CELLTRION Inc.

CT-P42 3.1

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

20th July 2023
Statistical Analysis Plan

Version 2.0 (A)

Prepared by:

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Approved by: [redacted] Date: ____/____/____

Upon review of this document, including table, listing and figure shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
ANCOVA	Analysis of Covariance
ATE	Arterial thromboembolic events
BCVA	Best Corrected Visual Acuity
BLQ	below lower limit of quantification
CI	Confidence interval
eCRF	Electronic Case Report Form
CRO	contact research organization
CRP	C-reactive protein
CSR	Clinical Study Reports
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percent coefficient of variation
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DRM	Data Review Meeting
DRSS	Diabetic Retinopathy Severity Scale
ECG	electrocardiogram
EOS	End-of-Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
FAS	Full Analysis Set
FP	fundus photography
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
IOP	Intraocular pressure
ITT	Intent-to-Treat
IVT	intravitreal
IWRS	Interactive Web Response System
LLoQ	lower limit of quantification
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NYHA	New York Heart Association
OCT	Optical Coherence Tomography
PFS	pre-filled syringe
PK	Pharmacokinetic(s)
PP	Per-Protocol

PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SD	standard deviation
SD-OCT	spectral-domain OCT
SI unit	System International unit
SMQ	Standardised MedDRA Queries
SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	Table, Listing and Figure
USA	United States of America

1. Administrative Structure

This study is being conducted under the sponsorship of CELLTRION, Inc. (hereinafter referred to as "CELLTRION"). The pharmacokinetics parameter analysis is being performed under contract with [redacted], in collaboration with CELLTRION. The randomization is being performed under contract with [redacted]. The statistical analyses are being performed by CELLTRION.

2. Introduction

This statistical analysis plan (SAP) defines the statistical methods to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P42 3.1, entitled as "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".

There are two clinical study reports (CSRs) planned for the following time points.

- 1st CSR: Data for each patient up to Week 24
- Final CSR: 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 database lock and unmasking process.

This SAP is based on the following documents:

- Study Protocol version 4.0, including country specific A.0 – 15th April 2022
- Unique Case Report Form version 4.0 – 21st April 2022

Table, listing and figure (TLF) shells will be provided as an addendum to this document.

2.1. Data Cut-off for Analysis

The 1st CSR will include all analysis results, using data up to Week 24 of the Main Study Period of each patient.

For the data that are monitored continuously (e.g. data collected on 'Adverse Event', 'Serious Adverse Event', 'Prior & Concomitant Medication', 'Non-drug Therapy for DME', 'Unscheduled Visit Checklist' and 'General Comments' Electronic case report form [eCRF] pages), the data reported on or prior to the visit date of Week 24 will be included. For the data collected on 'Adverse Event', 'Serious Adverse Event', or 'Prior & Concomitant Medication' pages, the data will be included if the start date is on or prior to the visit date of Week 24. If the Week 24 date is missing, cut-off date will be used as planned Week 24 visit date which will be calculated as (Day 1 visit date + 7 * 24).

For patients who have terminated the study participation and have the discontinuation date on or prior to Week 24 visit date (actual or planned), all collected data for the patients will be

included. For patients who skipped visit of Week 24, the data on or prior to the last scheduled visit before Week 24 will be included.

The final CSR will include all analysis results collected up to the completion or termination of all patients from the study.

3. Study Objective

Primary and secondary objectives are described as below.

3.1. Primary Objective

- To demonstrate 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 the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

3.2. Secondary Objectives

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

4. Study Design and Procedures

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 compared with Eylea via intravitreal (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 pre-filled syringe (PFS) in patients with Diabetic Macular Edema (DME).

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.

Approximately 360 patients with DME, secondary to type 1 or 2 diabetes mellitus (DM) will be enrolled and randomly assigned at Week 0 to one of the 2 treatment groups in a 1:1 ratio (approximately 180 patients in the CT-P42 group and 180 patients in the Eylea group). During the Main Study Period, all randomized patients will receive the study drug via 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 overall schedule of study procedure and assessments is provided in Appendix 1.

5. General Statistical Considerations

Continuous data will be summarized using descriptive statistics: number of patients (n), mean, standard deviation (SD), minimum, median and maximum, unless otherwise specified. The descriptive statistics will be calculated using raw data before rounding although rounded values are listed. The following rules will be followed with regards to the number of decimal places:

- Minimum and maximum will be presented to the same number of decimal places as reported.
- Mean, median, geometric mean and SD will be rounded to one more decimal place than the maximum decimal place of values in the source listing.
- Percent coefficient of variation (CV%) will be rounded to one decimal place.
- Point estimate and confidence intervals (CI) obtained from statistical procedures will be displayed to two decimal places.

Geometric mean will not be reported if the dataset includes zero values and CV% will not be reported if the mean is zero.

Categorical data will be summarized using frequency tables showing numbers and percentages of patients. Percentages will be rounded to one decimal place and will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of patients within each treatment group for the analysis sets of interest, unless otherwise specified.

If there are repeated measurements at a time point, the initial scheduled measurement at that time point will be used in the summary tables.

All data will be listed for both Main Study Period and Extension Study Period, if applicable. However, summary tables and the corresponding figures will be generated only for the assessment results of Main Study Period, unless otherwise specified.

Unscheduled visits will not be summarized in visit-based tables, unless otherwise specified. The first End-of-Study (EOS) visit will not be included for visit-based tables in 1st CSR. However, all data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, patient number and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

This SAP could be updated after the masked data review meeting (DRM) but prior to database hard lock to document any deviations.

5.1. Software

[redacted]

[redacted]

5.2. Sample Size

A sample size of 316 patients (158 patients in the CT-P42 group and 158 patients in the Eylea group) is estimated to provide a 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 with equivalence margin of ±3 letters using a 90% CI approach corresponding to two one-sided test with significance level of 5%. In this sample size calculation, the SD of the mean change from baseline in BCVA at Week 8 is assumed to be 8.2 and the expected mean difference to be 0. Considering drop-out rate 12%, a total sample size of 360 patients (180 patients in each treatment group of CT-P42 and Eylea) is required to achieve 316 evaluable patients.

5.3. Randomization, Stratification, and Masking

An interactive web response system (IWRS) will be used for the randomization. Unmasked biostatistician will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

For the Main Study Period, patients will be randomly assigned to receive CT-P42 (2 mg/0.05 mL) or Eylea (2 mg/0.05 mL) on Day 1 (Week 0) prior to the study drug administration.

The randomization to treatment assignment will be stratified by the followings:

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

Approximately 30 patients, regardless of the treatment groups that they were randomized to, can participate in the open-label Extension Study and receive a single dose of CT-P42 PFS at Extension Week 0.

This study will be double-masked during the Main Study Period. Under normal circumstances, the masking should not be broken. The masking should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. Suspected unexpected serious adverse reactions (SUSAR), which are subject to expedited reporting, should be unmasked prior to submission to the regulatory authorities if required.

After database lock for data up to Week 24 treatment, the study will be unmasked to pre-defined unmasked personnel from the sponsor and contract research organization (CRO) for reporting purposes. The unmasked personnel will be pre-defined before breaking the study masking. The study will remain masked to the investigators, patients and pre-defined masked personnel from the sponsor and CRO until all patients complete the study and all final clinical data have been entered into the database and the database is locked and released for analysis. The unmasked team will be pre-defined and documented prior to performing the analyses.

5.4. Analysis sets

Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each TLF.

A summary of the analysis sets includes the number of patients in each analysis set for all randomly assigned patients. All data will be also listed for all randomly assigned patients.

Patients to be excluded from analysis set because of major protocol deviation are defined in Section 6. Each analysis set will be specified in related sections.

For each analysis set, patients will be classified according to the below table.

