sensitivity analysis will be performed in the FAS to evaluate the impact of missing data on the primary efficacy results. Missing data will be imputed using multiple imputation with the missing at random assumption. Also, in case the missing rate is higher than expected, the trimmed means approach will be considered to address the possible bias from the potentially high and/or imbalanced missing rates in the treatment groups. The details will be described in the SAP.

Other secondary efficacy endpoints will be analyzed using the FAS and PP Set for Main Study Period and Safety set for Extension Study Period. These will be summarized using descriptive statistics (n, mean, median, SD, minimum, and maximum) for quantitative variables and frequency counts and percentages for categorical variables.

Safety Analysis:

Severity grading of AEs will be recorded based on the CTCAE v5.0. All reported terms for AE and medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medication will be coded using the World Health Organization drug dictionary, non-drug therapies will be coded according to the MedDRA. All safety data, including immunogenicity, will be listed and summarized by treatment group as appropriate in the Safety set for Main Study Period and Safety set for Extension Study Period.

Pharmacokinetic Analysis:

The PK set will be the primary analysis set for the summary of PK data. Plasma concentrations and PK parameters will be summarized using descriptive statistics (including geometric mean and coefficient of variation, as appropriate).

Usability Analysis:

The secondary usability endpoint will be summarized using the Usability set for vial kit and PFS, respectively. The number of injections successfully administered will be summarized using frequency tables.

List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AMD	age-related macular degeneration
ATE	arterial thromboembolic event
BCVA	Best Corrected Visual Acuity
BP	blood pressure
CFR	Code of Federal Regulations
COVID-19	Disease caused by SARS-CoV-2
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for AEs
DM	diabetes mellitus
DME	diabetic macular edema
DR	diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end-of-study
ETDRS	Early Treatment of Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
FDA	Food and Drug Administration
FP	fundus photography
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
IAI	intravitreal aflibercept injection
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin gamma 1
IOP	intraocular pressure
IRB	Institutional Review Board
IVT	intravitreal
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
n	number of observations
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
PFS	Pre-filled syringe

PK	pharmacokinetics
PT	preferred term
PVG	pharmacovigilance
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SD-OCT	spectral-domain optical coherence tomography
SmPC	Summary of Product Characteristics
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
US	United States
USPI	United States Prescribing information
VA	visual acuity
VEGF	vascular endothelial growth factor

1 Introduction

1.1 Background

1.1.1 Diabetic Macular Edema

Diabetic macular edema (DME) is a leading cause of vision impairment related to diabetes mellitus (DM) among people within the working-age population (Wenick and Bressler, 2012). It is a common microvascular complication in patients with DM along with diabetic retinopathy (DR). Diabetic macular edema may have a sudden and debilitating impact on visual acuity (VA), eventually leading to blindness (Ciulla *et al*. 2003).

Diabetic macular edema is a consequence of DR in the macular area and is secondary to blood-retinal barrier rupture resulting in leakage of dilated hyperpermeable capillaries and microaneurysms, which is in turn secondary to a range of metabolic changes brought about by hyperglycemia (Romero-Aroca *et al*. 2016). Chronic hyperglycemia leads to the upregulation of vascular endothelial growth factor (VEGF), resulting in angiogenesis, increased vascular permeability, and the production of proinflammatory cytokines (Boyer *et al*. 2013). The most important molecule in retinal barrier rupture is the VEGF. The VEGF is a molecule present in the vitreous of patients with DR and DME, with its levels being proportional to the severity of the diseases (Romero-Aroca *et al*. 2016). Over time, ongoing microvascular damage triggers a well-defined succession of pathogenic events in the retina, including capillary nonperfusion and inner retinal ischemia, upregulation of VEGF-A, macular edema, and retinal neovascularization. Thickening of the basement membrane and pericyte loss, both key hallmarks of DR, as well as sheer stress on endothelial cells, may further stimulate VEGF production (Boyer *et al*. 2013).

The intravitreal (IVT) anti-VEGF agents are now widely used for DME in countries with high-resource settings. However, in low- or intermediate-resource settings, issues with access, availability, and administration of anti-VEGF agents may not allow the intensive treatment schedule and regimen needed to provide the outcomes seen in clinical trials (Wong *et al*. 2018; Schmidt-Erfurth *et al*. 2017). In countries with low or intermediate resources, where possible, physicians can consider off-label alternatives such as bevacizumab (Avastin), or focal or grid laser treatment might be considered as a primary method of treatment for DME (Wong *et al*. 2018). Thus, availability of more cost-effective biosimilars to the anti-VEGF therapy can broaden patient access to the standard treatment.

Aflibercept is a recombinant protein composed of the extracellular domains of two human VEGF receptors (VEGFR-1 and VEGFR-2) fused with the Fc portion of human

immunoglobulin gamma 1 (IgG1). It is a soluble decoy receptor that binds to VEGF-A and placental growth factor with a greater affinity than the body's native receptors. This way, VEGF more favorably binds with aflibercept instead of its native receptors, reducing VEGF's activity. VEGF-A is a biochemical signal protein that promotes angiogenesis throughout the body and in the eye. By decreasing VEGF-A's activation of its native receptors, aflibercept reduces subsequent growth of new blood vessels and vascular permeability (Eylea Summary of product characteristics[SmPC] 2022; Eylea United States Prescribing information [USPI] 2021).

1.2 CT-P42

CT-P42, containing the active ingredient aflibercept, is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1 and is developed as a proposed biosimilar to reference product Eylea (aflibercept) by CELLTRION, Inc.

The reference product, Eylea (aflibercept ophthalmic solution) was originally approved for treatment of wet age-related macular degeneration (AMD) in European Union (EU) in November 2012 and United States (US) in November 2011. In the EU, Eylea is indicated for the following conditions: wet AMD, macular edema following retinal vein occlusion (RVO), DME, and myopic choroidal neovascularization; in the US, Eylea is indicated for wet AMD, macular edema following RVO, DME, and DR.

CT-P42 will be formulated as a solution for injection at the same strength as Eylea (40 mg/mL) containing qualitatively and quantitatively the same or similar excipients. The CT-P42 and Eylea vial will be used for Main Study Period and the CT-P42 pre-filled syringe (PFS) will be used for Extension Study Period. CT-P42 or Eylea is referred as "study drug" further in this protocol.

1.2.1 Nonclinical Studies

Detailed information regarding the nonclinical pharmacology and toxicology of CT-P42 can be found in the Investigator's Brochure (IB).

1.2.2 Clinical Studies

No clinical studies have yet been conducted with CT-P42. However, clinical data on Eylea has been published in the scientific literature, regulatory submissions, and approved product information (Eylea SmPC 2022; Eylea USPI 2021). As CT-P42 is being developed as a

proposed biosimilar to reference product Eylea, the clinical findings for CT-P42 are expected to be similar with the reference product in terms of safety, pharmacokinetics (PK), and efficacy.

The efficacy and safety of aflibercept in DME was established based on two randomized, double-masked, active-controlled pivotal Phase 3 studies (Korobelnik *et al.* 2014).

VISTA and VIVID studies were conducted in 872 patients with DME, who were randomized in a 1:1:1 ratio to receive either 2 mg intravitreal aflibercept injection (IAI) every 4 weeks (2q4), 2 mg IAI every 8 weeks (2q8) after 5 initial doses every 4 weeks (from baseline to Week 16) with sham injections on non-treatment visits (2q8), or macular laser photocoagulation at baseline and sham injections at every visit (laser control group). The 1-year results of the VISTA and VIVID studies demonstrate that IAI 2q4 and IAI 2q8 significantly improved visual outcomes and significantly decreased severe vision loss, while simultaneously improving the Diabetic Retinopathy Severity Scale (DRSS) score, compared with focal laser photocoagulation. In safety aspects, the overall incidences of adverse events (AEs) were similar across treatment groups. There were no clinically relevant differences between the treatment groups in terms of frequency or pattern of ocular serious adverse events (SAEs). The incidence of intraocular inflammation based on the total number of IVT injections in the IAI 2q4, IAI 2q8, and laser groups was 0.2% (4/1832 injections), 0.1% (1/1284 injections), and 0.5% (1/212 injections) in VISTA, and 0.2% (4/1656 injections), 0.4% (5/1168 injections), and 0.7% (1/135 injections) in VIVID, respectively. The incidence of non-ocular SAEs was slightly higher for some events in the combined IAI group (e.g., congestive cardiac failure and anemia), and for others in the laser group (e.g., acute myocardial infarction and osteoarthritis), with no apparent general trend. The incidences and patterns of deaths were not clinically different among treatment groups (Korobelnik *et al.* 2014).

1.3 Study Rationale

CT-P42 is currently being developed as a proposed biosimilar to reference product Eylea. For a proposed biosimilar to be approved, it must show no clinically meaningful differences in comparison with its reference product. The stepwise ‘totality of evidence’ approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis.

Generally, statistically-proven equivalence between the proposed biosimilar and reference product regarding PK and efficacy is required, as is a demonstration of acceptable safety and immunogenicity. However, in view of the limited detectability of aflibercept in patient’s blood and high interpatient variability during historical Eylea trials, a PK equivalence study is neither

meaningful nor ethical in healthy volunteers considering IVT injection. Hence, no PK equivalence study is proposed for the development of CT-P42.

Therefore, assessment of the efficacy, PK, safety, and immunogenicity will be carried out in this proposed comparative clinical study in patients with DME. Sponsor considers that the proposed clinical development program will be sufficient to demonstrate therapeutic equivalence and safety of CT-P42 to the reference product (Study CT-P42 3.1 comparative clinical similarity).

The design of this study takes into account the EU Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues (European Medicines Agency [EMA] 2012) and the Food and Drug Administration (FDA) Guideline on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (FDA 2015).

1.3.1 Rationale for Study Population

International regulations (World Health Organization 2013; EMA 2012; FDA 2015; FDA 2019) suggest that proposed biosimilars should be tested in a population representative of the approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the proposed biosimilar and the reference product.

In patients with DME, the results from two pivotal studies showed robust, large, and clinically relevant improvement in Best Corrected Visual Acuity (BCVA) and morphological ocular visual outcomes in patients receiving aflibercept in comparison with macular laser photocoagulation (Korobelnik *et al.* 2014). In addition, the variability of mean changes from baseline BCVA in patients with DME was relatively low, and hemoglobin A1c (HbA1c) did not have significant impact on anti-VEGF treatment effect based on subgroup analysis (Singh *et al.* 2017). Furthermore, the mechanism of action of aflibercept in DME is representative for the other indications and the incidence of AEs with aflibercept was similar across indications (Fogli *et al.* 2018; Pham *et al.* 2019).

Consequently, the study population, DME, in this study was selected in order to align with the indications approved for the reference product and to be representative of the original placebo-controlled studies supporting the development of the reference product, facilitating the detection of potential differences between CT-P42 and the reference product Eylea.

1.4 Benefit and Risk Assessment

The CT-P42 drug product will have the same pharmaceutical form and strength as the reference product Eylea (40 mg/mL). The proposed dosing regimen is with the same as the approved labeling for Eylea (Eylea SmPC 2022; Eylea USPI 2021).

The proposed safety monitoring is deemed sufficient to monitor potential risks of CT-P42 administration. In view of the structural, biological, and toxicological similarity to Eylea, CT-P42 is expected to display a similar safety profile. Eylea has been studied extensively and has been shown to be effective at improving VA in patients with AMD, DME, and RVO (Eylea SmPC 2022; Eylea USPI 2021).

Based on the current clinical evidence, as well as the safety profile of Eylea, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

The benefit and risk assessments and the risk mitigation plans for coronavirus disease 2019 (COVID-19) are specified in the Appendix 4. Risk assessments will be conducted during the study by the sponsor through a sufficient discussion with the investigators and data safety monitoring board (DSMB).

2 Study Objectives and Endpoints

2.1 Study Objectives

2.1.1 Primary Objective

- To demonstrate that CT-P42 is similar to Eylea in terms of efficacy as determined by clinical response according to the mean change from baseline at Week 8 in BCVA using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart

2.1.2 Secondary Objectives

- To evaluate additional efficacy, PK, usability, and overall safety including immunogenicity

2.2 Study Endpoints

2.2.1 Primary Endpoint

The primary efficacy endpoint is the mean change from baseline in BCVA using the ETDRS chart at Week 8.

