Clinical trial results:
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

Summary

EudraCT number	2020-004278-23
Trial protocol	DE SK HU CZ PL LT LV
Global end of trial date	18 October 2023

Results information

Result version number	v1 (current)
This version publication date	08 November 2024
First version publication date	08 November 2024

Trial information

Trial identification

Sponsor protocol code	CT-P42_3.1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04739306
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celltrion, Inc.
Sponsor organisation address	23, Academy-ro, Yeonsu-gu, Incheon, Korea, Republic of, 22014
Public contact	Keum Young Ahn, CELLTRION Inc., 82 328504190, KeumYoung.Ahn@celltrion.com
Scientific contact	Keum Young Ahn, CELLTRION Inc., 82 328504190, KeumYoung.Ahn@celltrion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

The clinical study protocol, protocol amendments, informed consent forms (ICFs), and any other appropriate study-related documents were reviewed and approved by independent ethics committees (IECs) and institutional review boards (IRBs) before implementation.
This study was conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations, in compliance with International Council for Harmonisation (ICH) E6 (R2): good clinical practice (GCP) guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.
Before entering the study, the investigator (or designee) explained to each patient (or his/her legally acceptable guardian, if applicable) the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patients were given adequate time and opportunity to read and understand the information and ask any questions

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 37
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	India: 104
Country: Number of subjects enrolled	Latvia: 14
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Slovakia: 47
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Ukraine: 11

Worldwide total number of subjects	348
EEA total number of subjects	199

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	196
From 65 to 84 years	150
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

First patient assigned to treatment date was on 22 July 2021.
This study was conducted at 83 study centers in Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Russia, Slovakia, Spain, Ukraine, Republic of Korea, and India. In these study centers, 484 patients were screened and 348 patients were enrolled in this study.

Pre-assignment

Screening details:

Patients with a diagnosis of either type 1 or 2 diabetes mellitus (DM) with DME involving the center of the macula were enrolled in the study if they had met all of the inclusion criteria and none of the exclusion criteria.

Period 1

Period 1 title	Main Study Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CT-P42

Arm description:

Subjects were randomly assigned to CT-P42 group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses

Arm type	Experimental
Investigational medicinal product name	CT-P42
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

2mg/0.05 mL of CT-P42 administrated by intravitreal injection via a single-dose vial

Arm title	Eylea

Arm description:

Subjects were randomly assigned to Eylea group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses

Arm type	Active comparator
Investigational medicinal product name	Eylea
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravitreal use

Dosage and administration details:

2mg/0.05 mL of Eylea administrated by intravitreal injection via a single-dose vial

Number of subjects in period 1	CT-P42	Eylea
Started	173	175
Completed	153	153
Not completed	20	22
Adverse event, serious fatal	3	2
Physician decision	1	1
Consent withdrawn by subject	8	6
Adverse event, non-fatal	3	5
Lost to follow-up	4	6
War in Ukraine	1	1
Protocol deviation	-	1

Period 2

Period 2 title	Extension Study Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

After the Main Study period, a total of 31 subjects, regardless of the treatment group in Main Study Period, were enrolled in a 4-week open-label, single-arm Extension study.

Arms

Arm title	CT-P42 (Extension Study Period)

Arm description:

Subjects were enrolled in the extension study to administer 2 mg/0.05mL of CT-P42 by pre-filled syringe IVT injection at Extension Week 0 (1 dose).

Arm type	Experimental
Investigational medicinal product name	CT-P42 PFS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg/0.05mL of CT-P42 by intravitreal injection via a single-dose pre-filled syringe

Number of subjects in period 2[1]	CT-P42 (Extension Study Period)
Started	31
Completed	31

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: After the Main Study period, a total of 31 subjects, regardless of the treatment group in Main Study Period, were enrolled in a 4-week open-label, single-arm Extension study. It was planned to enroll 30 patients for extension study period.