Analysis Set	**Treatment Group**
Analysis Sets for Main Study Period:	
Intent-to-Treat (ITT) Set Full Analysis Set (FAS) Per-Protocol (PP) Set	Randomized treatment group (CT-P42 or Eylea)
PK Set Safety Set for Main Study Period	Actual received treatment (CT-P42 or Eylea) during the Main Study Period[1]
Usability Set for Vial kit	Actual received treatment (CT-P42 or Eylea) at Week 0
Analysis Sets for Extension Study Period:	
Safety Set for Extension Study Period Usability Set for PFS	Actual received treatment (CT-P42) at Extension Week 0[2]

[1] If there is a discrepancy between the actual treatment and the randomized treatment, the patients receiving at least one dose of CT-P42 during Main Study Period will be grouped as "CT-P42" treatment group. All other patients will be grouped as "Eylea" treatment group.

[2] If there is a patient who received Eylea during Extension Study Period, the patient will be only presented in a listing but not included in tabulation.

5.4.1. Analysis Sets for Main Study Period

All data collected during the Main Study Period or before Extension Week 0 will be analyzed in the following analysis sets.

5.4.1.1. Intent-to-Treat Set

The ITT set is defined as all patients who are randomly assigned to receive either of the study drugs (CT-P42 or Eylea), regardless of whether or not any study drug was administered.

5.4.1.2. Full Analysis Set

The FAS is defined as all patients who are randomly assigned and receive at least 1 full dose of study drug during the Main Study Period. The FAS will be the primary analysis set for efficacy endpoint analyses.

5.4.1.3. Per-Protocol Set

The 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 DRM before unmasking. The PP set will be the supportive analysis set for efficacy endpoint analyses.

5.4.1.4. Pharmacokinetic Set

The PK set is defined as patients who receive at least 1 full dose of study drug and have at least 1 post-treatment PK concentration data in the Main Study Period. The PK set will be the primary analysis set for the summary of PK data. A major protocol deviation that may affect the interpretation of study results of PK endpoints will lead to exclusion from the PK set. Final determinations of the PK set will be made at the masked DRM before unmasking.

5.4.1.5. Safety Set for Main Study Period

The Safety set for Main Study Period is defined as all randomly assigned patients who receive at least 1 full or partial dose of study drug in the Main Study Period. The Safety set for Main Study Period will be the primary analysis set for the summary of safety data.

5.4.1.6. Usability Set for Vial kit

The Usability set for Vial kit is defined as all patients in the Safety set for Main Study Period who have evaluable usability measurements at Week 0. The Usability set for Vial kit will be used for the usability analysis of CT-P42 and Eylea vial kit.

5.4.2. Analysis Sets for Extension Study Period

All data collected on or after Extension Week 0 will be analyzed in the following analysis sets.

5.4.2.1. Safety Set for Extension Study Period

The Safety set for Extension Study Period is defined as all patients who receive a full or partial dose of study drug in the Extension Study Period. The Safety set for Extension Study Period will be used for the analyses of all safety and efficacy data collected on or after Extension Week 0.

5.4.2.2. Usability Set for PFS

The Usability set for PFS is defined as all patients in the Safety set for Extension Study Period who have evaluable usability measurements of PFS at Extension Week 0. The Usability set for PFS will be used for the usability analysis of CT-P42 PFS.

5.5. Definition of Baseline

The baseline value will be considered to be the last non-missing value before the first study drug administration of the Main Study Period. The same baseline value will be used for both

Main Study Period and Extension Study Period analyses. Post-baseline values will be considered to be all values collected after the first study drug administration.

5.6. Missing values and Outliers

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For DM and DME history date, imputation rules are described in Section 8.2. The handling of missing or incomplete dates for prior and concomitant treatments is described in Section 9.1, and for adverse events (AEs) in Section 13.1. Imputation rules adopted in the primary efficacy analyses are specified in Section 10.1.2.

Any outliers detected during the review of the data will be investigated and discussed during the masked DRM. In general, outliers will not be excluded from the analyses.

6. Protocol Deviation

Protocol deviation will be categorized as “major” or “minor”. A major protocol deviation is one that may affect significantly the interpretation of study results or the patient’s rights, safety or welfare. CELLTRION will identify major protocol deviation prior to database lock, and it will be discussed during the masked DRM. The potential major protocol deviations are defined as follows:

Potential Major Protocol Deviation	Excluded analysis set
Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any point during the study) up to Week 4	PP
Non-adherence to Inclusion or Exclusion criteria which affect primary efficacy result	PP
Significant Good Clinical Practice (GCP) non-compliance	All analysis sets
Receipt of prohibited therapy which affects primary efficacy results	PP

The major protocol deviations during the Main Study Period and other categories used for exclusion will be summarized by treatment group for all randomly assigned patients. The major protocol deviations in Extension Study Period and other categories will be summarized separately for all patients administered at Extension Week 0. A listing of major protocol deviations and other categories for exclusion in whole study period will also be provided with linked visit, Extension Study Period flag (If administered at Extension Week 0; Yes or No) and excluded analysis set by treatment group for all randomly assigned patients.

The number and percentage of patients with protocol deviations related to either COVID-19 or War in Ukraine during the Main Study Period will separately be summarized by treatment group and type of protocol deviation for all randomly assigned patients. The protocol deviations related to either COVID-19 or War in Ukraine during the Extension Study Period will be summarized by type of protocol deviation for Safety Set for Extension Study Period. A patient will be counted once for each type of deviation. Type of protocol deviation will be

grouped based on the protocol deviation log. A listing of protocol deviations related to either COVID-19 or War in Ukraine will also be separately provided with linked visit and Extension Study Period flag (Yes or No) by treatment group for all randomly assigned patients.

7. Patient Disposition

The number of patients who were screened and failed at screening will be displayed along with the primary reason for screening failure. The reasons for screening failure will be displayed using the following categories and ordering:

- Inclusion/Exclusion criteria not met
- Subject withdrew consent
- Lost to follow-up
- Other

A listing of patients reported as screening failures will be provided.

For analysis of 1st CSR, the number of patients who were randomized, initiated the study treatment for Main Study Period, continuing the study at Week 24 and discontinued early from the study on or before Week 24 will be summarized for ITT set along with percentage by treatment group. For analysis of final CSR, the number of patients who were randomized, initiated the study treatment for Main Study Period, completed the Main Study Period and discontinued early from the study during Main Study Period will be displayed for ITT set along with percentage by treatment group. The number and percentage of patients with each reason of early discontinuation will also be displayed for ITT set by reasons and treatment group, respectively.

Patient disposition of Main Study Period will be defined as follows:

- Randomized: A patient will be considered to be randomized if a randomization ID was allocated to the patient at Day 1 (Week 0) based on the ‘Randomization’ page of eCRF.

- Initiated the study treatment for Main Study Period: A patient will be considered to have initiated the study treatment for Main Study Period if it is recorded as ‘Yes’ to study drug administration on the ‘Study Drug Administration’ page of eCRF at least once in the Main Study Period.

- Continuing the study at Week 24: A patient will be considered to be continuing the study at Week 24 unless the answer was ‘No’ to complete treatment period and study discontinuation date was on or before Week 24 (recorded or planned) on ‘Study Discontinuation and Termination’ page of eCRF.

- Discontinued early from the study on or before Week 24: A patient will be considered to have discontinued the study by Week 24 with ‘No’ to complete treatment period on the ‘Study Discontinuation and Termination’ page of eCRF with study discontinuation date on or before Week 24 visit date (recorded or planned).

- Completed the Main Study Period: A patient will be considered to have completed the Main Study Period if it is recorded 'Yes' to complete treatment period on the 'Study Discontinuation and Termination' page of eCRF or recorded 'No' with study discontinuation date on or after the study drug administration date of Extension Week 0.