2.2.2 Secondary Endpoints

2.2.2.1 Efficacy Endpoints

The following secondary efficacy endpoints will be assessed at each applicable visit up to Week 52, Extension Week 0 and 4:

- Mean change in BCVA using the ETDRS chart from baseline
- Proportion of patients who gained ≥ 5, ≥ 10, and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Proportion of patients who lost ≥ 5, ≥ 10, and ≥ 15 ETDRS letters from baseline in BCVA using the ETDRS chart
- Mean change in central subfield thickness from baseline as determined by spectral-domain optical coherence tomography (SD-OCT)
- Percentage of patients with a ≥ 2-step improvement from baseline in the ETDRS DRSS score as assessed by fundus photography (FP)

2.2.2.2 Pharmacokinetic Endpoints

The following secondary PK endpoints will be assessed:

- Maximum plasma concentration after the first study drug administration (C_{max1})
- Maximum plasma concentration after the fifth study drug administration (C_{max2})
- Time of observed maximum plasma concentration after the first study drug administration (T_{max1})
- Time of observed maximum plasma concentration after the fifth study drug administration (T_{max2})

2.2.2.3 Usability Endpoint

The following secondary usability endpoint will be assessed:

- Number of injections with vial kit successfully administered by healthcare professionals at Week 0
- Number of injections with PFS successfully administered by healthcare professionals at Extension Week 0

2.2.2.4 Safety Endpoints

The following secondary safety endpoints will be assessed:

- Incidence and severity of AEs (ocular and non-ocular) including SAEs
- Incidence and severity of adverse event of special interest (AESI)
    a) Arterial thromboembolic events (ATEs)
    b) All AEs related to IVT injection procedure including but not limited to the following: endophthalmitis, increases in intraocular pressure (IOP), intraocular inflammation, rhegmatogenous retinal detachment, retinal tear and iatrogenic traumatic cataract.
- Intraocular pressure test, slit lamp examination, indirect ophthalmoscopy, finger count/hand motion/light perception, hypersensitivity monitoring, vital signs and weight measurement, electrocardiogram (ECG), New York Heart Association (NYHA) Functional Classification assessment, physical examination findings, pregnancy testing, clinical laboratory analyses including hemoglobin A1c (HbA1c)
- Immunogenicity, as assessed by incidence of anti-drug antibody and neutralizing antibody
- Prior and concomitant treatments

3 Investigational Plan

3.1 Study Design

This is a randomized, active-controlled, double-masked, parallel-group, multicenter, Phase 3 study designed to evaluate the efficacy, PK, usability, and overall safety including immunogenicity of CT-P42 and Eylea via IVT injection using a single-dose vial kit followed by a 4-week open-label, single-arm extension study to evaluate the usability, efficacy, and safety of CT-P42 via IVT injection using a single-dose PFS.

There will be 3 study periods: a Screening Period of 4 weeks, Main Study Period of 52 weeks and Extension Study Period of 4 weeks.

During the Screening Period, the eligibility of the patients for study enrollment will be checked. During the Main Study Period, approximately 360 patients will be administered CT-P42 or Eylea in 1:1 ratio via IVT injection using a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses.

After the completion of the Main Study Period, approximately 30 patients can enter the Extension Study Period to receive one additional dose of CT-P42 via IVT injection using a single-dose PFS at Extension Week 0 regardless of the treatment group in the Main Study Period.

A database lock is planned once data up to Week 24 for all patients are collected and the study results up to Week 24 will be reported in the first Clinical Study Report (CSR). The results will be generated by the predefined unmasked personnel from Sponsor and contract research organization (CRO). The randomization codes for the Main Study Period will not be revealed to patients, investigators, and predefined masked study center personnel until the final CSR has been generated except for predefined unmasked personnel from Sponsor and CRO.

3.2 Study Overview

The study design and patient assessment overview are presented in Figure 3-1. The schedule of assessments is presented in the schedule of assessment (Appendix 1).

Screening Period (Day –28 to Day –1)

Screening will take place between Day –28 and Day –1 (4 weeks), prior to the first study drug administration.

Main Study Period (Week 0 to Week 52)

On Day 1 (Week 0), patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. Only one eye per patient will be considered in this study and called as the 'study eye'. Detailed criteria for selection of the study eye are described in Section 4.1.

Eligible patients will be randomly assigned to either the CT-P42 or Eylea treatment group in a 1:1 ratio. The randomization to treatment assignment will be stratified as follows:

- BCVA score (< 55 letters versus ≥ 55 letters) using the ETDRS chart on Day 1
- Country
- PK subgroup (Yes versus No)

During the Main Study Period, all randomized patients will receive the study drug every 4 weeks for 5 doses, then every 8 weeks for 4 doses. Among them, approximately 40 patients (20 patients per treatment group) will make additional visits for PK evaluation.

Usability assessments of vial kit will be performed at Week 0 for approximately 60 patients (30 patients per treatment group).

First End-of-Study (EOS1) Visit (Week 52):

The first EOS visit (referred as EOS1) will occur at Week 52, 4 weeks after the last dose at Week 48. Patients who discontinue early from the study will visit the study center at least 4 weeks after the last dose of study drug, or at Week 8 in case of patients who discontinue study drug prior to the completion of Week 8 for EOS1 evaluations.

Extension Study Period (Extension Week 0 to Extension Week 4)

Approximately 30 patients who completed the Main Study Period up to Week 52, regardless of the treatment groups that they were randomized to, can participate in the open-label Extension Study Period. The patients must sign the ICF before participation in Extension Study Period. At Extension Week 0, patients will receive a single dose of CT-P42 PFS.

CT-P42 PFS on Extension Week 0 is recommended to be administered 8 weeks after last study drug administration in Main Study Period (Week 48). However, the actual dosing interval from the last administration of study drug in Main Study Period (Week 48) can be determined based on investigator's discretion considering the approved regimen of Eylea where treatment

interval after first 12 months of treatment with Eylea may be extended based on investigator's judgement of visual and/or anatomic outcomes, and there are limited data for treatment interval longer than 4 months (Eylea SmPC 2022).

The Second End-of-Study (EOS2) Visit (Extension Week 4):

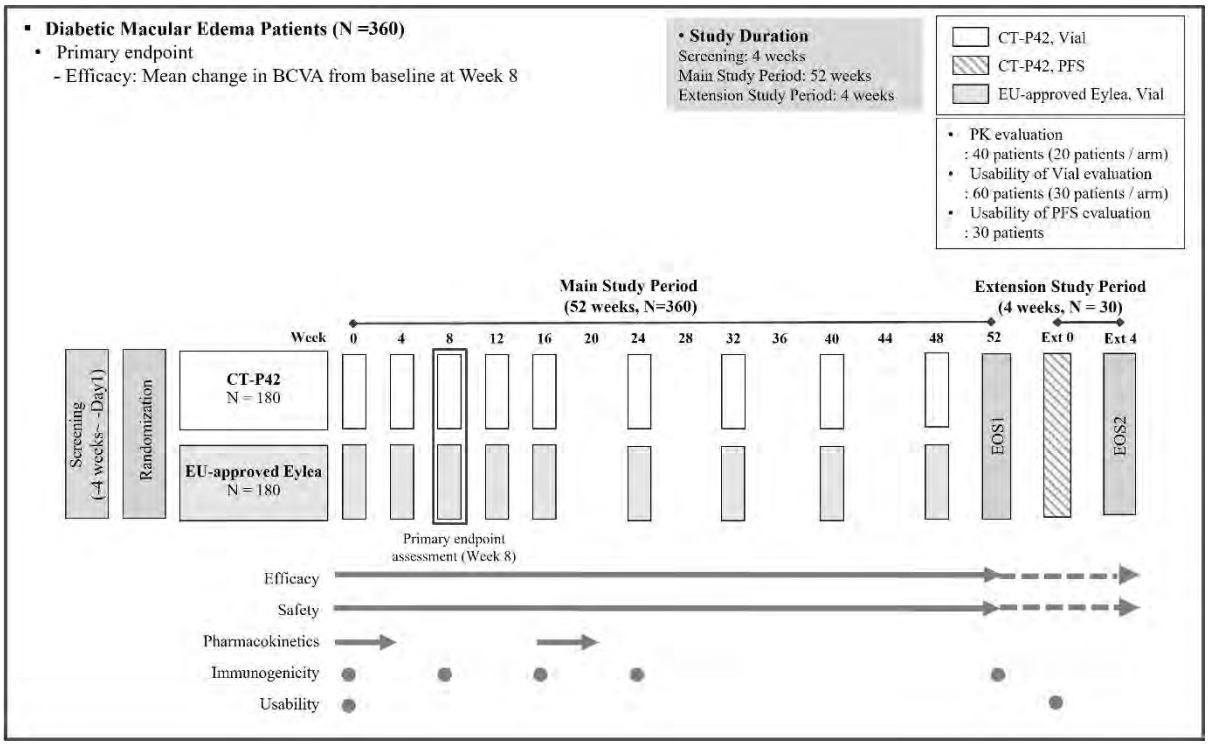
The second EOS visit (referred as EOS2) will occur at Extension Week 4, 4 weeks after the dose of Extension Study Period.

General considerations for study visits

Patients will be asked to comply with all appropriate visits and assessments. All patients will return to the study center at scheduled visits for study drug administration, clinical assessments, and blood samplings. To minimize the risk of potential AEs associated with serial IVT injections, aseptic techniques will be performed (Section 5.3.1). At each visit, the patients will be monitored for AEs and questioned about concomitant treatments until the last EOS visit (Section 6.4).

If any abnormal signs and symptoms are reported (e.g., any decreases in vision, eye pain, unusual redness, or any other new ocular symptoms in the study eye), patients will be instructed to visit the study center.

Figure 3-1 Study Design Overview



Abbreviations: BCVA = Best Corrected Visual Acuity; EOS = End-of-Study; Ext 0 = Extension Week 0; Ext 4 = Extension Week 4; PFS = Pre-filled syringe; PK = Pharmacokinetics; EU = European Union.

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 360 patients will be enrolled at approximately 104 study centers in 13 countries. Patients with DME secondary to type 1 or type 2 DM will be considered for enrollment in the study if they meet all the inclusion criteria and none of the exclusion criteria.

For patients who met criteria in both eyes, the eye with the worst BCVA will be selected as the study eye. If a patient has DME with similar BCVA in both eyes, the eye with the clearest media will be selected as the study eye. If the ocular media of both eyes are similar in clarity, the patient's non-dominant eye (if identifiable) will be selected as the study eye. If neither eye is dominant, the right eye will be designated as the study eye. Eligible patients will be randomly assigned to either the CT-P42 or Eylea treatment group in a 1:1 ratio.

4.1.1 Inclusion Criteria

Each patient must meet all the following criteria to be enrolled in this study:

1. Male or female patient aged ≥ 18 years.
2. Patient who has type 1 or 2 DM.
3. Patient with DME secondary to DM involving the center of the macula (defined as the OCT central subfield) in the study eye.
4. Patient whose central subfield retinal thickness is ≥ 350 μm as assessed by OCT based on central results in the study eye at Screening.
5. Patient who has BCVA score of 73 to 34 (approximate Snellen equivalent of 20/40 to 20/200) using ETDRS charts in the study eye at Screening and Day 1 (for more detailed BCVA procedures, see the study procedure manual).
6. Decrease in vision determined to be primarily the result of DME in the study eye.
7. Patient and/or their legally authorized representative are informed and will be given ample time and opportunity to read and/or understand the nature and purpose of this study including possible risks and side effects and must sign the informed consent form (ICF) before any specific procedures.
8. Female patient must agree to use highly effective methods of contraception consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug (excluding women who are not of childbearing potential). Examples include the following:

a) Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation

b) Intrauterine device or intrauterine hormone-releasing system

c) True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.

A woman is considered of childbearing potential, following menarche and until becoming post-menopausal unless surgically sterile. Menopausal female patients must have experienced their last period more than 1 year prior to the date of informed consent to be classified as not of childbearing potential. Male patient who is sexually active with a woman of childbearing potential must agree to use highly effective method described as above or 2 acceptable methods of contraception (e.g., male or female condom AND additional hormonal or barrier contraceptive method other than condom by female partner) consistent with local regulations during the course of the study and for at least 3 months following discontinuation of study drug. Contraception is not required if either patient or his/her partner who has been surgically sterilized more than 24 weeks prior to the date of informed consent.