Baseline characteristics

Reporting groups	
Reporting group title	CT-P42
Reporting group description:	
Subjects were randomly assigned to CT-P42 group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses	
Reporting group title	Eylea
Reporting group description:	
Subjects were randomly assigned to Eylea group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses	

Reporting group values	CT-P42	Eylea	Total
Number of subjects	173	175	348
Age categorical			
Units: Subjects			
Adults (18-64 years)	101	95	196
From 65-84 years	71	79	150
85 years and over	1	1	2
Age continuous			
Units: years			
arithmetic mean	62.5	62.9	
standard deviation	± 9.6	± 10.3	-
Gender categorical			
Units: Subjects			
Female	67	78	145
Male	106	97	203
BCVA at Baseline			
Baseline visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 73 to 34 (= Acuity of 20/40 to 20/200) in the study eye were included; a higher score represents better functioning.			
Units: Letters			
arithmetic mean	60.3	60.4	
standard deviation	± 9.7	± 10.1	-

End points

End points reporting groups

Reporting group title	CT-P42

Reporting group description:

Subjects were randomly assigned to CT-P42 group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses

Reporting group title	Eylea

Reporting group description:

Subjects were randomly assigned to Eylea group (2mg/0.05 mL) to administer by intravitreal injection via a single-dose vial every 4 weeks for 5 doses, then every 8 weeks for 4 doses

Reporting group title	CT-P42 (Extension Study Period)

Reporting group description:

Subjects were enrolled in the extension study to administer 2 mg/0.05mL of CT-P42 by pre-filled syringe IVT injection at Extension Week 0 (1 dose).

Primary: Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 8

End point title	Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 8

End point description:

Mean change from baseline in BCVA as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 8.
Subjects with a BCVA ETDRS letter score of 73 to 34 (= Acuity of 20/40 to 20/200) in the study eye at Screening and Day 1 were included. Visual acuity of the study eye was assessed using the ETDRS charts; a higher score represents better functioning.
An analysis of covariance (ANCOVA) was performed for study eye with change from baseline in BCVA at Week 8 as dependent variable, treatment as a factor, and baseline BCVA and country as covariates. Least squares means and standard errors were calculated from the ANCOVA model.

End point type	Primary

End point timeframe:

Baseline and Week 8

End point values	CT-P42	Eylea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169	172		
Units: Letters				
least squares mean (standard error)	9.43 (± 0.798)	8.85 (± 0.775)		

Statistical analyses

Statistical analysis title	Primary efficacy: Estimate of treatment difference

Statistical analysis description:

The FAS was defined as all patients who were randomly assigned and received at least 1 full dose of study drug during the Main Study Period. The FAS was the primary analysis set for efficacy endpoint analyses.

The analysis was conducted by analysis of covariance (ANCOVA) for study eye. The ANCOVA model included the change from baseline in BCVA as the dependent variable, treatment as a factor, baseline BCVA and country as covariates.

Comparison groups	CT-P42 v Eylea
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	equivalence
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.73
upper limit	1.88
Variability estimate	Standard error of the mean

Secondary: Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 52

End point title	Mean change from baseline in Best Corrected Visual Acuity (BCVA) at Week 52

End point description:

Mean change from baseline in BCVA as assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) letters at week 52.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	CT-P42	Eylea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	156		
Units: Letters				
arithmetic mean (standard deviation)	12.1 (± 8.9)	11.1 (± 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects who gained ≥15 letters from baseline in BCVA as Measured by ETDRS Letter Score Compared with baseline at Week 52

End point title	Proportion of subjects who gained ≥15 letters from baseline in BCVA as Measured by ETDRS Letter Score Compared with baseline at Week 52

End point description:

Proportion of subjects who gained ≥15 letters from baseline in BCVA, assessed in change from baseline in ETDRS letters over time

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	CT-P42	Eylea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	175		
Units: Participants	60	52		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with ≥2-step Improvement from baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Scale) score as Assessed by FP (Fundus Photography) at Week 52

End point title	Proportion of subjects with ≥2-step Improvement from baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Scale) score as Assessed by FP (Fundus Photography) at Week 52

End point description:

The ETDRS DRSS score was grouped into 13 severity scores based on the ETDRS Severity Level.