- Discontinued early from the study during Main Study Period: A patient will be considered to have discontinued the study during the Main Study Period if it is recorded 'No' to complete treatment period on the 'Study Discontinuation and Termination' page of eCRF with study discontinuation date before the study drug administration date of Extension Week 0, or no Extension Week 0 visit.

The number of patients who initiated the study treatment for Extension Study Period, and completed Extension Study Period will be displayed for Safety set for Extension Study Period along with percentage. The number and percentage of patients who discontinued early from the study during Extension Study Period will also be displayed for Safety set for Extension Study Period by reasons.

Patient disposition of Extension Study Period will be defined as follows:

- Initiated the study treatment for Extension Study Period: A patient will be considered to have initiated the study treatment for Extension Study Period if it is recorded as 'Yes' to study drug administration on the 'Study Drug Administration' page of eCRF on Extension Week 0 visit.

- Completed the Extension Study Period: A patient will be considered to have completed the Extension Study Period if it is recorded 'Yes' to study drug administration on the Extension Week 0 visit and also 'Yes' to complete treatment period on the 'Study Discontinuation and Termination' page of eCRF.

- Discontinued early from the study during Extension Study Period: A patient will be considered to have discontinued the study if it is recorded 'No' to complete treatment period on the 'Study Discontinuation and Termination' page of eCRF with study discontinuation date on or after the study drug administration date of Extension Week 0.

In addition, time on study prior to discontinuation will also be summarized for those patients who initiate the study treatment and prematurely discontinue the study by Week 24 or during the Main Study Period for ITT set by treatment group. The study duration in days will be calculated as (date of the last administration – date of the first administration + 1). The date of the first and the last administration of study drug will be taken as the earliest and the latest date recorded on the 'Study Drug Administration' page of eCRF during Main Study Period, respectively.

All patient disposition data will be listed for ITT set by treatment group.

8. Demographics, Baseline and Background Characteristics

Demographics, baseline and background characteristics recorded at screening will be summarized on ITT set, unless otherwise specified. Also all data will be listed for ITT set.

8.1. Demographics and Baseline characteristics

The demographic measures (including age, sex, ethnicity, race, smoking history and female patients' fertility status) and baseline characteristics (including height, body weight, hemoglobin A1c [HbA1c, ≤8% vs. >8%] and stratification details) will be summarized for the ITT set by treatment group and Safety set for Extension Study Period separately.

Stratification details include the following data; Country, BCVA score using the ETDRS chart on Day 1 (<55 letters vs. ≥55 letters) and PK subgroup (Yes vs. No).

The stratification factors will be summarized using the final data collected on the 'Randomization' page of eCRF.

Demographics and baseline characteristics will be presented in separate listings with Safety set for Extension Study Period flag for the ITT set by treatment group.

8.2. Medical History

Medical and ophthalmic history including history of DM and DME are captured at screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 25.1 or the higher version). The total number of medical/ophthalmic history except for DME and non-drug therapy for DME will be summarized. The number and percentage of patients with at least one medical/ophthalmic history except for DME and non-drug therapy for DME will also be tabulated by treatment group, category, system organ class (SOC) and preferred term (PT) for ITT set. Category will consist of "Non-Ocular events", "Ocular events in study eye" and "Ocular events in fellow eye". All data of medical history except for DME and non-drug therapy for DME will be listed by treatment group for ITT set.

8.3. DM and DME History

The total number of DM/DME history will separately be summarized for ITT set. The number and percentage of patients with at least one DM/DME history also will be tabulated by treatment group. DM history will be captured when High Level Term (HLT) is coded as 'Diabetes mellitus (incl subtypes)' in medical history. DME history will be separately collected in 'Diabetic Macular Edema History' page of eCRF.

DM and DME history will be summarized including following data (Table 1).

Table 1. Medical History of DM and DME

DM History	• Duration of DM (years) • Type of DM
DME History	• Location of DME before 1st study drug administration • Prior medication/non-drug therapy for DME[1] • Duration of DME (years) [1]

[1] 'Study eye' data is only considered in the analysis.

Prior medication for DME will be collected in 'Prior & Concomitant Medication' page of eCRF, the indication of which will be recorded as DME. Prior medication for DME will be classified as 'Intravitreal anti-VEGF', 'Intravitreal steroid', or 'Other medication'. Number and percentage of patients with at least one prior medication for DME will be summarized by category. Definitions are as following:

Common condition: Prior medication and 'DME' indication

- Intravitreal anti-VEGF
  ATC4 is 'ANTINEOVASCULARISATION AGENTS'
- Intravitreal steroid
  ATC4 is 'CORTICOSTEROIDS, PLAIN'
- Other medication
  Not 'Intravitreal anti-VEGF' and 'Intravitreal steroid'

Prior use of laser photocoagulation will be collected in 'Non-drug therapy for DME', the PT of which will be recorded as 'Retinal laser coagulation'. It will be summarized in 'Laser Photocoagulation' of non-drug therapy for DME. Number and percentage of patient with no prior medication and non-drug therapy for DME will be summarized.

Duration of DM and DME (years) will be calculated as ([the first administration date of study drug – start date of disease]/365.25). Duration of DME will be based on the initial diagnosis in study eye. If an incomplete start date of disease is recorded for a patient, the data will be imputed using the latest possible date as below.

- Missing day (e.g. XXFEB2020): Assume the last day of the month.
- Missing day and month (e.g. XXXXX2020): Assume December 31st.
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as Missing.

If the imputed date is later than the first administration date of study drug, it will be imputed using the first administration date of study drug. If the whole date is missing, duration of DME and DM (years) will not be calculated.

Summary of prior medication, prior non-drug therapy for DME, duration of DME will be presented only for study eye.

All the data related to DM and DME history will be listed for ITT set. Other medication for DME will be presented with PT.

8.4. Inclusion and Exclusion Criteria

Details of inclusion and exclusion criteria can be found in Sections 4.1.1 and 4.1.2 of the protocol. Non-adherence of inclusion/exclusion criteria will be presented in a listing for ITT set by treatment group.

9. Treatments and Medications

9.1. Prior and Concomitant Treatment

All prior and concomitant treatments including medications and non-drug therapies for DME (e.g., laser, surgery) during the study will be recorded. Use of any potential previous treatments for DME will be collected from the diagnosis of disease to the last EOS visit. All treatment used for other purposes, taken from 30 days prior to the first administration of study drug until the last EOS visit, will be recorded in the patients' eCRF. All medications will be coded according to the World Health Organization drug dictionary (September 2022 or the later version). All non-drug therapies for DME will be coded according to the MedDRA version 25.1 or the higher version.

For the purpose of inclusion in prior or concomitant treatment tables, incomplete start and stop dates of medications will be imputed as follows:

If the stop date is incomplete, the following rules will be applied:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as Missing.

In the case of the death of a patient, if the imputed stop date is after the date of death, the stop date will be imputed as the date of death.

If the start date is incomplete, the following rules will be applied. If the stop date is incomplete, imputed stop date will be used instead of reported stop date:

- Missing day: Assume the first day of the month.
    - If the month and the year of the partial start date are equal to the date of first study drug administration, and the date of first study drug administration is not after the recorded/imputed stop date of the treatment, set to the date of first study drug administration.
    - If the date of first study drug administration is after the recorded/imputed stop date of the treatment, set to the recorded/imputed stop date of the treatment.
- Missing day and month: Assume January 1st.
    - If the year of the partial start date is equal to the date of first study drug administration, and the date of first study drug administration is not after the recorded/imputed stop date of treatment, set to the date of first study drug administration.
    - If the date of first study drug administration is after the recorded/imputed stop date of the treatment, set to the recorded/imputed stop date of the treatment.

- Missing day, month and year: Assume date of first study drug administration, if not after the recorded/imputed stop date for the treatment. Otherwise, set to the recorded/imputed stop date for the treatment.

A prior medication is defined as any medication where both the start and stop dates (recorded or imputed) are before the date of the first study drug administration. According to the definition, a medication can be classified as a prior medication when:

- it has recorded or imputed stop date of medication before the first study drug administration or

- it is checked as yes to "If stop date is unknown, was this drug stopped before the study drug administration (Day 1)?" on the eCRF, if the stop date is still missing.

A concomitant medication is defined as any medication that has the stop date (recorded or imputed) on or after the date of the first study drug administration or missing. Any medication not classified as a prior medication will be classified as a concomitant medication.

For classifying non-drug therapy for DME as prior or concomitant, the incomplete date of therapy will be imputed as following rules:

- Missing day:
    - If the month and the year of the partial therapy date are equal to the date of the first study drug administration, set to the date of the first study drug administration.
    - If the month and the year of the partial therapy date are not equal to the first study drug administration, assume the first day of the month.
- Missing day and month:
    - If the year of the partial therapy date is equal to the date of first study drug administration, set to the date of first study drug administration.
    - If the year of the partial therapy date is not equal to the first study drug administration, assume the first day of the year.
- Missing day, month and year: Leave it as Missing.

A prior non-drug therapy for DME is defined as any therapy that has the therapy date (recorded or imputed) before the date of the first study drug administration.

A concomitant non-drug therapy for DME is defined as any therapy that has the therapy date (recorded or imputed) on or after the date of the first study drug administration or missing. Any treatment not classified as a prior non-drug therapy for DME will be classified as a concomitant non-drug therapy for DME.

All prior medications will be summarized by treatment group, drug class and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication in Safety set for Main Study Period. The separate table will be also

generated for the concomitant medications during the study period by treatment group, drug class, and PT in Safety set for Main Study Period and Safety set for Extension Study Period.

Concomitant medications will be classified for Main Study Period and Extension Study Period according to the table below:

	Main Study Period	**Extension Study Period**
Patients who enter the Extension Study Period	Start date of CM[1] < Date of Extension Week 0 visit	Start date of CM[1] >= Date of Extension Week 0 visit
Patients who do not enter the Extension Study Period	All CM	-

CM: Concomitant Medication
For the 1st CSR, CMs with a start date on or before the date of Week 24 visit (recorded or planned) will be included. If the patient discontinued the study on or prior to Week 24 visit, all CMs will be included.
[1] Based on the recorded/imputed date each event will be classified as either Main Study Period or Extension Study Period.

All prior non-drug therapies for DME will be summarized by treatment group, SOC and PT along with the total number of prior non-drug therapies for DME and the number and percentage of patients with at least one prior non-drug therapy for DME in Safety set for Main Study Period. The separate table will be also generated for the concomitant non-drug therapies for DME during the study period by treatment group, SOC and PT in Safety set for Main Study Period and Safety set for Extension Study Period.

All prior and concomitant treatments will be listed by treatment group for Safety set for Main Study Period. Concomitant treatments will be listed with information of study period (Main or Extension) and Safety set for Extension Study Period flag (Yes or No).

9.2. Exposure to Study Drug

Main Study Period

Summary of study drug administration during the Main Study Period will be presented in Safety Set for Main Study Period. Summarization will contain as below.

- Descriptive statistics for total number of dose received
- Number and percentage of patients with dose administered (‘Yes’ or ‘No’) by visit
  If ‘Yes’, delay of dose and reason for the delay will be summarized.
- Number and percentage of patients with successful injection by visit

Extension Study Period

The number and percentage of patients with dose administered and successful injection will be summarized by treatment group at Extension Week 0 in Safety Set for Extension Study Period.

A listing will also be provided by treatment group on Safety set for Main Study Period showing the details of study drug administration including information of Extension Week 0.

10. Efficacy Analyses

The mean change from baseline in BCVA using the ETDRS chart at Week 8 is the primary efficacy endpoint in this study. The primary efficacy analysis will be conducted using FAS and supportive analysis will be conducted on PP set. The following secondary efficacy endpoints will be assessed for both Main Study Period and Extension Study Period:

- 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

For these efficacy endpoints, the assessment results collected in Main Study Period will be summarized on FAS and PP set. The assessment results of Extension Study Period will be summarized separately on Safety set for Extension Study Period. All data will be listed on FAS with PP set flag and Safety Set for Extension Study Period flag (Yes or No).

The following secondary efficacy endpoints will be assessed only for Main Study Period:

- Mean change in central subfield thickness (CST) from baseline as determined by spectral-domain Optical Coherence Tomography (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 (FP)

The assessment results of these efficacy endpoints will be summarized on FAS and PP set. All data will be listed on FAS with PP set flag.

Statistical analysis for all efficacy endpoints including relevant tables and figures will be conducted only for study eye.

10.1. Best Corrected Visual Acuity

The BCVA will be assessed for both eyes using the ETDRS chart at each study visit as scheduled in the Appendix 1. The BCVA results assessed before pupil dilation will be only included for statistical analyses of the primary and secondary endpoints.

BCVA score will be summarized using descriptive statistics of actual value and change from baseline by treatment group at each scheduled visit and study period. For the data collected during Main Study Period, the mean (±SD) change from baseline in BCVA score versus scheduled visit profiles will be presented graphically.

Additionally, descriptive statistics for actual result and change from baseline of BCVA at Week 8 will be generated by treatment group and the following subgroups:

- Anti-drug antibody (ADA) positive subgroup or ADA negative subgroup

- Age (<65 or ≥65)
- Sex (male or female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Allowed by Investigator Country Regulations or Other)
- Baseline HbA1c (≤8% or >8%)
- Baseline BCVA (<40 letters, ≥40 to <55 letters, ≥55 to <65 letters, ≥65 letters)

Patients who show at least one "Positive" result in immunogenicity test obtained after study drug exposure up to Week 8 will be considered as "ADA positive subgroup" regardless of ADA status at pre-dose assessment. All patients who have only "Negative" results obtained after study drug exposure up to Week 8 will be considered as "ADA negative subgroup".

The proportion of patients who gained/lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA will be summarized using frequency tables by study period. Proportions of patients who gained/lost ≥5, ≥10, and ≥15 ETDRS letters from baseline in BCVA will also be presented using bar plot by treatment group and each scheduled visit of Main Study Period.

All data collected on 'Best Corrected Visual Acuity' page of eCRF and change from baseline in BCVA will be listed.

10.1.1. Primary analysis

Mean change from baseline in BCVA using the ETDRS chart at Week 8 is the primary efficacy endpoint in this study. The primary efficacy analysis will be performed using an Analysis of Covariance (ANCOVA) model with the baseline BCVA and country as covariates and treatment group as a factor only for study eye. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region (defined as either Europe or Non-Europe), for use in the statistical model. Therapeutic equivalence of CT-P42 with respect to Eylea will be concluded if the 2-sided 90% CI of difference of least square means (LS means) falls entirely within an equivalence margin [±3 letters]. The primary analysis set for the primary endpoint is the FAS. Primary endpoint will be also analyzed using the PP set as a supportive analysis set.

10.1.2. Sensitivity analysis for Primary Efficacy Endpoint

In order to evaluate the impact of missing data on the primary efficacy endpoint results, additional analyses with missing data imputation will be conducted for the primary efficacy endpoint of BCVA at Week 8 in FAS.

Multiple imputation (MI) with the Missing at Random (MAR) assumption will be applied [redacted]. All patients with non-missing baseline BCVA score in FAS will be included in the analysis. The multiple imputed datasets will be generated based on linear regression models on baseline BCVA score, country and treatment group as covariates. If any of covariates is missing, it will not be considered in MI. The 10 imputed datasets will be generated. These multiple imputed datasets are then analyzed by using the identical analysis

method specified in Section 10.1.1. The results from each set of imputed data sets will then be pooled [redacted].