4.1.2 Exclusion Criteria

A patient meeting any of the following criteria are not eligible for inclusion in this study:

1. Patient who has only one functional eye, even if the eye met all other study requirements, or has and/or is likely to have amblyopia, amaurosis or ocular disorder with BCVA $\leq$ 34 ETDRS letter score (approximate Snellen equivalent of $\leq$ 20/200) in the fellow eye.
2. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in the study eye:
   a) Active proliferative DR, or pre-retinal fibrosis involving the macula
   b) Aphakia
   c) Vitreomacular traction or epiretinal membrane that is expected to affect central vision
   d) Iris neovascularization, vitreous hemorrhage, or tractional retinal detachment
   e) Ocular inflammation (including trace or above)
   f) Uncontrolled glaucoma or filtration surgery for glaucoma in the past or likely to be needed in the future

g) Intraocular pressure ≥ 25 mmHg

h) Spherical equivalent of the refractive error of worse than -6 diopters myopia

i) Structural damage to the center of the macula that is likely to preclude improvement in BCVA following the resolution of macular edema including atrophy of the retinal pigment epithelium, subretinal fibrosis or scar, significant macular ischemia or organized hard exudates

j) Concurrent and/or history of disease, other than DME, that could compromise VA, require medical or surgical intervention during the study period, or could confound interpretation of the results (including retinal vascular occlusion, retinal detachment, macular hole, or choroidal neovascularization of any cause) as assessed by the investigator

k) Inability to obtain fundus and OCT images due to, but not limited to, insufficient media clarity or inadequate pupil dilation

3. Patient who currently has, or has a history (where indicated) of ocular condition including one or more of the following in either eye:

   a) Concurrent and/or history of idiopathic or autoimmune uveitis

   b) Evidence or suspicion of infection including blepharitis, keratitis, scleritis, or conjunctivitis. However, a patient who has completely recovered from the infection at Day 1 is allowed to be enrolled at the investigator's discretion.

4. Patient who currently has, or has a history of (where indicated) systemic condition including one or more of the following:

   a) Uncontrolled DM as defined by HbA1c > 10%

   b) Uncontrolled blood pressure (BP) defined as systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg measured after 5 minutes of rest while sitting

   c) History of vascular disease such as cerebrovascular accident, myocardial infarction, transient ischemic attack, or thromboembolic reaction including pulmonary embolism within 180 days prior to the first study drug administration

   d) New York Heart Association Functional Classification Class III or IV heart failure, or severe uncontrolled cardiac disease (i.e., unstable angina)

   e) Current treatment for serious systemic infection

   f) History of recurrent significant infections in the opinion of the investigator

   g) Renal failure requiring dialysis or renal transplant

h) History of malignancies within 5 years prior to the first study drug administration, except adequately treated squamous or basal cell carcinoma of the skin or cervical carcinoma *in situ*

i) History of other disease, metabolic dysfunction, physical examination finding, ECG finding or clinical laboratory finding giving reasonable suspicion of a disease or condition that, in the opinion of the investigator, contraindicates the use of the study drug or that might affect interpretation of the study results or render the patient at high risk for treatment complications

j) Evidence of significant uncontrolled concomitant diseases including cardiovascular system, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal disorders, or psychiatric condition as assessed by the investigator

5. Patient who has one or more previous/concomitant treatments of the following:

a) Previous systemic or ocular treatment with aflibercept including potential biosimilars

b) Previous treatment with ocular anti-angiogenic agents (e.g., pegaptanib sodium, bevacizumab, ranibizumab) in the study eye

c) Administration of systemic anti-angiogenic agents and/or ocular anti-angiogenic agents in fellow (non-study) eye within 180 days prior to the first study drug administration

d) Previous use of intraocular or periocular corticosteroids including dexamethasone implant (e.g., Ozurdex) within 180 days, or fluocinolone acetonide implant (e.g., Iluvien) within 36 months prior to the first study drug administration in the study eye

e) Laser photocoagulation (panretinal or macular) in the study eye within 90 days prior to the first study drug administration

f) More than two previous macular laser treatments, and/or focal laser scars in the fovea that could limit BCVA improvement in the study eye

g) History of vitreoretinal surgery including scleral bucking in the study eye

h) Any intraocular surgery including cataract surgery in the study eye within 90 days prior to the first study drug administration or planned or expected during the study

i) Yttrium-aluminum-garnet capsulotomy in the study eye within 30 days prior to the first study drug administration

j) Treatment with any investigational medicinal product and/or device within 30 days or 5 half-lives, whichever is longer, prior to the first study drug administration

6. Patient with a hypersensitivity to immunoglobulin products, or patient who has allergies to

any of the excipients or components of study drug, any other human proteins, or diagnostic process (e.g., anesthetics, topical broad-spectrum microbicides, fluorescein).

7. Female patient who is currently pregnant or breastfeeding.
8. Patient who, in the opinion of the investigator, should not participate in the study.

4.2 Withdrawal of Patients from the Study

Patients are free to withdraw from the study at any time for any reason. If the therapeutic effect is considered insufficient by either the patient or the investigator, the patient may discontinue the study drug and is able to receive whatever treatment is considered necessary. The investigator may also discontinue the study drug at any time in the interest of patient's safety. The primary reason for the discontinuation of the study drug must be recorded in the patient's medical record and in the electronic case report form (eCRF), with any comments (spontaneous or elicited) or complaints made by the patient.

For patients who discontinue the study drug during the Main Study Period, all attempts should be made to undertake protocol-specified safety procedures including assessments for the EOS1 visit. The EOS1 visit will be performed at least 4 weeks after the last dose of study drug administration.

If the patients discontinue the study drug prior to the completion of Week 8 visit, they will be asked to return to the site at Week 8 to complete all planned assessments for the EOS1 visit. Additional visits for the safety monitoring can be made at the investigator's discretion. Whenever the EOS1 visit is made at Week 8, the BCVA data of the EOS1 visit needs to be recorded in the relevant page of Week 8 in the eCRF.

Reasons for withdrawal include the following:

- Patient withdraws consent or refuses to continue procedures/observations or study drug
- Patient develops signs of disease progression in the judgment of the investigator
- Patient has any ocular AE in the study eye or non-ocular AE that would compromise his or her safety if he or she continues to participate in the study. The AEs are including but not limited to:

  a) Rhegmatogenous retinal detachment or stage 3 or 4 macular holes

  b) Transient ischemic attack or a stroke

  c) Decrease in BCVA of ≥ 30 letters compared with the last study visit assessment

d) Subretinal hemorrhage involving the center of the fovea, or if the size of the hemorrhage is ≥ 50% of the total lesion area

e) Any AEs requiring intraocular surgery

f) Any AEs for which he or she cannot continue to participate in this study

- Patient has a significant protocol deviation(s)
- Patient is pregnant
- Investigator's decision
- Study termination by the Sponsor
- Patient is lost to follow-up

When possible, the Sponsor should be notified of the withdrawal of a patient from the study. If necessary, the investigator may discuss with Sponsor or its designee any patient's reason for withdrawal. The Sponsor may be contacted if clarification is required on a case-by-case basis. All patients who terminate from the study will retain their patient number. Patient numbers will not be reused.

4.2.1 Replacement of Patients

Patients who receive the study drug and discontinue prior to study completion will not be replaced. Patients, who failed screening for any reason, can be rescreened only once. If there is an unusual situation that justifies consideration for additional rescreening, the investigator is recommended to discuss with the Sponsor. Rescreened patient will be assigned with new patient identification number.

4.3 Premature Termination of the Study

The Sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

If the study is terminated prematurely by the Sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

[redacted]

Patients who qualify for randomization will be randomly assigned at Day 1 (Week 0) in a 1:1 ratio to the CT-P42 or Eylea treatment group. The randomization will be stratified by BCVA score (< 55 letters versus ≥ 55 letters) using the ETDRS chart on Day 1, country, and PK subgroup (Yes versus No).

Baseline BCVA is considered as a stratification factor since it is considered one of important prognostic factors (Nguyen *et al*. 2012; Brown *et al*. 2015). Country will be also used as one of stratification factors because it is expected to be confounded with other known or unknown prognostic factors. Following that PK evaluation will be conducted in a subgroup of patients, it is considered as a stratification factor to resolve imbalance between subgroups.

Stratification details will be described in the randomization specification document, which will be provided separately.

For the open-label, single arm Extension Study Period, randomization is not applicable.

5.2 Identity of Investigational Product

The company code of the investigational product is CT-P42. It is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1, which is being developed by Sponsor as a proposed biosimilar to Eylea.

The International Non-proprietary name of the commercially available reference material (Eylea) is aflibercept and the Anatomical Therapeutic Chemical Classification System code is L01XX44. CT-P42 and Eylea are dimeric IgG1 fusion glycoprotein with a protein [redacted]. In this study, EU-approved Eylea will be used as a reference drug in Main Study Period. Further details can be found in the IB.

The CT-P42 and Eylea solution for injection will be provided in a single-dose vial kit for the Main Study Period and CT-P42 in a single-dose PFS for the Extension Study Period.

Each presentation will provide a usable amount to deliver a single dose of 0.05 mL containing 2 mg aflibercept. Each vial and PFS will contain clear to slightly opalescent, colorless to very pale brownish yellow solution for IVT injection.

The vial kit will contain one glass vial and injection components (filter needle, syringe, and injection needle).

Each vial and PFS should only be used for the treatment of a single eye as extraction of multiple doses from a vial or PFS may increase the risk of contamination and subsequent infection.

Each vial and PFS contains more than the recommended dose of 2 mg aflibercept. The extractable volume of the vial or syringe is not to be used in total and the excess volume should be expelled before injection. Dosing instruction described in the Eylea prescribing information is to be followed (Eylea SmPC 2022; Eylea USPI 2021).

Sponsor will provide adequate supplies of CT-P42 and Eylea for distribution to the study centers. The following drug supplies will be used in the study:

Table 5-1 Identity of investigational Products

Product	Supplied as:
CT-P42 vial kit with injection components	• One single-dose vial to deliver 2 mg/0.05 mL aflibercept with excess volume • One filter needle for withdrawal of the vial contents • One syringe for administration • One injection needle for IVT injection
CT-P42 PFS	• One single-dose PFS to deliver 2 mg/0.05 mL aflibercept with excess volume
EU-approved Eylea vial kit with injection components	• One single-dose vial to deliver 2 mg/0.05 mL aflibercept with excess volume • One filter needle for withdrawal of the vial contents • One syringe for administration • One injection needle for IVT injection

Abbreviations: IVT = intravitreal; EU = European Union; PFS = pre-filled syringe.

5.3 Study Drug Administration

5.3.1 CT-P42 and Eylea

Patients will be dosed with either CT-P42 or Eylea as specified in the schedule of assessments (Appendix 1). Patient will receive 2 mg/0.05 mL of CT-P42 or Eylea IVT injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses during the Main Study Period. Approximately 30 patients who completed the Main Study Period up to Week 52 regardless of treatment group that they were randomized to can receive a single dose of

2 mg/0.05 mL CT-P42 IVT injection via a single-dose PFS at Extension Week 0 during the open-label Extension Study Period.

During the Main Study Period, study drug will be administered at the fixed visit schedule with an allowed visit window of ± 7 days, based on the first study drug administration (Appendix 1). Except for Week 4, study drug should be administered preferably within 2 weeks from the planned dosing date with a minimum of 21 days between doses considering dose delay including temporary interruption. At Week 4, study drug should be administered within visit window of ± 7 days unless temporary interruption of the study drug is required. If study drug administration cannot be done within an allowed visit window or missed dose is expected, it should be discussed with Sponsor or its designee regarding the patient's eligibility to continue study treatment.

Injecting the entire volume of the vial or PFS could result in overdose and thus, excess volume should be expelled before injection to deliver intended amount (2 mg/0.05 mL) to the patients. To eliminate all of the bubbles and to expel excess study drug, slowly depress the plunger to align the plunger tip with the line that marks 0.05 mL on the syringe (preparation for administration of vial) or align the plunger dome edge with the 0.05 mL dosing marker on the syringe (preparation for administration of PFS). Each sterile vial or PFS should only be used for the treatment of a single eye. After injection, any unused product must be discarded.