DR absent (level 10); Mild to moderate nonproliferative DR (levels 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71, 75, 81, and 85). 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.

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	CT-P42	Eylea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	175		
Units: Participants	41	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in Central Subfield Thickness (CST) at Week 52 as Assessed on Optical Coherence Tomography (OCT)

End point title	Mean change from baseline in Central Subfield Thickness (CST)

	at Week 52 as Assessed on Optical Coherence Tomography (OCT)

End point description:

The mean change from baseline in Central Subfieldl Thickness as determined by Spectral domain-Optical coherence tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Baseline and Week 52

End point values	CT-P42	Eylea		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151	154		
Units: micrometer				
arithmetic mean (standard deviation)	-220.7 (± 147.1)	-191.2 (± 137.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Main Study Period: From Week 0 to 52 Weeks, Extension Study Period: On or After Extension Week 0, assessed up to 4 weeks

Adverse event reporting additional description:

Safety analyses were performed in the Safety set and was pre-specified to only report the most severe event if one or more events were occurred to the same subject.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	CT-P42 (Main Study Period)

Reporting group description:

The safety set for Main Study Period was defined as all randomly assigned patients who received at least 1 full or partial dose of CT-P42 (2mg/0.05mL) regardless of the randomized treatment groups in the Main Study Period.
The safety set for Main Study Period was the primary analysis set for the summary of safety data.

Reporting group title	Eylea (Main Study Period)

Reporting group description:

The safety set for Main Study Period was defined as all randomly assigned patients who received at least 1 full or partial dose of Eylea (2mg/0.05mL) and did not receive CT-P42 during the Main Study Period.
The safety set for Main Study Period was the primary analysis set for the summary of safety data.

Reporting group title	CT-P42 (Extension Study Period)

Reporting group description:

The Safety set for Extension Study Period was 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 was used for the analyses of all safety and efficacy data collected on or after Extension Week 0.
Subjects were administrated 2 mg/0.05mL of CT-P42 by intravitreal injection via a single-dose at Extension Week 0 (1 dose).

Serious adverse events	CT-P42 (Main Study Period)	Eylea (Main Study Period)	CT-P42 (Extension Study Period)
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 174 (10.92%)	17 / 174 (9.77%)	0 / 31 (0.00%)
number of deaths (all causes)	3	2	0
number of deaths resulting from adverse events	3	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Clear cell renal cell carcinoma			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			

subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular occlusion			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 174 (0.00%)	2 / 174 (1.15%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree			
subjects affected / exposed	1 / 174 (0.57%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 174 (0.57%)	2 / 174 (1.15%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Coronary artery disease			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Deficiency anaemia			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			

subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	2 / 174 (1.15%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	2 / 174 (1.15%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ulcer			
subjects affected / exposed	0 / 174 (0.00%)	2 / 174 (1.15%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Vertebral end plate inflammation			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbuncle			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous pyelonephritis			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 174 (0.57%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			

Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 174 (0.00%)	1 / 174 (0.57%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 174 (0.57%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	CT-P42 (Main Study Period)	Eylea (Main Study Period)	CT-P42 (Extension Study Period)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	64 / 174 (36.78%)	71 / 174 (40.80%)	3 / 31 (9.68%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 174 (0.00%)	0 / 174 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Blood uric acid increased			
subjects affected / exposed	0 / 174 (0.00%)	0 / 174 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 174 (0.00%)	5 / 174 (2.87%)	1 / 31 (3.23%)
occurrences (all)	0	5	1
Intraocular pressure increased			
subjects affected / exposed	3 / 174 (1.72%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	5	9	0
Intraocular pressure increased-Study eye	Additional description: Study eye		
subjects affected / exposed	3 / 174 (1.72%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	5	8	0
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 174 (6.32%)	16 / 174 (9.20%)	0 / 31 (0.00%)
occurrences (all)	12	17	0
Eye disorders			