In case the missing rate is higher than expected, the trimmed means approach (Permutt T and Li F, 2017) will be additionally considered to address the possible bias from the potentially high and/or imbalanced missing rates in the treatment groups. Trimmed means approach is a permutation method using trimmed datasets. Since high trimming rate lowers the power, the trimmed fraction will be chosen considering the higher value among the missing rates of each treatment group in an adaptive method. The nearest multiple of 10 greater than the higher value will be chosen as the trimming rate. For example, if missing rates of each treatment group are 8% and 17% respectively, the trimming rate should be 20%, the nearest multiple of 10 greater than 17%. Therapeutic equivalence of CT-P42 with respect to Eylea will be concluded if the following two requirements are satisfied: (i) When the lower fraction is trimmed, the lower limit of CI of the mean difference should be greater than the lower equivalence margin, which is -3. (ii) When the upper fraction is trimmed, the upper limit of CI should be smaller compared to the upper equivalence margin, which is 3. The CIs will be calculated as $(d+d_{\alpha/2}, d+d_{1-\alpha/2})$, where d is the estimate of the mean difference between the randomized treatment groups, and $d_{\alpha/2}$ and $d_{1-\alpha/2}$ are the $\alpha/2$ and $1-\alpha/2$ quantile of estimates of the mean difference between the treatment groups generated using the permutation, respectively. Each estimate will be based on the ANCOVA model with the baseline BCVA and country as covariates and treatment group as a factor.

10.2. Central Subfield Thickness by Optical Coherence Tomography

Retinal characteristics will be evaluated at each study visit using the OCT as scheduled in the Appendix 1 and results will be considered regardless of pupillary dilation. A spectral-domain OCT (SD-OCT) will be used in this study. The actual value and the change from baseline in CST as determined by SD-OCT will be summarized using descriptive statistics by each treatment group and scheduled visit. Change from baseline in CST by SD-OCT will also be presented graphically using mean (±SD) change from baseline versus scheduled visit profiles. All results evaluated by SD-OCT and change from baseline in CST will be listed. The unit of all continuous values will be presented as 'μm' except for total volume.

10.3. Fundus Photography and Fluorescein Angiography

The ETDRS DRSS score will be evaluated by FP as scheduled in the Appendix 1 and results will be considered regardless of pupillary dilation. The number and percentage of patients with each score will be summarized by treatment group and visit. The ETDRS DRSS score will be grouped into 13 Severity Scores based on the ETDRS Severity Level (Appendix 2). The Severity Score will be used to determine step change in the ETDRS DRSS score. The number and percentage of patients with a ≥2-step improvement from baseline in the ETDRS DRSS score will also be summarized using frequency tables by treatment group and visit, except for the case the baseline value is 90. Proportions of patients with a ≥2-step improvement from baseline will also be presented using bar plot by treatment group and each scheduled visit.

All results evaluated by fundus photography and ≥2-step improvement from baseline in the ETDRS DRSS score will be listed. All results of fluorescein angiography (FA) will also be listed, separately.

11. Pharmacokinetic Analyses

The PK analyses will be conducted for free (VEGF-unbound) study drug concentrations in plasma. PK data will be summarized on PK set. Also all plasma concentrations data and PK parameters will be listed for all patients in Safety set for Main Study Period who agreed to the collection of PK blood samples.

11.1. Pharmacokinetic Sampling Schedule

Pharmacokinetic blood samples for the determination of plasma concentration of aflibercept will be collected at the time points specified in the schedule of assessments (Appendix 1).

According to the last version of protocol, samples of 12 hours and 168 hours after study drug administration will not be considered for PK parameter calculation and concentration summary including figures. However, all collected results will be included in a listing.

11.2. Handling of the Difference between the Scheduled and the Actual Sampling Times

For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing, which will always be treated as zero (0), regardless of the time difference.

11.3. Plasma Concentrations

For plasma concentrations summary, the following rules will apply:

- Below lower limit of quantification (BLQ) will be treated as zero (0) for calculation of all descriptive statistics except for geometric means. For the calculation of geometric means, BLQ values will be set to 0.5 * lower limit of quantification (LLoQ).
- No further imputation will be applied to any missing values.

Descriptive statistics (n, mean, SD, geometric mean, CV%, minimum, median, and maximum) for plasma concentrations will be presented by treatment group at each scheduled visit and time point. Geometric mean will be only calculated if at least 2/3 of all plasma concentration values are valid and higher than LLoQ for respective time point. Also, the proportion of patients with plasma concentration higher than LLoQ will be summarized using frequency tables by each scheduled visit and time point period.

An overlay plot (Spaghetti plot) of patients within each treatment will be presented graphically on both linear and semi-logarithmic scales for each treatment using actual sampling times. The mean (±SD) plasma concentration versus time profiles for study drugs will be presented graphically on both linear and semi-logarithmic scales by treatment. For ease of presentation, scheduled sampling times will be used to present results for the mean figures.

Plasma concentrations will be presented in the listing with PK set flag by treatment group, visit and time point:

- All concentration values that are BLQ are reported as BLQ, using inequality sign. i.e. '<xxx' where xxx is LLoQ.
- The unit of concentrations are presented as 'mcg/L'.
- Listing of PK sampling times includes nominal and actual time elapsed from dose with the deviation from the nominal time and measured concentrations of the drug.

11.4. Pharmacokinetic Parameters

Free (VEGF-unbound) study drug concentrations in plasma data will be used to calculate the following parameters by standard non-compartmental methods:

- C_{max1}: Maximum plasma concentration after 1st study drug administration
- C_{max2}: Maximum plasma concentration after 5th study drug administration
- T_{max1}: Time of observed C_{max1}
- T_{max2}: Time of observed C_{max2}

For the derivation of PK parameter, the following rules will apply:

- All concentration BLQ values that occur will be treated as zero (0).
- All valid concentration will be used for PK parameters except 12 hour and 168 hour samples which were deleted from the last version of Protocol.
- The sampling time of pre-dose samples relative to dosing will also be treated as zero.
- Actual blood sampling times will be used to derive PK parameters. If the actual time of sampling is missing, then nominal PK sampling time point will be considered.
- In case that all concentration show BLQ value in all post-treatment sampling timepoints, first data point after dosing will be selected as C_{max} and T_{max}.

PK parameter will also be summarized using descriptive statistics (n, arithmetic mean, SD, CV%, minimum, median, maximum, and geometric mean). If C_{max1} or C_{max2} is zero (0), 0.5 * LLoQ will be used for the calculation of geometric means. All PK parameters will also be presented in the listing by treatment group.

12. Usability Analyses

The usability of CT-P42 or Eylea vial kit will be evaluated at Week 0 and the usability of CT-P42 PFS will be evaluated at Extension Week 0. Usability assessment results will be listed and tabulated on the Usability set for Vial kit and Usability set for PFS, respectively.

12.1. Assessment of the successful injection

The usability endpoint is to assess the number of injections with Vial kit and PFS successfully administered by healthcare professionals at Week 0 and Extension Week 0, respectively. The assessment will be evaluated by study center personnel.

The assessment checklists are followed below for Vial kit (Table 2).

Table 2. 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.

Completion of each individual task at Week 0 will be summarized based on the number and percentage of patients for Usability set for Vial kit.

The assessment checklists are followed below for PFS (Table 3).

Table 3. 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

Completion of each individual task at Extension Week 0 will be summarized based on the number and percentage of patients for Usability set for PFS.

The injection will be defined as "successfully completed injection" if all the product-use tasks in the Usability Assessment Checklist are checked as success. The proportion of successfully completed injection will be summarized along with the number and percentage of patients for Vial kit and PFS, respectively.

The usability assessment data will also be listed for vial kit and PFS separately, including whether the injection was successfully administered. If the procedures for use errors and close calls on all tasks occur, all events will be listed, specifically.

13. Safety Analyses

Safety assessments will include the evaluation of AEs (ocular and non-ocular) including serious adverse events (SAE), AE of special interest , intraocular pressure (IOP) test, slit lamp examination, indirect ophthalmoscopy, finger count/hand motion/light perception, immunogenicity assessment including ADA and neutralizing antibody (NAb), hypersensitivity monitoring, vital sign and weight measurement, electrocardiogram (ECG), NYHA Functional Classification assessment, physical examination findings, pregnancy testing, clinical laboratory analyses including HbA1c, and prior and concomitant treatments monitored throughout the study.

All safety data collected during the Main Study Period and/or before Extension Week 0 will be summarized on Safety set for Main Study Period. All data collected on 'Adverse Event' page and 'Serious Adverse Event' page of eCRF on or after Extension Week 0 will be summarized on Safety set for Extension Study Period. Other safety data collected during the Extension Study Period, except for AEs, will not be summarized. However, all safety data collected during the whole study period will be listed on Safety set for Main Study Period with Safety Set for Extension Study Period flag (Yes or No).

13.1. Adverse Events

An AE is any untoward medical occurrence in a patient enrolled (i.e., when the informed consent form is signed) into this study regardless of its causal relationship to study drug.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure to study drug or any event already present that worsens in severity after exposure to study drug.

The MedDRA version 25.1 or the higher version will be used to code all AEs. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If the stop date of an AE is partial or missing the following rules will be applied.

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as Missing.

In case a patient dies during the study, the stop date will be imputed as the date of death if the imputed stop date is after the date of death.

If the start date of an AE is partial or missing, the following rules will be applied. If the stop date of the AE is partial, imputed stop date will be used instead of reported stop date.

- If the day of an Adverse Event is missing, the month and year of the partial date will be compared to the date of the first exposure to study drug.
    - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.
    - If the month or year are not equal, the AE start date will be imputed as the first day of the month.
- If the day and month is missing, the year of the partial date will be compared to the date of the first exposure to study drug.
    - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.
    - If the year is not equal, start date will be imputed as the 1st of January of the partial date year.
- If the AE start date is missing, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE. If the AE stop date is missing, the AE start date will be imputed as the date of the first exposure to study drug.

The recorded/imputed dates of AEs will be used to decide the Study Period and whether the event is TEAE.

Adverse events will be classified for Main Study Period and Extension Study Period according to the table below:

	Main Study Period	**Extension Study Period**
Patients who enter the Extension Study Period	Start date of AE < Date of Extension Week 0 visit	Start date of AE >= Date of Extension Week 0 visit
Patients who did not enter the	All AE	-

Extension Study Period		

AE: Adverse Event
For the 1st CSR, AEs with a start date on or before the date of Week 24 visit (recorded or planned) will be included. If the patient discontinued the study on or prior to Week 24 visit, all AEs will be included.

All AEs will be categorized as "Overall", "Ocular events in study eye", "Ocular events in fellow eye" and "Non-Ocular events". Brief summary of AEs will be generated, which includes total number of AEs, SAEs, TEAEs and TESAEs along with the number of patients with at least one AE, SAE, TEAE, TESAE, TEAE/TESAE leading to study drug discontinuation, TEAE/TESAE of special interest, TEAE/TESAE related to study drug and TEAE leading to death. All TEAEs will also be summarized for each study period separately by category, treatment group, severity and relationship to study drug. The details of AEs will also be listed in Safety Set for Main Study Period with information of study period (Main or Extension) and Safety Set for Extension Study Period flag (Yes or No) by treatment group.

13.1.1. Treatment-Emergent Adverse Event

The TEAEs during the study will be summarized for each study period by category, by treatment group and by SOC, PT, relationship and intensity displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and the number and percentage of patients with at least one TEAE over all SOCs will also be displayed.

TEAEs will also be summarized for each study period by category, by treatment group and by SOC, PT and intensity, regardless of relationship to the study drug displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. TEAEs with PT reported for at least 1% of patients in either treatment group will be summarized separately for each period by category, by treatment group and by SOC, PT, relationship and intensity displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization.

13.1.2. Death

All patients who have a SAE with serious criteria of "Death" will be presented for each study period in a listing, which will include the detailed information of each event.

13.1.3. Serious Adverse Events

A SAE is defined as any event that 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 or results in death. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAE 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.

Treatment-Emergent Serious Adverse Events (TESAEs) will be summarized for each study period by category, treatment group, SOC, PT, relationship and intensity displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. Additional tabulation of TESAEs will be made for each study

period by category, treatment group, SOC, PT, relationship and serious criteria. The total number of events and the number and percentage of patients with at least one TESAE over all SOCs will also be displayed.

A listing will be provided by treatment group showing the details of SAEs. Also, a listing for additional information will be provided by treatment group showing the details of serious criteria and SAE description. Both listings will include information of study period (Main or Extension) and Safety Set Extension Study Period flag (Yes or No).

13.1.4. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All patients who have a TEAE leading to study drug discontinuation will be summarized for each study period by category, treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE leading to study drug discontinuation, using only the most severe TEAE recorded at each level of summarization. The total number of events and the number and percentage of patients with at least one TEAE which led to study drug discontinuation will also be displayed.

A listing will be provided by treatment group showing the details of TEAEs leading to study drug discontinuation with information of study period (Main or Extension) and Safety Set for Extension Study Period flag (Yes or No).

13.1.5. Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest are as following:

- Arterial thromboembolic events (ATEs)
  - ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause) except cases of transient ischemic attack (TIA) according to the Antiplatelet Trialists' Collaboration.

  - In line with the above definition, preferred terms to be included in the ATE analysis will be identified from the AE dataset excluding the case when PT is 'Transient ischaemic attack' by using the following MedDRA SMQs. A narrow PT search will be used for all SMQs.

Code	SMQ
20000063	Ischaemic central nervous system vascular conditions
20000064	Haemorrhagic central nervous system vascular conditions
20000166	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents
20000083	Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous
20000082	Embolic and thrombotic events, arterial
20000047	Myocardial infarction
20000168	Other ischaemic heart disease

  - Medical review will be performed to determine if additional cases identified by broad PT search using the above SMQs and all death cases should be included in the ATE analysis.
  - A list of TEAEs to be included in the ATE analysis will be reviewed during the masked DRM.

- TEAEs related to IVT injection procedure
  TEAEs recorded as 'Related' to 'Relationship of adverse events to injection procedure' on 'Adverse Event' page of eCRF

TEAEs of ATEs and TEAEs related to IVT injection procedure are separately summarized for each study period by category, treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the most severe TEAE recorded at each level of summarization. The total number of events and the number and percentage of patients with at least one TEAE of special interest will also be displayed.

Listings will be provided by treatment group showing the details of TEAEs of special interest with information of study period (Main or Extension) and Safety Set for Extension Study Period flag (Yes or No).

13.2. Clinical Laboratory Evaluations

Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples will be analyzed at the central laboratory at each scheduled visit. All summaries and listings will be based on the SI (System International) units, and only the parameters specified in the protocol will be analyzed and listed (Table 4).

Actual value and change from baseline of all numeric laboratory parameters will be summarized using descriptive statistics for Main Study Period by treatment group, test parameter and scheduled visit (clinical chemistry, hematology, and urinalysis, respectively). All numeric values recorded BLQ or above the upper limit of quantification are set to the respective limit for all summaries.

The laboratory test results are categorized as "Normal" or "Abnormal" and will be summarized in a shift table from baseline to each scheduled visit of Main Study Period by laboratory category excluding urinalysis and microscopic examination, respectively. The number and percentage of patients will be displayed for post-baseline visits by treatment group, test parameter and visit.

Some numeric parameters of clinical chemistry and hematology will be labeled with a CTCAE term and grading will be applied to post-baseline values for numeric parameters where possible according to CTCAE version 5.0 (Appendix 3). Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. If different grades share the same criteria due to exclusion of clinical input, lower grade will be used. The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as "No Grade". If either a baseline value or the baseline

condition (normal or abnormal) is considered for CTCAE grading and there is no baseline value, the post-baseline result could not be graded and left as 'missing' for CTCAE grades. The number and percentage of patients by laboratory category, treatment group and CTCAE term will be summarized using the most severe grade after the first study drug administration of Main Study Period. The most severe grade will be selected including all post-baseline scheduled and unscheduled visits in Main Study Period.

All clinical laboratory results of clinical chemistry, hematology and urinalysis including microscopic examination will be presented by treatment group and visit in separate listings along with Safety Set for Extension Study Period flag (Yes or No), high and low flags, if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters.

Table 4. Clinical Laboratory Test

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 • C-reactive protein (CRP)
Hematology	• Red blood cells count • Total and differential white blood cell count • Absolute lymphocytes count • Absolute neutrophil count • Platelet count • Hemoglobin	• Mean corpuscular volume • Mean corpuscular hemoglobin • Mean corpuscular hemoglobin concentration • Hematocrit • HbA1c
Urinalysis	• Bilirubin • Blood • Color • Glucose • Ketones • Leukocytes	• Nitrite • pH • Protein • Specific gravity • Urobilinogen • Microscopic examination

13.3. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and weight will be assessed at the time points specified in the schedule of

assessments (Appendix 1). For hypersensitivity monitoring, vital signs will also be assessed at the following one time point at each scheduled visit:

- Within 1 hour after study drug administration

All scheduled assessments of vital signs and weight will be summarized using descriptive statistics of actual value and change from baseline by treatment group and parameter at each scheduled visit of Main Study Period.

The number and percentage of patients who have clinically notable hypersensitivity results will be summarized in a table for Main Study Period by treatment group, visit and parameter. The criteria for clinically notable results are defined as follows:

Table 5. Hypersensitivity Classification for Vital Signs

Parameter	Low	High
Systolic blood pressure (mmHg)	≤ 90	≥ 160
Diastolic blood pressure (mmHg)	≤ 50	≥ 90
Heart rate (beats per minute)	≤ 50	≥ 100
Respiratory rate (breaths per minute)	≤ 12	≥ 20
Body temperature (°C)	≤ 35.0	≥ 38.0

All vital signs data including hypersensitivity monitoring results and weight will be listed by treatment group, visit and parameter in the whole study period. High and low flags will also be presented in the listing to show whether a value is outside of the normal range.

13.4. Electrocardiograms

12-lead ECGs will be performed locally at the time points specified in the schedule of events (Appendix 1). Findings of 12-lead ECG will be collected as "Normal", "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant".

The number and percentage of patients will be summarized for Main Study Period by treatment group and visit, in the form of a shift table to detect changes from baseline. All ECGs data will be listed for the whole study period by treatment group and visit.

13.5. New York Heart Association Functional Classification

The New York Heart Association (NYHA) functional classification assessment will be performed at the time points specified in the schedule of assessments (Appendix 1) using following criteria (Table 1):

Table 1. New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
1 (Mild)	No limitations of physical activity. Ordinary physical activity does not cause under fatigue, palpitation, dyspnea (shortness of breath)

2 (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath)
3 (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea
4 (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases

Heart failure and NYHA assessment results at each scheduled visit will be summarized by treatment group and all results will be listed by treatment group.

13.6. Physical Examination

Physical examinations will be performed at the time points specified in the schedule of events (Appendix 1). Abnormal findings of physical examination will be collected as "Abnormal, Not Clinically Significant", or "Abnormal, Clinically Significant".

All physical examination data will be only listed for the whole study period by treatment group, visit and body system.

13.7. Finger Count, Hand Motion and Light Perception

Finger count, hand motion, and light perception will be assessed within 15 minutes after the IVT injection at the time points specified in Appendix 1.

The number and percentage of patients regarding the result of assessment will be summarized for Main Study Period by treatment group and time point. Finger count, hand motion and light perception will also be listed for the whole study period by treatment group and visit.

13.8. Intraocular Pressure Test

IOP test will be measured pre-dose for both eyes and within 60 minutes for study eye after the study drug administration. IOP test results will be summarized for Main Study Period using descriptive statistics of actual value and change from baseline by treatment group, scheduled visit and time point.

A listing will be provided for the whole study period by treatment group and visit.

13.9. Slit Lamp Examination and Indirect Ophthalmoscopy

Slit Lamp Examination will be performed for both eyes before IVT injection at every scheduled visit. Indirect Ophthalmoscopy will be assessed before IVT injection for both eyes and within 60 minutes post IVT injection for study eye.

Interpretation of slit lamp examination and pre-dose assessments of indirect ophthalmoscopy will be summarized for study eye and fellow eye by treatment group, visit and location in a shift table comparing the results at each scheduled post-baseline visit on Main Study Period with the baseline value. All assessment results of one visit is "Normal", it will be classified in "Normal". If the assessment result of one visit is interpreted as "Abnormal" it will be specified as either "Abnormal, Clinically Significant" or "Abnormal, Not Clinically Significant"

according to the interpretation of each symptom in the same visit. If at least one symptom is interpreted as "Abnormal, Clinically Significant" the interpretation of the visit will be counted as "Abnormal, Clinically Significant". The other "Abnormal" cases will be counted as "Abnormal, Not Clinically Significant".

Post-dose assessments of indirect ophthalmoscopy will be summarized by treatment group and visit for Main Study Period using a frequency table.

Lens status (Phakic, Pseudophakic or Aphakic) by slit lamp examination will separately be summarized for study eye and fellow eye by treatment group and visit in a shift table comparing the status at each scheduled post-baseline visit on Main Study Period with the status at the baseline visit.

Information on abnormality findings of OD and OS will be listed as "Yes" or "No" for the whole study period by treatment group and visit. If "Yes", all abnormal finding results including the location, symptom and interpretation (Abnormal Clinically Significant or Abnormal, Not Clinically Significant) will be presented.

13.10. Pregnancy Test

Pregnancy tests will be conducted and summarized only for female patients of childbearing potential. Pregnancy tests consist of serum and urine pregnancy tests. Serum pregnancy tests will be performed by central laboratory at screening. Urine pregnancy tests will be performed locally prior to dosing at each scheduled visit or more frequently if required by country-specific legislation. If a urine pregnancy test result is positive or equivocal, a confirmatory serum pregnancy test will be performed at the local laboratory.

The number and percentage of the results of serum and urine pregnancy test will be summarized for Main Study Period by treatment group and visit. All pregnancy test results will be listed for the whole study period by treatment group and visit.

13.11. Immunogenicity

Serum sample for immunogenicity testing will be collected prior to dosing of study drug at the time points specified in the schedule of events (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. Sample analysis will be performed at the central laboratory. Immunogenicity assessments consist of both ADA and NAb assays.

The ADA assay will follow a three-tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. The test outcome for the screening assay will be: {"Potential Positive" or "Negative"}. Samples that are "Potential Positive" in the screening assay will undergo further testing in the confirmatory assay to determine if patients are a true positive. The test outcome for the confirmatory assay will be: {"Positive" or "Negative"}. "Positive" result of the confirmatory assay indicates a true positive test outcome and will be labeled as "Positive" in outputs. Patients with a "Negative" test outcome for either screening or confirmatory assays will be considered negative for the overall ADA assessment. For further characterization, the antibody level will be assessed by titration in confirmed positive samples.

Samples that are positive in the ADA confirmatory assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be: {"Positive" or "Negative"}.

The results of the immunogenicity assessments consisting of ADA and NAb assays will be summarized for the Safety set for Main Study Period. The number and percentage of patients will be presented by treatment group and test at each scheduled visit of Main Study Period. The proportion of patients who reported at least one ADA positive result and all ADA negative results (including all scheduled and unscheduled visits) during the Main Study Period after the first study drug administration, regardless of ADA status at pre-dose visit, will be also presented for the Safety set for Main Study Period.

In addition, the results of ADA titration will be summarized by treatment group and visit using descriptive statistics. The ADA titer values can be reported as minimum required dilution (MRD), 50, or higher. All values recorded below MRD will be set to a half of MRD, 25, for summaries.

All immunogenicity test results will be listed by treatment group and visit.

14. General Comment

All comments including COVID-19 collected on the 'General Comment' page of eCRF will be listed in the ITT set.

15. Interim Analysis

Although no formal interim analyses are planned, the Sponsor plans to prepare 2 CSRs.

A planned database unmasking will occur after database lock for data up to Week 24 for each patient in Main Study Period as described in Section 2.1 to evaluate the initial efficacy, PK, usability and safety including immunogenicity in the 1st CSR. Initial analysis will include all tables, listings, and figures as planned in this document.

All data at the end of study and statistical analyses will be included in Final CSR.

16. Changes in the Planned Analysis

16.1. Changes in the Protocol

Definition of Safety Set for Extension Study Period changes includes the following;

- Includes all study drugs administered in the Extension Study Period

17. Reference List

1. 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, Version 4.0 A.0, 15th APR 2022.
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5. Korobelnik JF, Do DV, Schmidt-Erfurth U, Boyer DS, Holz FG, Heier JS, et al. Intravitreal aflibercept for diabetic macular edema. Ophthalmology. 2014;121(11):2247 54.
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7. Eylea (aflibercept) [Prescribing information]. Regeneron NY USA, 2021. Available at: https://www.regeneron.com/sites/default/files/EYLEA_FPI.pdf
8. Eylea (aflibercept) [Summary of product characteristics]. Bayer AG, German; 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/eylea-epar-product-information_en.pdf

18. Appendices

Appendix 1: Schedule of Events

	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	

	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
Post-injection ophthalmologic assessments														
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: ETDRS Diabetic Retinopathy Severity Scale (for Individual Eyes)

Severity Score	ETDRS Diabetic Retinopathy Severity Level		Definition
1	**10**	DR absent	10 Microaneurysms and other characteristics absent
	12*	Non-DR abnormalities	12
2	14*	DR questionable	14A HE definite; microaneurysms absent
			14B SE definite; microaneurysms absent
			14C IRMA definite; microaneurysms absent
			14Z Venous loops > D/1; microaneurysms absent
	15*	DR questionable	15 Hemorrhage(s) definite; microaneurysms absent
	20	Microaneurysms only	20 Microaneurysms definite, other characteristics absent
3	35	Mild NPDR	35A Venous loops ≥ D/1
			35B SE, IRMA, or VB = Q
			35C Retinal hemorrhages present
			35D HE ≥ D/1 (< STD 3 in any field)
			35E HE ≥ M/1 (≥ STD 3 in any field)
			35F SE ≥ D/1 (any definite)
4	43	Moderate NPDR	43A H/Ma = M/4-5 (> STD 1(4+ fields) -OR- ≥ STD 2A (1 field))
			43B IRMA = D1-3 (any definite < STD 8A)
5	47	Moderately Severe NPDR	47A Both level 43 characteristics
			47B IRMA = D/4-5 (< STD 8A)
			47C H/Ma = S/2-3 (< STD 2B)
			47D VB = D/1
6	**53**	Severe NPDR	53A ≥ 2 of the level 47 characteristics
			53B H/Ma ≥ S/4-5 (≥ STD 2A in 4+ fields or ≥ 2B in any field)
			53C IRMA ≥ M/1 (≥ STD 8A)
			53D VB ≥ D/2-3 or S1 (≥ STD 6 in 2+ fields or ≥ 6B in any field)
	53E*	Very Severe NPDR	53E ≥ 2 of 53B, 53C, and 53D
7	61	Mild PDR	61A FPD and/or FPE only (regressed PDR)
			61B NVE < ½ DA in ≥ 1 field
8	65	Moderate PDR	65A NVE ≥ M/1 (≥ ½ DA in ≥ 1 field)
			65B NVD = D (< STD 10A); and VH and PRH = A or Q
			65C VH or PRH = D (< 1 DA) and NVE < M (< ½ DA) and NVD absent
9	71	High-risk PDR	71A VH or PRH ≥ M/1 (≥ 1 DA)

			71B NVE ≥ M/1 (≥ ½ DA 1 field) and VH or PRH ≥ D/1 (any)
			71C NVD = D (< STD 10A) and VH or PRH ≥ D/1 (any)
			71D NVD ≥ M (≥ STD 10A)
10	75		75 NVD ≥ M (≥ STD 10A) and VH or PRH ≥ D/1 (any)
11	81	Advanced PDR: fundus partially obscured, center of macula attached	81 NVD = cannot grade, or NVD < D and NVE = cannot grade in ≥ 1 field and absent in all others; and retinal detachment at center of macula < D
12	85	Advanced PDR: posterior fundus obscured, or center of macula detached	85A VH = VS (obscuring) in Field 1 or 2 85B Retinal detachment at center of macula = D (present)
90	90	Cannot grade, even for 81 or 85	90

Abbreviations: DR = diabetic retinopathy; NPDR = nonproliferative DR; PDR = proliferative DR; HE = hard exudates; SE = soft exudates; IRMA = intraretinal microvascular abnormalities; VB = venous beading; H/Ma = hemorrhages/microaneurysms; NVE = new vessels elsewhere; NVD = new vessels on or adjacent to optic disc; VH = vitreous hemorrhage; PRH = preretinal hemorrhage; FPD = fibrous proliferations disc; FPE = fibrous proliferations elsewhere; DA= disc area.
Note: Severity Score is used to determine step change in ETDRS DRSS score based on ETDRS severity level recode value.
Severity categories are of the form (maximum severity/extent), where maximum severity can be absent (A), questionable (Q), definitely present (D), moderate (M), severe (S), or very severe (VS), and extent is the number of photographic fields at that severity level. For example, M/2-3 means there are two or three fields from fields 3 to 7 with moderate severity, and none with higher severity.
* Levels 12, 14, 15 and 53E are not considered separate steps in the scale, but are pooled with level 10, 20, 20 and 53, respectively.

Appendix 3: CTCAE Terms and Grades for Clinical Laboratory Test Results

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
Alkaline phosphatase increased	Alkaline phosphatase (ALP)	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Leukocytosis	White Blood Cells	High	-	-	>100,000/mm^3	-
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm^3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L
Creatinine increased [1)]	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Eosinophilia	Eosinophils	High	>ULN and >baseline	-	-	-
Hypoglycemia	Glucose	Low	<LLN - 55mg/dL; <LLN - 3.0 mmol / L	< 55 - 40mg/dL; < 3.0 – 2.2 mmol / L	< 40 -30mg/dL; < 2.2 – 1.7 mmol / L	<30mg/dL; <1.7 mmol/L
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L; <LLN – 6.2 mmol/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 – 80 g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	-

Blood lactate dehydrogenase increased	Lactate Dehydrogenase (LDH)	High	>ULN	-	-	-
Lymphocyte count decreased	WBC Differential, Lymphocytes	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$ /L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	WBC Differential, Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3; <LLN - 75.0 x $10e^9$ /L	<75,000-50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000-25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm^3; <25.0 x $10e^9$ /L
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	-	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Neutrophil count decreased	WBC Differential, Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125 - 129 mmol/L	120 - 124 mmol/L regardless of symptoms	<120 mmol/L

Abbreviation: LLN = lower limit of normal, ULN = upper limit of normal.
Note: The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.
1) The most severe grade is counted if the CTCAE grade is discrepant by multiple definitions.

The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory at each relevant transfer. In case numeric value for grading is identical such as Hypokalemia, CTCAE grade which includes numeric value will only be applied, because abnormal laboratory value with clinical input was reported as an adverse event and graded accordingly.