The study drug in vials will be supplied in kits. When CT-P42 and Eylea vial kit or CT-P42 PFS are removed from the refrigerator, the solution should be visually inspected, and should have no evidence of turbidity. If any particulates, cloudiness, or discoloration is visible in the vials or PFS, they must not be used. Prior to usage, the unopened vial or blister of study drug may be stored at room temperature (below 25°C) for up to 24 hours. Details of the study drug accountability and destruction will be specified in the pharmacy manual.

Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering IVT injections. In general, adequate anesthesia and asepsis, including topical broad–spectrum microbicide (e.g., povidone iodine applied to the periocular skin, eyelid and ocular surface), will be given prior to the injection. Surgical hand disinfection and use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended.

The injection needle should be inserted 3.5 to 4.0 mm posterior to the limbus into the vitreous cavity, avoiding the horizontal meridian and aiming toward the center of the globe. The injection volume of 0.05 mL is then delivered; a different scleral site should be used for subsequent injections.

Following the IVT injection, patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment (e.g., eye pain, redness of the eye, photophobia, blurring of vision) immediately. Patients will be monitored for elevation in IOP. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

Other ancillary components, including injection needle for PFS, required for the administration of CT-P42 or Eylea will be supplied by the study center. All preparation steps have to take place under aseptic conditions after opening the vial or blister. The study drug in vials will be withdrawn using aseptic technique through the filter needle attached to the syringe. The filter needle will be discarded after withdrawal of the vial contents and should not be used for IVT injection. The sterile 30-gauge needle should be attached for the IVT injection for both presentations.

5.3.2 Temporary Interruptions of Study Drug

Temporary interruptions of study drug should be considered for the following cases as per Eylea SmPC 2022 and Eylea USPI 2021. Study drug will be resumed at investigator's discretion and dosing schedule will be adjusted as described in Section 5.3.1 considering patient's safety.

- In the event of a retinal break in the study eye, the dose should be withheld and should not be resumed until the break is adequately repaired.
- In the event of IOP ≥ 30 mmHg in the study eye, study drug may be resumed when the IOP is normalized to a safe range as determined by the investigator, either spontaneously or with treatment.
- The dose should be withheld within the previous or next 28 days in the event of a performed or planned intraocular surgery in the study eye.
- In the event of any active intraocular inflammation in the study eye, study drug should be withheld and should not be resumed until the active intraocular inflammation is repaired adequately.
- Administration of study drug can be interrupted temporarily when the patient has ocular and/or periocular infection(s) in either eye as determined by the investigator, and should not be resumed until the condition is repaired adequately.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Package, Labeling, and Storage

The appropriate number of study drug (kit with vial) will be allocated to each patient [redacted] at each visit in Main Study Period. In Extension Study Period, study drug (PFS) will be allocated manually.

A label will be attached to the outer carton of each study drug, as well as to the vial and PFS blister.

All study drug supplies must be stored in a secured area with limited access, in a refrigerator between 2°C and 8°C and must not be frozen. The immediate containers, as well as sterile PFS blister, must be kept in the outer carton until use to protect the study drug from light. The recommended storage conditions and expiry date, where required, will be stated in the product label approved by each regulatory authority.

5.4.2 Study Drug Accountability

It is the responsibility of the investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form will be maintained at the study center. The study drug accountability will be verified by the monitor during on-center monitoring visits. The study drug will be stored in a limited access area under appropriate environmental conditions.

The investigator will not supply the study drug to any person other than sub-investigators, designated staff, and the patients participating in the study. The study drug may not be relabeled or reassigned for use by other patients, unless approved by the Sponsor.

Unused study drugs (vial and PFS) should be returned to sponsor. Study drug accountability must be completed at the study center level and discrepancies, if any, need to be resolved prior to return. The used vials and syringes can only be destroyed if it is written in local Standard Operating Procedures (SOP) and a specific authorization is given by the Sponsor, which is required prior to patient randomization. Permission will be granted by the Sponsor on a study center-by-study-center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used vials and syringes immediately after administering to patients. Authorization from the Sponsor is required before a patient is enrolled. The list of destroyed vials and syringes must be recorded. The investigator will neither dispense nor store the study drug from any study center other than the study centers agreed with the Sponsor.

5.5 Masking

The study will be conducted in a double-masked manner during the Main Study Period and in an open-label manner during the Extension Study Period. The randomization codes for the Main Study Period will not be revealed to study patients, investigators, and study center personnel until the final CSR has been generated except for predefined unmasked personnel from Sponsor and CRO.

5.5.1 Breaking the Masking

Under normal circumstances, the masking should not be broken. The masking should be broken only if specific emergency treatment and medical management requires the study drug to be known. In such emergencies, the investigator may determine the identity of the study drug by using the applicable procedure [redacted] (instructions in the study manual, which is provided as a separate document).

The date, time, and reason for the unmasking must be documented in source document and the appropriate field of the eCRF and the medical monitor will be informed as soon as possible. All calls resulting in an unmasking event will be recorded and reported [redacted] to the medical monitor and the Sponsor. In cases where there are ethical reasons for the patient to remain in the study, the investigator will consult with the Sponsor or its designee for the patient to continue in the study.

The Sponsor and/or delegate responsible for pharmacovigilance (PVG) will have access to the randomization code, if suspected unexpected serious adverse reactions (SUSARs), which are patient to expedited reporting, should be unmasked before submission to the regulatory authorities.

The Data Safety Monitoring Board (DSMB) and the assigned staff who provide the safety analyses for the DSMB can also be unmasked on a case-by-case basis upon the request from DSMB members during closed session.

The overall randomization code will be broken only for reporting purposes. This will occur after database lock for data up to Week 24 for each patient. Efficacy, PK, usability, and safety endpoints including immunogenicity will be evaluated by the predefined unmasked personnel from Sponsor and CRO. The unmasked personnel will be predefined and documented before performing the analyses. The randomization codes for the Main Study Period will not be revealed to study patients, investigators, and study center personnel until the final CSR has been generated except for predefined unmasked personnel from Sponsor and CRO.

5.6 Treatment Compliance

Treatment compliance with the dosing protocol will be monitored by reviewing clinical records as all study drugs will be administered in a medical facility by authorized center personnel. Every effort will be made to encourage patients' compliance with the study day visits. When a patient does not show up at planned visit, the study center must make every effort to regain contact with the patient (when possible, at least 3 contact attempts before the patient is deemed lost to follow-up). The date and time of the study drug administration will be documented in both the source documents and eCRF.

5.7 Prior and Concomitant Therapy

All prior and concomitant therapies will be recorded in both the source documents and eCRF.

5.7.1 Prior and Concomitant Treatment

Information (e.g., drug name, date[s] of administration, etc.) about prior medications taken by the patients within 30 days prior to the first study drug administration will be recorded in both the source documents and eCRF. This will include all prescription drugs, vitamins, minerals, and over-the-counter medications. In addition, in order to check eligibility, prior medications will be reviewed from the date specified in the exclusion criterion #5 (Section 4.1.2). In particular, use of any potential previous treatments for DME including anti-VEGF medication, steroids, or lasers will be recorded in the eCRF from the diagnosis of disease.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the source documents and eCRF. Any changes in concomitant medications also will be recorded in the patient's eCRF and source documents. All concomitant medications used during the study will be recorded until the last EOS visit. The non-drug therapies (e.g., laser, surgery) will be also collected in both the source documents and eCRF.

Treatments that are related to the IVT injection procedure or planned assessments will be used in accordance to local health authorities' guidelines for each site and be recorded in both the source documents and eCRF (e.g., drugs or agents for anesthesia, asepsis, mydriatics, fluorescein or topical broad-spectrum microbicide).

The participant in this study will not replace the standard of care treatment of the underlying DM. The treatment of DM itself has to be continued over the duration of the trial as recommended by the responsible physician.

5.7.1.1 Fellow Eye Treatment

If the fellow (non-study) eye requires any treatment, the most applicable treatment option that is approved by the governing health authorities may be selected at the investigator's discretion and in the patient's best interest.

Only intravitreal aflibercept will be permitted when anti-VEGF agents are considered for the fellow eye treatment during the whole study period. For the first 18 weeks of the Main Study Period, the IVT injection of aflibercept in the fellow eye should be administered at least 2 weeks after and prior to the scheduled study drug administration. Afterwards, the IVT injections of aflibercept in the fellow eye can be administered anytime including the same day as the study eye. The fellow eye will not be considered an additional study eye even though treated with aflibercept.

If bilateral treatment of aflibercept is performed on the same day, this could lead to increased risk of systemic AEs theoretically. Therefore, the fellow eye treatment should be performed with caution.

5.8 Prohibited Therapy

The following medications, treatments, or procedures during the whole study period are prohibited:

Study eye

Patients will not receive any standard or investigational agents for DME treatment in the study eye other than their assigned study drug as specified in this protocol. This includes medications administered locally (e.g., IVT, by juxtascleral or periorbital routes), laser photocoagulation (panretinal or macular), and any intraocular surgeries.

Fellow eye

Anti-VEGF agents except aflibercept is not allowed.

Systemic

Systemic therapies including anti-angiogenic agents and anti-angiopoietin-2 agents for DME treatment of either eye are not permitted. Any medications that may be associated with macular edema in the opinion of the investigator are prohibited. Also, systemic medications which include any medications that can cause vision loss or known to be toxic to the lens, retina, or optic nerve, including (but not limited to) deferoxamine, chloroquine/hydroxychloroquine (Plaquenil), tamoxifen, phenothiazine, and ethambutol are prohibited. Any other investigational device, medical product, or interventions of any type suspected to influence outcome (i.e., which might influence the course of the underlying ocular disease or the study

drug results, respectively) are not allowed.

6 Study Assessments and Procedures

6.1 Efficacy Assessments

6.1.1 Best Corrected Visual Acuity

Visual function of the study eye and the fellow eye will be assessed using ETDRS (1985) protocol at an initial distance of 4 meters at each study visit as scheduled in the schedule of assessment (Appendix 1).

The person performing the assessments of refraction and BCVA will be qualified to ensure consistent measurement of BCVA. Refraction is to be done at each visit before BCVA assessment. The overall BCVA score will be calculated and be kept in the source data and recorded in the eCRF. Best Corrected Visual Acuity will be the first assessment made at every visit, before any other ocular procedures are performed, and prior to dilating the pupils.

A detailed method for conducting refraction and BCVA assessments can be found in the study procedure manual.

6.1.2 Optical Coherence Tomography

Retinal characteristics will be evaluated at each study visit using the SD-OCT after pupil dilation as scheduled in the schedule of assessment (Appendix 1).

Spectral-domain optical coherent tomography images will be captured for both eyes at Screening and only the study eye at other scheduled visits. Assessments will be performed prior to study drug administration. Images will be sent to an independent reading center and read by masked readers. All OCT images will be electronically archived at the study centers as a part of the source documentation. Optical coherence tomography is to be performed by a qualified technician on an acceptable device. The same device will be used at all time points at a patient level to avoid variability in the patient's measurements. Image acquisition with another OCT device should be discussed and approved by the central image center prior to being used. If a switch is inevitable, the switched machine type should be used for the remainder of the study. All details for acceptable OCT machines and OCT image acquisition/transmission will be provided in the study procedure manual.

6.1.3 Fundus Photography and Fluorescein Angiography

The anatomical state of the retinal vasculature of the study eye will be evaluated by FP and fluorescein angiography (FA) after pupil dilation as scheduled in the schedule of assessment (Appendix 1). Fundus photography and FA images for both eyes at Screening and only the

study eye at other scheduled visits will be captured and transmitted to an independent reading center to ensure a standardized evaluation by masked readers.

The 7-field or 4 wide-field FP images will be sent to an independent reading center for ETDRS DRSS grading. The same field image, 7-field or 4 wide-field, will be used for each individual patient throughout the whole study period.

All FA and FP images will be performed by qualified photographers and archived electronically at the center as part of the source documentation. Further details will be provided in the study procedure manual. For screening, FA images which are obtained within 4 weeks prior to first study drug administration can be used as screening data if the FA images were acquired by qualified photographers according to the procedures described in the study procedure manual.

6.2 Pharmacokinetic Assessments

Pharmacokinetic blood samples for the determination of plasma concentration of study drug will be collected in approximately 40 patients (20 patients per treatment group) at the time points specified in the schedule of assessments (Appendix 1). Blood samples for assessment of C_{max} and T_{max} of free (VEGF-unbound) study drug concentrations in plasma will be collected at pre-dose within 60 minutes, 24 ± 2 hours, 48 ± 2 hours, and 72 ± 6 hours after the first and the fifth study drug administration, respectively.

Analysis will be performed at the central laboratory.

Actual sampling times for each patient will be recorded in both the source documents and eCRF. Instructions for the blood collection, storage, and shipment to the central laboratory are described in Section 6.6.

6.3 Usability Assessments

In Main Study Period, usability assessments for vial kit of CT-P42 or Eylea will be performed at Week 0 in approximately 60 patients (30 patients per treatment group) who are administered the study drug (CT-P42 or Eylea vial) at Week 0. In Extension Study Period, usability assessments for CT-P42 PFS will be performed at Extension Week 0 in approximately 30 patients who are administered with the study drug (CT-P42 PFS) at Extension Week 0.

Usability will be assessed to evaluate the ability of healthcare professionals to follow the instructions for use to prepare and administer the IVT injection to patients while maintaining aseptic conditions in the intended use environment, and to document any use errors on all tasks.

Tasks specific to the unpacking, preparing, properly administering, and disposing the study drug will be assessed by the study center personnel. At the time of usability assessment, injections will be administered by investigators assisted with the study drug preparation by assistants. The study center personnel will observe and evaluate the procedures for use errors and close calls on all tasks, and will complete the injection assessment checklist (Appendix 3. Usability Assessment Checklist) during the injection.

6.4 Safety Assessments

Safety assessments will include the evaluation of AEs (ocular and non-ocular) including SAEs, AESIs, IOP test, slit lamp examination, indirect ophthalmoscopy, finger count/hand motion/light perception, immunogenicity assessments including anti-drug antibody and neutralizing antibody, hypersensitivity monitoring, vital signs and weight measurements, ECGs, NYHA Functional Classification assessment, physical examination findings, pregnancy testing, clinical laboratory analyses including HbA1c, and prior and concomitant treatments monitored throughout the study. Retest of any assessments during the Screening Period in terms of safety may be done only once at the investigator's discretion if medically justifiable.

6.4.1 Medical/Ophthalmic History and Demographic Information

Medical/ophthalmic history (general medical history including DM and DME) and demographic information (age, sex, ethnicity, race, body weight and height, smoking history) will be recorded on the source documents and eCRF.

6.4.2 Adverse Events

6.4.2.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs observed or reported by the patient during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after the ICF was signed if any symptoms develop. Any new condition noted at Screening will be regarded as an AE, but not a treatment-emergent adverse event (TEAE).

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in severity after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity from the baseline condition.

Abnormal results of diagnostic procedures, including laboratory test abnormalities, are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

Disease progression of DME in the study eye will not be recorded as an AE or SAE.

Medical interventions such as surgery, diagnostic procedures, and therapeutic procedures are not AEs, but are actions taken to treat medical conditions. They should be recorded as treatment(s) of the AEs, if medical condition for which the procedure was performed meets the definition of an AE. The AE term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.4.2.1.1 Adverse Events of Special Interest

Adverse events of special interest should be closely monitored.

The following AEs are considered as AESIs and will be reported using the same process as for AEs:

- Arterial thromboembolic events: Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause) according to the Antiplatelet Trialists' Collaboration. The Preferred Terms (PTs) for ATE analysis will be reviewed and determined in a masked manner prior to database lock and final determination for the PTs will be specified in the statistical analysis plan (SAP).
- All AEs related to IVT injection procedure including but not limited to the following: endophthalmitis, increases in IOP, intraocular inflammation, rhegmatogenous retinal detachment, retinal tear, and iatrogenic traumatic cataract. Adverse events considered by the investigator to be related to the IVT injection procedure will be included in safety analysis.

6.4.2.1.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples or such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered SAEs. Any admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a tuberculosis unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include the following:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or worsening of the preexisting condition (for workup of persistent pretreatment laboratory abnormality)
- Social admission (e.g., patient has no place to sleep)
- Purely for convenience (e.g., for easier performance of study assessments)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE

- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the whole study period and/or for the individual patient
- Hospitalization solely due to disease progression without any other AEs as decided by the investigator

6.4.2.1.3 Unlisted (Unexpected) Serious Adverse Events

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable reference documents (e.g., study drug IB).

6.4.2.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until the last EOS visit, regardless of the relationship to the study drug. The condition of the patient will be monitored throughout the study for any signs or symptoms. After the last EOS visit, serious adverse drug reactions will be reported to the Sponsor or its designee.

At every study visit, patients will be asked a standard non-leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant treatments regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., ophthalmologic assessments findings, laboratory values, physical examination findings, ECG changes) or identified from review of other documents that are relevant to patient safety will be documented on the AE page in the eCRF and the source documents.

6.4.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded in both the source documents and AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, date and/or time of onset, investigator-specified assessment of severity and relationship to study drug or injection procedure, assessment category (non-ocular, ocular in study eye, ocular in fellow eye), date and/or time of resolution of the event, seriousness, action taken with study drug, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, or concurrent medications, or worsening of preexisting conditions must also be reported.

Adverse events will be graded for severity according to the Common Terminology Criteria for AEs (CTCAE) v5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator's assessment of an AE's relationship to study drug or injection procedure is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The severity and the relationship or association of the study drug or injection procedure in causing or contributing to the AE will be characterized as defined in Section 6.4.2.6 and Section 6.4.2.7, respectively.

6.4.2.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.4.2.1.2) must be reported to CRO PVG within 24 hours from the time study center staff first learns about the event. The following contact information is to be used for SAE reporting:

[redacted]

[redacted]

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and e-mail or FAX it to CRO PVG within 24 hours of awareness of the event per the contact information specified above. The remote data capture system should be updated as soon as it is available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or sub-investigator. All SAEs will be followed up as specified in this protocol (Section 6.4.2.8).

The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting fatal or life-threatening SUSARs

(expedited reports) to the regulatory agencies and competent authorities within 7 calendar days after being notified of the event. Sponsor or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and IECs by a written safety report within 15 calendar days of notification.

6.4.2.5 Suspected Unexpected Serious Adverse Reactions

The Sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the Sponsor will assess the expectedness of these events using the applicable reference documents (e.g., study drug IB).

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6.4.2.6 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE v5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of daily living (ADL)*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The investigator will assess of the maximum severity that occurred over the duration of the event. However, if an AE changes from a non-serious to a serious event, a new SAE needs to be reported separately.

6.4.2.7 Assessment of Causality

6.4.2.7.1 Relationship of Adverse Events to Study Drug

As discussed in Section 6.4.2.3, the investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P42 or Eylea in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, e.g., the event follows a reasonable temporal sequence from the time of study drug administration or follows a known response pattern to the study drug but could also have been produced by other factors

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug

Definite: This relationship suggests that a definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered

6.4.2.7.2 Relationship of Adverse Events to Injection Procedure

The relationship of AEs to IVT injection procedure will be assessed using the following classification and criteria and will be a clinical decision based on all available information.

Unrelated: There is no reasonable possibility that the AE may have been caused by the injection procedure. Adverse events that were clearly and incontrovertibly due to causes other than the IVT injection procedure (e.g., disease, environment), or were felt with a reasonable degree of certainty to be unrelated to the IVT injection procedure

Related: There is a reasonable possibility that the event may have been caused by the injection procedure. Adverse events for which a connection with the IVT injection procedure could not be ruled out with certainty, or which were felt with a reasonable degree of certainty to be related to the IVT injection procedure, or which were incontrovertibly related to the IVT injection procedure

6.4.2.8 Follow-up of Adverse Events

All reported AEs will be followed up until one of the following: resolution or improvement from baseline, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure.

6.4.3 Immunogenicity Assessments

The immunogenicity of CT-P42 and Eylea will be assessed by anti-drug antibody and neutralizing antibody test in validated immunoassay. Neutralizing antibody test will be performed only on samples that are confirmed to have drug-specific anti-drug antibody. Serum samples for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of assessments (Appendix 1). Additional immunogenicity will be assessed when immune-related AEs occur. Immune-related AEs are defined as hypersensitivity events including intraocular inflammation with no clear underlying cause.

Blood samples for immunogenicity for patients with immune-related AEs will be obtained on the onset date of immune-related AEs, if possible. Blood samples obtained at the same date of study drug administration can also be used.

Sample analysis will be performed at the central laboratory.

6.4.4 Hypersensitivity Monitoring

Hypersensitivity monitoring will be assessed by vital signs (including BP, heart and respiratory rates, and body temperature) at the following time points at each visit specified in the schedule of assessments (Appendix 1):

- Within 1 hour after study drug administration

If patients have signs and symptoms of hypersensitivity at home (such as but not limited to rash, pruritus, urticaria, anaphylactic/anaphylactoid reactions, or intraocular inflammation), patients or caregivers should be advised to call the study center or get immediate help. Patients should be instructed to report any signs or symptoms of intraocular inflammation, e.g., pain, photophobia, or redness, which may be a clinical sign attributable to hypersensitivity.

In addition, hypersensitivity will also be monitored by patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation, must be available; in addition, any type of ECG can be performed, if deemed necessary. For patients who experience or develop life-threatening treatment-related anaphylactic reactions, study drug must be stopped immediately, and the patient must be withdrawn from the study if necessary.

6.4.5 Finger Count, Hand Motion, and Light Perception

Finger count, hand motion, and light perception will be done within 15 minutes after the IVT injection for study eye at the time points specified in the schedule of assessments (Appendix 1). It is to detect severe loss of vision following the IVT injection (from vitreous hemorrhage, central retinal artery occlusion, etc.). This starts with counting fingers. If the patient is unable to count fingers, hand motions will be shown. Finally, if patient cannot catch hand motion, light perception will be checked. When the patient fails in any of these steps, it will be recorded as AE at investigator's discretion. Details will be recorded in both the source documents and the eCRF.

6.4.6 Intraocular Pressure Test

Intraocular pressure will be measured pre-dose prior to pupil dilation for both eyes and within 60 minutes after the study drug administration for study eye, using Goldmann applanation tonometry or Tono-pen at time points specified in the schedule of assessment (Appendix 1). For the post-dose assessment, the last measured IOP within 60 minutes will be recorded as post-dose value. The same method of IOP measurement will be used throughout the study for each individual patient. If using same method is not available, the center should discuss with Sponsor in advance. The measurement of IOP will be performed by the investigator or trained staff and the values will be recorded in mmHg and will be entered into the eCRF and source documents. The results will be categorized using normal; abnormal, not clinically significant; abnormal, clinically significant and recorded in both the source documents and the eCRF. Any clinically significant abnormality will be recorded as an AE at investigator's discretion.

If the IOP in the study eye is $\geq$ 30 mmHg at any time during the study for any reason, it will be considered as clinically significant abnormality and the study treatment will be temporarily

withheld. It is recommended to resume the study drug administration after the IOP has been normalized to a safe range as determined by the investigator.

6.4.7 Slit Lamp Examination

The anterior segments structures and ocular adnexa of both eyes will be carefully examined before IVT injection at every scheduled visit as per the schedule of assessment (Appendix 1). Additional examination may also be performed at any time during the study at the investigator's discretion, if required. During the examination, the investigator will examine the eyelids, conjunctiva, sclera, cornea, anterior chamber, iris, pupil, and lens according to local medical practice and medical standards at the site. The results will be categorized using normal; abnormal, not clinically significant; abnormal, clinically significant and recorded in both the source documents and the eCRF. Any clinically significant abnormality will be recorded as an AE at investigator's discretion.

6.4.8 Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be performed pre-dose after pupil dilation for both eyes and within 60 minutes for the study eye after the study drug administration at time point specified in the schedule of assessment (Appendix 1). The investigator will examine the posterior segment on dilated pupil and also the peripheral retina to ensure if the IVT injection can be safely performed (i.e., iatrogenic retinal detachment, should not receive IVT injections). After IVT injection, the investigator will examine the study eye as part of the safety check up to be able to detect procedure related complications. The results will be categorized using normal; abnormal, not clinically significant; abnormal, clinically significant and recorded in both the source documents and the eCRF. Any clinically significant abnormality will be recorded as an AE at investigator's discretion.

6.4.9 Vital Signs and Weight

Vital signs and weight measurements will be performed at the time points specified in the Schedule of Assessments (Appendix 1). Vital signs (including systolic and diastolic BP, heart rate, respiratory rate, and body temperature) while sitting will be measured after 5 minutes of rest. All measurements will be documented at each study visit. Details will be recorded in both the source documents and the eCRF.

Vital sign measurements will also be monitored after study drug injection as part of the hypersensitivity monitoring (Section 6.4.4).

6.4.10 Electrocardiogram

All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the schedule of assessments (Appendix 1), and at any time when a patient experiences any cardiac symptoms during the study. If following the ECG review by the investigator there are any ECG findings that would indicate clinically significant abnormalities, the patient will be referred to a cardiologist to confirm the abnormality. For some sites requiring support in ECG reading, any abnormal ECG strips will be sent to independent reading center, and read by masked reader to confirm abnormality in further details. The investigator will then assess the clinical significance, and report the event in the source documents and the eCRF.

All ECG results will be archived as a part of the source documentation and will be recorded in the eCRF by the investigator.

Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion. In case of hypersensitivity, any type of ECG can be performed if necessary.

6.4.11 New York Heart Association Functional Classification

The NYHA functional classification (Appendix 2) assessment will be performed at the time points specified in the Schedule of Assessments (Appendix 1). Results will be recorded in both the source documents and the eCRF.

6.4.12 Physical Examination

A detailed physical examination will be performed at the time points specified in the schedule of assessments (Appendix 1). Physical examinations will be performed as verbal assessment of the health status. Additionally, other physical assessments may be performed at the investigators' discretion. In case of any complaints, the patient will be referred to an appropriate specialist by the investigator. Investigators should carefully evaluate patients for any indication of ATEs and AEs related to IVT injection procedure and pursue further investigation and treatment indicated in accordance with the investigator's medical judgment.

Information about the physical examinations will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded in both the source documents and eCRF.

6.4.13 Pregnancy

A woman is considered of childbearing potential, following menarche and until becoming post-menopausal unless surgically sterile. For women of childbearing potential, serum pregnancy test will be conducted at Screening and analyzed at the central laboratory. Only patients with a negative serum pregnancy test result can be enrolled in the study. For women of childbearing potential, a urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit specified in the Schedule of Assessments (Appendix 1) or more frequently if required by country-specific legislation. Urine pregnancy test will be performed locally. If a urine pregnancy test result is positive or equivocal, a confirmatory serum pregnancy test will be performed at the local laboratory.

In the event of an unexpected pregnancy during study participation and within 3 months after the last dose of study drug, patients should inform the investigator. If a patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to the Sponsor or designee Safety Department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug and be withdrawn from the study. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to the Sponsor or designee Safety Department within 24 hours after acquisition of the consent for the pregnancy form.

Pregnant patients or the pregnant partners of male patients will be followed up until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed up for 1 year after the birth, provided consent is obtained. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.4.2.1.2).

6.4.14 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected prior to study drug administration at the time points specified in the Schedule of Assessments (Appendix 1). Blood samples do not need to be collected in a fasting state unless required in the opinion of the investigator. At Week 40, only HbA1c will be assessed.

The following clinical laboratory analyses will be performed:

- Clinical chemistry: total protein, total serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, uric acid, creatinine, creatine kinase, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose,

lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and C-reactive protein

- Hematology: red blood cells, total and differential white blood cell count, absolute lymphocytes count, absolute neutrophils count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and HbA1c
- Urinalysis: color, bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination

Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples will be analyzed at the central laboratory.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

All samples should be collected as close as possible to the scheduled time point, and the actual sampling date must be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be obtained in accordance with the laboratory manual from each patient at the time points specified in the schedule of assessments (Appendix 1).

6.5.2 Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained prior to study drug administration at the time points specified in the Schedule of Assessments (Appendix 1), or when immune-related AEs occur.

6.5.3 Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of assessments (Appendix 1).

6.5.4 Urine Sampling

Urine samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the Schedule of Assessments (Appendix 1).

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

Each sample tube will be clearly labeled with the following information: study number, patient number, tube identification, and scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, immunogenicity, and safety analyses.

Where appropriate, blood samples should be transferred into a sufficient number of transfer tubes for transportation to the assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK and immunogenicity should be retained at the central laboratory as a back-up for up to 5 years after the end of the study in case additional analysis is required. Regardless of additional analysis for PK and immunogenicity, the sample will be stored at the Sponsor or a designated biobank for a further 5 years (after the end of the study) unless a specific authorization is given by the Sponsor to destroy the sample. Additional tests can be conducted at the Sponsor or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

6.7 Overdose Management

The CT-P42 and Eylea vials and CT-P42 PFS will contain more than the recommended dose of 2 mg/0.05 mL. The excess volume needs to be expelled before injection to avoid overdose due to injecting the entire volume.

The excess study drug and the air bubbles should be expelled by slowly depressing the plunger to align the plunger tip with the line that marks 0.05 mL on the syringe (preparation for administration of vial) or align the plunger dome edge with the 0.05 mL dosing marker (shown on the inside barrel) on the syringe (preparation for administration of PFS). The details will be provided in the pharmacy manual.

Overdosing with increased injection volume may increase IOP. Therefore, in case of overdose, IOP should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

7 Statistical Analysis Plan

[redacted] Continuous variables will be summarized by reporting descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.

Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the CSR. Full details of the statistical methods will be described in the SAP, which will be finalized before database lock.

7.1 Sample Size Calculation

Assuming an equivalence margin of ±3 letters with two one-sided significance levels of 0.05, a sample size of 316 patients (158 patients in each treatment group) provides an 89% statistical power to demonstrate the therapeutic equivalence of CT-P42 to Eylea based on the mean change from baseline in BCVA at Week 8. In the sample size calculation, the common SD of the mean change from baseline in BCVA was assumed as 8.2 and the expected mean difference was assumed to be 0. The dropout rate has been hypothesized at 12%; therefore, approximately 360 patients (180 patients in each treatment group of CT-P42 and Eylea) will be required to be enrolled in this study. [redacted]

7.2 Analysis Sets

All data collected during the Main Study Period will be analyzed in the following analysis sets.

Intent-to-Treat (ITT) set is defined as all patients who are randomly assigned to receive either of the study drugs, regardless of whether or not any study drug was administered.

Full analysis set (FAS) is defined as all randomly assigned patients who receive at least one full dose of study drug.

Per-Protocol (PP) set is defined as all randomly assigned patients who receive all full doses of study drug up to Week 4 (total 2 injections) and have a BCVA assessment at Week 8. A major protocol deviation that may affect the interpretation of study results of primary efficacy endpoint will lead to exclusion from PP set. Final determinations of the PP set will be made at the masked data review meeting before unmasking.

Safety set for Main Study Period is defined as all randomized patients who receive at least one full or partial dose of study drug.

The **PK set** is defined as patients who receive at least one full dose of study drug and have at least one post-treatment PK concentration data. A major protocol deviation that may affect the interpretation of study results of PK endpoints will lead to exclusion from PK set. Final determinations of the PK set will be made at the masked data review meeting for the PK endpoints before unmasking.

The **Usability set for vial kit** is defined as all patients in the Safety set for Main Study Period who have evaluable usability measurements.

All data collected from the Extension Study Period will be analyzed in the following analysis sets.

Safety set for Extension Study Period is defined as all patients who receive full or partial dose of study drug via PFS in the Extension Study Period.

Usability set for PFS is defined as all patients in the Safety set for Extension Study Period who have evaluable usability measurements.

7.3 Description of Subgroups to be Analyzed

Subgroup analysis will be detailed out in the SAP.

7.4 Efficacy Analysis

All efficacy data collected during the Main Study Period will be analyzed in the FAS and/or PP set unless otherwise specified. All efficacy data collected during Extension Study Period will be analyzed in the Safety set for Extension Study Period.

7.4.1 Primary Efficacy Analyses

7.4.1.1 Best Corrected Visual Acuity at Week 8

The primary efficacy analysis will be performed for the FAS with the mean change from baseline in BCVA at Week 8 using an analysis of covariance model with the baseline BCVA and country as covariates and treatment group as a factor. Therapeutic equivalence of CT-P42 with respect to Eylea will be concluded if the two-sided 90% confidence interval of difference falls entirely within an equivalence margin [± 3 letters]. Primary endpoint will also be analyzed using the PP set.

The sensitivity analysis will be performed in the FAS to evaluate the impact of missing data on the primary efficacy results. Missing data will be imputed using multiple imputation with the missing at random assumption. Also, in case the missing rate is higher than expected, the trimmed means approach will be considered to address the possible bias from the potentially high and/or imbalanced missing rates in the treatment groups (Permutt and Li. 2016). The details will be described in the SAP.

7.4.2 Secondary Efficacy Analyses

All secondary efficacy endpoints will be analyzed using the FAS and PP set for Main Study Period and Safety set for Extension Study Period. These will be summarized using descriptive statistics (n, mean, median, SD, minimum, and maximum) for quantitative variables and frequency counts and percentages for categorical variables and listed by treatment arm as appropriate.

7.4.2.1 Best Corrected Visual Acuity

The actual value and mean change from baseline in BCVA at each time point will be summarized descriptively by treatment group. The mean (± SD) BCVA score versus scheduled visit profiles will be presented graphically. The proportion of patients who gained/lost ≥ 5, ≥ 10, and ≥ 15 ETDRS letters from baseline in BCVA will be summarized using frequency tables and will also be presented using bar plot by treatment group and each scheduled visit.

7.4.2.2 Central Subfield Thickness by Optical Coherence Tomography

The actual value and mean change from baseline in central subfield thickness by OCT will be summarized descriptively by each treatment group.

7.4.2.3 Diabetic Retinopathy Severity Scale Score

The percentage of patients with a ≥ 2-step improvement from baseline in the ETDRS DRSS score as assessed by FP will be summarized using frequency tables.

7.5 Pharmacokinetic Analyses

Plasma concentration and PK parameters will be summarized using quantitative descriptive statistics (including geometric mean and coefficient of variation, as appropriate) by treatment group, study visit, and time point. All analyses will be performed based on the PK set.

7.6 Usability Analyses

The secondary usability endpoint will be summarized using the Usability set for vial kit and PFS, respectively. The number of injections successfully administered will be summarized using frequency tables.

7.7 Safety Analyses

For following assessments, all safety data collected will be analyzed in the Safety set for the Main Study Period and Extension Study Period, respectively.

- Adverse events (ocular and non-ocular) including SAEs
- Adverse events of special interest
- Immunogenicity assessments including anti-drug antibody and neutralizing antibody
- Hypersensitivity monitoring
- Finger count, hand motion, light perception
- Intraocular pressure test
- Slit lamp examination
- Indirect ophthalmoscopy
- Vital signs and weight
- Electrocardiogram
- New York Health Association functional classification
- Physical examination
- Pregnancy
- Clinical laboratory analyses including HbA1c
- Prior and concomitant treatments

7.7.1 Demographics, Baseline, and Background Characteristics

Baseline demographics (age, sex, ethnicity, and race) and background characteristics will be

summarized on ITT set by presenting data in summary tables. Qualitative data (e.g., medical/ophthalmic history) will be summarized in contingency tables, and quantitative data (e.g., age and height) will be summarized using quantitative descriptive statistics.

7.7.2 Adverse Events

AEs will be recorded according to the CTCAE v5.0 and will be coded to system organ class and PT according to MedDRA. A TEAE is defined as described in Section 6.4.2.1. Non-ocular, ocular AEs in the study eye, and ocular AEs in the fellow eye will be displayed separately. The following TEAE summaries will be reported by system organ class, PT, severity, relationship, and treatment group:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 treatment-emergent SAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with TEAE of special interest

7.7.3 Immunogenicity

All data will be listed and summarized by treatment group, where appropriate.

7.7.4 Clinical Laboratory Analyses

Clinical laboratory tests (clinical chemistry, hematology, urinalysis) including HbA1c, and pregnancy testing will be summarized by treatment at each scheduled collection time of Main Study Period. For continuous parameters, change from baseline will also be summarized for all scheduled collection times of Main Study Period after the first administration of study drug, if applicable.

7.7.5 Electrocardiograms, Physical Examination, Vital Signs, and Weight

Electrocardiograms, vital signs (systolic and diastolic BP, heart rate, respiratory rate, and body temperature) including hypersensitivity monitoring, and weight will be summarized by treatment for each scheduled collection time of Main Study Period. Physical examination will be listed by treatment group, where appropriate. Changes from baseline will also be summarized for all scheduled collection times of Main Study Period after the first administration of study drug, if applicable.

7.7.6 Prior and Concomitant Treatment

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. All prior and concomitant medications data will be listed and summarized by treatment group as appropriate. The non-drug therapies will be coded according to the MedDRA.

7.7.7 Other Safety Analyses

All other safety data will be listed and summarized by treatment group as appropriate.

7.8 Interim Analysis

Although no formal interim analysis is planned, the Sponsor plans to prepare 2 CSRs (Section 9.7).

7.9 Data Quality Assurance

This study will be conducted according to the ICH Good Clinical Practice (GCP) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH GCP guidelines on quality and risk management.

Steps will be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff prior to the study, periodic monitoring visits by the Sponsor or designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRF will be reviewed for accuracy and completeness by the monitor during on-center monitoring visits and after their return to the Sponsor or designee; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from the Sponsor or designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Enough prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should

immediately notify the Sponsor or designee if contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to changes based on industry and government SOP, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendment.

8.1 Confidentiality and Data Protection

All laboratory samples, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legally authorized representative), except as necessary for monitoring and auditing by the Sponsor, designee, the regulatory authorities, or the IRB/IEC.

The investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee or Institutional Review Board

Regulations and the ICH guidelines require an approval to be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonized tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the Sponsor or designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the data approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the Sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing risk to patients.

8.3 Patient Information and Consent

A written ICF in compliance with the ICH E6(R2) guidelines shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the ICF should be reviewed by the Sponsor, designee, or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legally authorized representative will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legally authorized representative understands the implications of participating in the study, the patient/legally authorized representative will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient’s right to withdraw from the clinical study at any time without giving reason and without jeopardizing the patient’s further course of medical treatment
- The existence of patient insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the principal investigator (or sub-investigator) and the patient or patient’s legal representatives (according to the local regulations) before the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legally authorized representative.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator's study file. The investigator will allow inspection of the forms by authorized representatives of the Sponsor, IRB/IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRFs, that ICF has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the principal investigators or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.4.2.1.2. In addition, the principal investigator or sub-investigator agrees to submit annual report to his or her IRB/IEC as appropriate.

8.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the study and for 1 year following the completion of the study.

Neither the Sponsor nor its designee is financially responsible for further testing or treatment or any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor its designee is financially responsible for further treatment of the patient's disease.

8.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the following essential documents, including but not limited to:

- Institutional Review Board/ Independent Ethics Committee approval
- Original investigator-signed investigator agreement page of the protocol
- Curriculum vitae of the principal investigator and each sub-investigator. Current licensure must be noted in the curriculum vitae. The curriculum vitae will be signed and dated by the principal investigators and sub-investigators at the study start-up, indicating that they are accurate and current
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements in accordance with local regulations. In addition, the

investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study

- Institutional Review Board/ Independent Ethics Committee-approved ICF, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legally authorized representative, and

- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with local regulations

8.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

Prior to the study onset, the protocol, ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient or the patient's legally authorized representative must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with the ICH E6(R2) guidelines will be maintained by the study center and will be available for review by the Sponsor or designee.

All IRB/IEC approvals will be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

The principal investigator or designated sub-investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or designated sub-investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to

maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc.

The analysis data sets will be combination of these data and data from other sources (e.g., laboratory data).

An eCRF is accessed through the appropriate system, which allows for on-center data entry and data management. Study center users can read from and write to the Sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon account and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators and individuals who have entered or modified records.

8.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

8.10 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide IRB/IEC with a summary of the study's outcome and the Sponsor and regulatory authorities with any reports required.

8.11 Record Retention

All correspondence (e.g., with Sponsor, IRB/IEC, or center monitors) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRFs, and drug inventory sheets pertaining to the study must kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the

Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the Sponsor.

8.12 Patient Identification Register

The investigator agrees to complete a patient identification register. This form will be treated as confidential and will be filed in the investigator site file. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

8.13 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

[redacted]

9.2 Vendor Contact

[redacted]

9.3 Central Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. Details of analytical facilities are presented in the ICF.

9.4 Monitoring

9.4.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist,

statistician, chairing physician, and an independent physician. The DSMB will review and evaluate accumulating safety data to ensure the safety of study patients and also review study results in a masked fashion during the study except a certain situation where an unmasked review of data on a case-by-case may be required for a discussion of potential safety concerns during the closed session.

Formal DSMB meetings will be held on pre-defined milestones as listed in the table below (Table 9-1). During each meeting, the committee will review the data and provide recommendations on whether the study can continue or any modification is needed. Initial safety data of the study was evaluated on the first safety review meeting which occurred to review the safety data reported up to approximately 7 days after enrollment of 20 patients, and the committee provided a recommendation for the study to continue without modification.

Table 9-1 Meeting milestones of DSMB

Milestone
7 days after enrollment of 20 patients
30 days after enrollment of 100 patients
Completion of Week 12 for all patients
Completion of 1st Clinical Study Report
Completion of Last Clinical Study Report

In addition to planned meeting, ongoing safety data will be reviewed on a regular basis. All SAEs are to be provided in a cumulative line-listing on a monthly basis (SUSARs whenever submission to the regulatory agency) to each DSMB member. Ad hoc meetings of the DSMB may be called at any time by the DSMB, should questions of subject safety arise. After each safety review meeting, the committee will provide the recommendations to the Sponsor.

Further details will be provided in the independent DSMB charter.

9.4.2 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. In case where a monitoring visit cannot be made because of the pandemic situation of corona virus disease 19, known as COVID-19, the monitor will discuss with the Sponsor, CRO, and the investigator for further plan, which will be specified in monitoring plan.

All aspects of the study will be carefully monitored by the Sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) and

SOPs.

9.4.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the Sponsor and CRO of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from the Sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the Sponsor for agreement and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the investigator. A major deviation occurs when there is non-adherence to the protocol by the patient or investigator that results in a major and additional risk to the patient's right, safety and well-being. Major deviations can include non-adherence to inclusion or exclusion criteria, or non-adherence to regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined before unmasking. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

9.6 Study Termination

The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date of the final CSR generated.

9.7 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the CSRs are prepared and provided to the regulatory authorities as required by the applicable regulatory requirement(s). The Sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonized tripartite guideline E3: Structure and content of CSRs.

The Sponsor plans to prepare 2 CSRs to report the following:

- Data for each patient up to Week 24
- All data after completion of the whole study period

If additional CSRs are required for regulatory or academic purposes, CSRs will be generated after the first database lock and unmasking process.

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11 Appendices

Appendix 1. Schedule of Assessments

	Screening	Main Study Period											Extension Study Period	
Dose		1	-	2	3	4	5	6	7	8	9	EOS1[1]	10	EOS2
Study visit (Week)	-4	0	1	4	8	12	16	24	32	40	48	52	Ext 0	Ext 4
Study visit (Day)	-28 to -1	1	8	29	57	85	113	169	225	281	337	365	1	29
Visit window (days)[2]	-	-	-1 to +2	±7									-	±7
Screening/Baseline														
Informed consent	X												X[3]	
Demographics, Medical/ophthalmic history	X													
New York Heart Association (NYHA) Functional Classification	X	X										X		
Weight	X											X		X
Physical examination	X											X		X
12-lead ECG[4]	X											X		X
Inclusion and exclusion criteria	X	X[5]												
Randomization[6]		X												
Pre-injection assessments														
Pregnancy test[7]	X	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[8]	X	X			X			X		X[9]		X		X
Pharmacokinetic sampling[10]		X					X							
Immunogenicity sampling[11]		X			X		X	X				X		
Pre-injection ophthalmologic assessments														
Best corrected visual acuity (ETDRS chart) [12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IOP test[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Slit lamp examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Indirect ophthalmoscopy[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Optical coherence tomography[13, 14]	X	X#	X#	X#	X#	X#	X#	X#	X#	X#	X#	X#		
Fundus photography (FP) [13, 15]	X	X#			X#			X#				X#		
Fluorescein angiography (FA) [13]	X[16]											X#		
Study drug administration														
Study drug administration (CT-P42 or Eylea)		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#,17	
Hypersensitivity monitoring[18]		X		X	X	X	X	X	X	X	X		X	
Post-injection ophthalmologic assessments														

	Screening	Main Study Period											Extension Study Period	
Dose		**1**	**-**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOS1[1]**	**10**	**EOS2**
Study visit (Week)	**-4**	**0**	**1**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**Ext 0**	**Ext 4**
Study visit (Day)	**-28 to -1**	**1**	**8**	**29**	**57**	**85**	**113**	**169**	**225**	**281**	**337**	**365**	**1**	**29**
Visit window (days)[2]	-	-	-1 to +2	±7									-	±7
Finger count, hand motion, light perception[19]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
Indirect ophthalmoscopy[20]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
IOP test[20]		X#		X#	X#	X#	X#	X#	X#	X#	X#		X#	
Other assessments														
Injection task assessment (usability)[21]		X											X	
Prior/concomitant treatments[22]	X												X	
AEs monitoring[23]	X												X	

Abbreviations: AEs, adverse events; BP, blood pressure; DME, diabetic macular edema; ECG, electrocardiogram; EOS, end-of-study; ETDRS, Early Treatment of Diabetic Retinopathy Study; Ext 0, Extension Week 0; Ext 4, Extension Week 4; FA, fluorescein angiography; FP, fundus photography; HbA1c, hemoglobin A1c; ICF, informed consent form; IOP, intraocular pressure; NYHA, New York Heart Association Functional Classification; OCT, optical coherence tomography; PFS, pre-filled syringe; SD-OCT, spectral-domain optical coherence tomography.

Note: The ophthalmologic assessments marked as 'X#' will be performed only for study eye. If not specified, the ophthalmologic assessments will be performed for both eyes throughout the study.

1. The first EOS assessments will be performed at Week 52 for all patients who complete the Main Study Period. Patients who discontinue early from the study will visit the study center at least 4 weeks after the last dose of study drug administration for EOS1 evaluations. For the patients who discontinued the study drug prior to the completion of Week 8 visit, the patients will be asked to return to the site at Week 8 to complete all planned assessments for the EOS1 visit.
2. A visit window of -1 to +2 day(s) is allowed at Week 1 and a visit window of ±7 days is allowed thereafter up to last EOS visit, based on the first study drug administration date. If any study visit has to be rescheduled, subsequent visits should follow the original visit date and allowed window.
3. The patient participating in the Extension Study Period must sign the ICF before participation in Extension Study Period.
4. All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. If patients have signs and symptoms of hypersensitivity or other cardiac origin, additional ECGs could be performed at any time during the whole study period. Regardless of the ECG result, further cardiological evaluation can be done at the investigator's discretion.
5. The inclusion and exclusion criteria need to be confirmed by screening results prior to the randomization on Day 1.
6. The randomization will be performed prior to the first study drug administration (Day 1).
7. For women of childbearing potential, serum pregnancy test will be conducted at Screening and analyzed at the central laboratory. Only patients with a negative serum pregnancy test result can be enrolled in the study. For women of childbearing potential, a urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit or more frequently if required by country-specific legislation. Urine pregnancy test will be performed locally. If a urine pregnancy test result is positive or equivocal, a confirmatory serum pregnancy test will be performed at the local laboratory.
8. Clinical laboratory tests will be carried out as scheduled; **Hematology** (red blood cells count, total and differential white blood cell count, absolute lymphocytes count, absolute neutrophils count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hematocrit, and HbA1c), **Clinical chemistry** (total protein, total serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, blood urea nitrogen, creatinine, creatine kinase, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, C-reactive protein, and uric acid), **Urinalysis** (color, bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination). Clinical laboratory test samples will be analyzed at the central laboratory.
9. At Week 40, only HbA1c will be assessed.

10. Pharmacokinetic blood samples for the determination of plasma concentration of study drug will be collected in approximately 40 patients (20 patients per treatment group). Pharmacokinetic sampling can be performed In-House Stay basis upon the investigator's discretion. The sampling schedule is as follows.

Study Visit	Sampling Time point	Window
First dose (Week 0, Day 1) / Fifth dose (Week 16, Day 113)	Pre-dose	within 60 minutes
	24 hours after study drug administration	± 2 hours
	48 hours after study drug administration	± 2 hours
	72 hours after study drug administration	± 6 hours

11. Samples for immunogenicity testing will be collected prior to dosing of study drug. Additional immunogenicity will be assessed when immune-related AEs occur.
12. Assessment will be performed prior to pupil dilation.
13. Assessment will be performed after pupil dilation.
14. The same device of SD-OCT will be used throughout the study. Image acquisition with another OCT device should be discussed and approved by the central image center prior to being used. If a switch is inevitable, the switched machine type should be used for the remainder of the study.
15. The same field image, 7-field or 4 wide-field, will be used for each individual patient throughout the whole study period.
16. For screening, FA images which are obtained within 4 weeks prior to first study drug administration can be used as screening data if the FA images were acquired by qualified photographers according to the procedures described in the study procedure manual.
17. Patients can receive treatment with CT-P42 PFS. CT-P42 PFS on Extension Week 0 is recommended to be administered 8 weeks after the last study drug administration in Main Study Period (Week 48). However, the actual dosing interval from the last administration of study drug in Main Study Period (Week 48) can be determined based on investigator's discretion.
18. Additional vital signs including BP, heart and respiratory rates, and body temperature will be monitored within 1 hour after study drug administration for possible hypersensitivity reactions. Hypersensitivity will also be monitored by patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed, if indicated.
19. Assessment will be performed within 15 minutes after the study drug administration.
20. Assessment will be performed within 60 minutes after the study drug administration.
21. Tasks specific to the unpacking, preparing, properly administering, and disposing the study drug by healthcare professionals will be assessed by the study center personnel.
22. Use of all prior and concomitant treatments for DME, from the diagnosis of disease to the last EOS visit, will be recorded. Use of all medications for other purposes, taken from 30 days prior to the first administration of study drug until the last EOS visit, will be recorded. For eligibility check, relevant medication history will be also recorded.
23. Adverse events will be assessed from the date the ICF is signed until the last EOS visit, regardless of the relationship to the study drug. Adverse events of special interest should be closely monitored. After the last EOS visit, serious adverse drug reactions will be reported to Sponsor or its designee.

Appendix 2. New York Heart Association Functional Classification

As defined in Zhang *et al.* 2018, the NYHA classification is used in patients with heart failure.

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause under fatigue, palpitation, dyspnea (shortness of breath)
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

Appendix 3. Usability Assessment Checklist

1. Usability Assessment Checklist for Vial Kit

No.	Product Use Tasks
1	Using aseptic technique, place the vial kit on a clean, flat surface.
2	Look at the vial and make sure you have the correct medicine and dosage.
3	Check the expiration date on the label to make sure it has not passed.
4	Remove the protective plastic cap from the vial.
5	Clean the top of the vial with an alcohol wipe.
6	Remove the filter needle and the 1-mL syringe from their packaging.
7	Attach the filter needle to the syringe by twisting it onto the Luer lock syringe tip.
8	Push the filter needle into the center of the vial stopper until the needle is completely inserted into the vial and the tip touches the bottom or bottom edge of the vial.
9	Using aseptic technique withdraw all of the vial contents into the syringe, keeping the vial in an upright position, slightly inclined to ease complete withdrawal. To deter the introduction of air, ensure the bevel of the filter needle is submerged into the liquid. Continue to tilt the vial during withdrawal keeping the bevel of the filter needle submerged in the liquid.
10	Ensure that the plunger rod is drawn sufficiently back when emptying the vial in order to completely empty the filter needle.
11	Remove the filter needle from the syringe and properly dispose of the filter needle.
12	Remove the injection needle from its packaging and attach the injection needle to the syringe by firmly twisting the injection needle onto the Luer lock syringe tip.
13	When ready to administer the study drug, remove the plastic needle shield from the needle.
14	Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top.
15	To eliminate all of the bubbles and to expel excess drug, SLOWLY depress the plunger so that the plunger tip aligns with the line that marks 0.05 mL on the syringe.
16	Insert syringe at injection site.
17	Slowly inject full dose.
18	Remove syringe from injection site.
19	Dispose of used syringe and needle.

2. Usability Assessment Checklist for PFS

No.	Product Use Tasks
1	Open the carton
2	Remove contents from carton
3	Carefully peel open the blister pack ensuring the sterility of its contents
4	Remove the syringe from the sterilized blister using aseptic technique
5	Twist off the syringe cap to remove the syringe cap
6	Using aseptic technique, firmly twist the injection needle onto the Luer lock syringe tip
7	Holding the syringe with the needle pointing up, check the syringe for bubbles. If there are bubbles, gently tap the syringe with your finger until the bubbles rise to the top
8	Remove the needle cap
9	Slowly depress the plunger rod to align the plunger dome edge to eliminate all bubbles
10	To expel excess drug and prepare the dose by aligning the plunger dome edge with the 0.05 mL dosing marker on the syringe
11	Insert syringe at injection site
12	Slowly inject full dose
13	Remove syringe from injection site
14	Dispose of used syringe and needle

Appendix 4. Benefit and Risk Assessment and Risk Mitigation Plan for COVID-19

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as coronavirus disease 2019, known as COVID-19. On 11 March 2020, WHO declared the SARS-CoV-2 infection outbreak a global pandemic as there were over 1 million deaths have been reported globally (WHO disease outbreak new, 2020).

Due to the global impact of the COVID-19 pandemic, the Sponsor is taking proactive measures to guarantee that all site staff and patients involved in trial are secure and the patients remain in the study until their last visit, with continuation of treatment during study period.

1. Benefit and Risk Assessment on Study Population

Diabetic macular edema has low chance to be deteriorated due to concurrent COVID-19 itself, considering the most common symptoms of COVID-19 are fever, dry cough, and tiredness (Q&A On Coronaviruses [COVID-19], 2020) and the irrelevance between cause of COVID-19 and DME disease. But diabetic and elderly patients are at a high risk for COVID-19 complications and should not be exposed to avoidable risk; however, continuation of care where possible is important to avoid irreversible vision loss (Korobelnik *et al.* 2020). Without appropriate treatment in short time periods, the visual loss could be definitive by fibrosis of edematous macular and photoreceptors death. Therefore, the SARS-CoV-2 pandemic might have poor consequences for visual acuity of patients. Because of this, finding a positive benefit-risk balance is very difficult, between evidence for a functional emergency (vision loss) and a high risk of life-and death emergency in vulnerable elderly patients (Navel *et al.* 2020).

Basically, the quarantine of COVID-19 should be carried out based on the SOP of each site and local regulatory guidelines. Sponsor plans to further implement and recommend the following procedures to minimize the risk of COVID-19 infection for the patients with DME and healthcare professionals during the IVT injection of study drug (Shmueli *et al.* 2020, Table 11-1). Taking this into account, the risk of COVID-19 infection for each patients is not expected to increase by participating in this study. Yet there is a possibility of increasing safety risk as being involved in this study, risk assessment will be conducted during the study by the sponsor through a sufficient discussion with the investigators and data safety monitoring board (DSMB).

Table 11-1 Summary of measures to prevent COVID-19 transmission while

maintaining adequate care of IVT injections

Reschedule	• Confirmed COVID-19 patients. • In isolation. • Travelled or exposed to somebody who travelled to high-risk areas. • Suspected COVID-19 (fever or flu-like symptoms)
Clinic injection control	• Wear surgical masks at all times. • Frequent hand sanitation by all personnel and patients. • Sanitation of equipment between patients. 1~2 meter(s) distance between personnel and patients, except when required for examination and treatment. • Only one visitor, unless an aide or assistant is required. • Alertness to patients who present with conjunctivitis or with flu-like symptoms.
Injection procedure	Routine measures to prevent post injection endophthalmitis: • Topical povidone-iodine. • Retraction of eyelids to avoid eyelashes. • Postpone injection in active blepharitis. • Avoid extensive eyelid manipulation. • Hand hygiene and gloves. • Surgical mask and refrainment from speaking. Measures to prevent COVID-19 transmission during the injection procedure: • Not suspected as COVID-19 case: - Prefer same-day bilateral injections where applicable. - Face mask and non-talking policy. - Cover the patient's nose and mouth with a drape. • Suspected/confirmed COVID-19 case: - Injection rescheduled, unless permanent vision loss is anticipated. - If injecting: use full personal protective equipment including gloves, N-95 respirator facemask, gown and eye-shield/goggles.

2. Mitigation Plans

Investigational Medical Product Management

To better cope with the sudden imposition of movement restriction and/or increase shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient IMP will be supplied to cover patient visit for longer period. Inter-country study drug transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, Sponsor will prepare site-to-site transfer of study drug from nearby clinical sites in

case agile resupply is required (e.g., patients are enrolled in a site more than anticipated but additional supplied IMP could not be sufficient).

Rescheduling of Visit and Study Drug Administration Schedule of Patients

The COVID-19 screening tests will be performed locally based on each site and/or local regulatory guidelines upon the investigator's discretion throughout the study period. If COVID-19 is confirmed positive during the Screening period, the patient should not be enrolled in this study until confirmation of complete recover from COVID-19 as per site and/or local regulatory guidelines. Although patients can be screened only once in normal circumstance as specified in Section 4.2.1, additional rescreening can be performed only in limited cases considering COVID-19. If COVID-19 is confirmed after randomization, the investigators will discuss a case-by-case about the position of patient with the Sponsor. In case of patient who has contact with COVID-19 patients within 14 days from any site visit, investigator will reconsider the enrollment or visit schedule following the site and/local regulatory guidelines

Investigators will promptly notify to the Sponsor if any unfavorable situation is occurred in relation to local COVID-19 status (e.g., site shut down, lock down of city, cohort isolation, etc.). For sites where the patients are unable to travel or use public transportation, the Sponsor will support the patients with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can be proceeded at the earliest.

In case patients cannot visit the study center on scheduled day, the treatment schedule will be adjusted following Section 5.3.1. However, if study drug administration cannot be done within an allowed visit window or missed dose is expected, whether to continue with the subsequent study treatment will be discussed with the Sponsor, ensuring the compliance with the trial protocol to such an extent that an ongoing benefit-risk assessment for the clinical trial and patients is still possible. Even if study visit cannot be made, possible data will be collected via phone call and during the next visit, if applicable. Investigator will keep following up with patients regarding any safety issues by phone call before the patients visit the site.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than normal circumstance, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed.

Site Monitoring and Audit

In case where a monitoring visit cannot be made because of the situation of COVID-19, centralized monitoring will be performed by the Sponsor and/or CRO as alternatives particularly considering the situation of the site, for the sites where the first patient is randomized but the first monitoring visit is not performed. Manual data review on eCRF will be performed and if any mistakes or deviations are observed, proper guidance will be provided to avoid them in the future on the site. Sponsor and/or CRO will review the data entered in

CRF continuously and ensure raising queries and support the sites as necessary. If necessary, Sponsor will create and review a report based on the eCRF data to check whether visits, assessments and administrations of study treatment are in progress according to protocol and the same will be shared with CRO for site management.

Audits are needed as part of implementing quality assurance throughout the study period in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. In case where an audit cannot be made due to COVID-19 pandemic situation, Sponsor will postpone audits or consider the remote audits after careful consideration of COVID-19 pandemic situation according to Guidance on the management of clinical trials during the COVID-19 (coronavirus) Pandemic (EMA 2020). Audits will be conducted only when permitted under national, local and/or organizational social distancing restrictions.

Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to Centralized monitoring plan and Risk based monitoring plan. After data collection, missing data on the primary analysis due to COVID-19 will be handled equally as specified in Section 7.4.1 as other missing cases. However, if a different approach is required for missing data due to COVID-19, it will be discussed at the masked data review meeting in a case-by-case manner and method of handling missing data will be specified in the SAP.