Cataract			
subjects affected / exposed	6 / 174 (3.45%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	6	4	0
Conjunctival haemorrhage			
subjects affected / exposed	2 / 174 (1.15%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	2	5	0
Conjunctival haemorrhage-Study eye	Additional description: Study eye		
subjects affected / exposed	2 / 174 (1.15%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	2	5	0
Diabetic retinal oedema			
subjects affected / exposed	17 / 174 (9.77%)	23 / 174 (13.22%)	1 / 31 (3.23%)
occurrences (all)	18	26	1
Posterior capsule opacification			
subjects affected / exposed	4 / 174 (2.30%)	3 / 174 (1.72%)	0 / 31 (0.00%)
occurrences (all)	5	3	0
Visual acuity reduced			
subjects affected / exposed	5 / 174 (2.87%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	5	4	0
Vitreous floaters			
subjects affected / exposed	3 / 174 (1.72%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	3	4	0
Vitreous haemorrhage			
subjects affected / exposed	4 / 174 (2.30%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	5 / 174 (2.87%)	0 / 174 (0.00%)	0 / 31 (0.00%)
occurrences (all)	5	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	8 / 174 (4.60%)	10 / 174 (5.75%)	0 / 31 (0.00%)
occurrences (all)	8	10	0
Influenza			
subjects affected / exposed	1 / 174 (0.57%)	6 / 174 (3.45%)	1 / 31 (3.23%)
occurrences (all)	1	7	1
Nasopharyngitis			

subjects affected / exposed	9 / 174 (5.17%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	11	5	0
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	7 / 174 (4.02%)	7 / 174 (4.02%)	0 / 31 (0.00%)
occurrences (all)	7	7	0
Dyslipidaemia			
subjects affected / exposed	1 / 174 (0.57%)	4 / 174 (2.30%)	0 / 31 (0.00%)
occurrences (all)	1	4	0
Hyperkalaemia			
subjects affected / exposed	4 / 174 (2.30%)	5 / 174 (2.87%)	0 / 31 (0.00%)
occurrences (all)	4	5	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2021	-Updated sponsor contact information. -Changed the reference drug from US licensed Eylea to EU approved Eylea. -Added test items for immunogenicity assessment. -Updated the number of study centers and countries. -Added detailed definition for a woman of childbearing potential -Added new conditions for temporary interruption of the study drug. -Added specific time point of SD-OCT assessment.
14 January 2022	-Updated the target number of patients to reflect changes in study plan. -Deleted condition of axial length considering current clinical practice. -Added description to reflect change in the EOS visit plan. -Blood sampling time points for Pharmacokinetic were reduced due to operational reason. -Updated the total number of patients and statistical assumptions for the sample size to reflect changes in study plan. -Updated the version of PASS software. -Revised to add more details about analysis plan. -Added phrase to reflect change in the EOS visit plan in order to reduce missing data for primary endpoint at Week8. -Added to describe EOS visit plan in details in order to reduce missing data for primary endpoint at Week8. -Updated as per pharmacy manual. -Updated plan for FA image acquisition at screening. -Added to provides detailed operation plan for DSMB. -Updated to allow longer window for Week 1 visit.
12 April 2022	-Treatment Period and EOS visit are retitled. -Extension Study Period and information of CT-P42 pre-filled syringe is newly added. -Study design for Extension Study Period is added in details. -Study design for Extension Study Period and 2nd EOS visit is added in details. -Assessment time points are added for the Extension Study Period. -CT-P42 PFS usability assessment is added. -Analysis sets are retitled and new analysis sets are added for Extension Study Period. -Added usability assessment checklist for PFS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the global impact of the COVID-19 pandemic, the Sponsor took proactive measures for the safety of participants. Due to the war in Ukraine during the study, increase in protocol deviations was unavoidable and some procedures were changed.

Notes: