



Clinical trial results:

A Longitudinal, Biomarker Study of Anti-VEGF, to Explore the Relationship Between Aqueous Humor Composition and Multimodal Retinal Imaging in Neovascular Age-related Macular Degeneration and Diabetic Macular Edema

Summary

EudraCT number	2020-003515-10
Trial protocol	CZ PL IT
Global end of trial date	19 December 2022

Results information

Result version number	v1 (current)
This version publication date	28 August 2025
First version publication date	28 August 2025

Trial information

Trial identification

Sponsor protocol code	BP41783
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4058
Public contact	F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche Ltd., F. Hoffmann-La Roche Ltd., +41 616878333, global.trial_information@roche.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	19 December 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	19 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to explore the aqueous humor (AH) biomarkers and multimodal retinal imaging features before and during a six-month treatment period with aflibercept in subjects with neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME).

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	Korea, Republic of: 62
Country: Number of subjects enrolled	Colombia: 10
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Czechia: 4
Worldwide total number of subjects	209
EEA total number of subjects	31

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)	60
From 65 to 84 years	133
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

A total of 116 subjects with nAMD and 93 subjects with DME took part in the study across 36 sites in the United States, the Republic of Korea, Colombia, Italy, Poland, and the Czech Republic from 12 April 2021 to 19 December 2022.

Pre-assignment

Screening details:

Subjects with nAMD and DME who were treatment-naïve in the study eye received aflibercept as an intravitreal (IVT) injection.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	nAMD-treatment Naive
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Arm description:

Subjects received aflibercept, 2 milligrams (mg), as an IVT injection, every 4 weeks (Q4W) for the first 3 doses, and thereafter once every 8 weeks (Q8W) up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea®
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Aflibercept, 2 mg, as an IVT injection, Q4W for the first 3 doses, and thereafter once Q8W up to Week 24.

Arm title	DME-treatment Naive
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Arm description:

Subjects received aflibercept, 2 mg, as an IVT injection, Q4W for the first 5 doses, and thereafter once Q8W up to Week 24.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea®
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Aflibercept, 2 mg, as an IVT injection, Q4W for the first 5 doses, and thereafter once Q8W up to Week 24.

Number of subjects in period 1	nAMD-treatment Naive	DME-treatment Naive
Started	116	93
Completed	112	82
Not completed	4	11
Adverse event, serious fatal	1	1
Consent withdrawn by subject	1	3
Adverse event, non-fatal	1	4
Lost to follow-up	1	3

Baseline characteristics

Reporting groups

Reporting group title	nAMD-treatment Naive
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Reporting group description:

Subjects received aflibercept, 2 milligrams (mg), as an IVT injection, every 4 weeks (Q4W) for the first 3 doses, and thereafter once every 8 weeks (Q8W) up to Week 24.

Reporting group title	DME-treatment Naive
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Reporting group description:

Subjects received aflibercept, 2 mg, as an IVT injection, Q4W for the first 5 doses, and thereafter once Q8W up to Week 24.

Reporting group values	nAMD-treatment Naive	DME-treatment Naive	Total
Number of subjects	116	93	209
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	75.2	63.7	
standard deviation	± 8.6	± 8.6	-
Gender Categorical			
Units: subjects			
Female	60	43	103
Male	56	50	106

End points

End points reporting groups

Reporting group title	nAMD-treatment Naive
Reporting group description: Subjects received aflibercept, 2 milligrams (mg), as an IVT injection, every 4 weeks (Q4W) for the first 3 doses, and thereafter once every 8 weeks (Q8W) up to Week 24.	
Reporting group title	DME-treatment Naive
Reporting group description: Subjects received aflibercept, 2 mg, as an IVT injection, Q4W for the first 5 doses, and thereafter once Q8W up to Week 24.	

Primary: Best Corrected Visual Acuity (BCVA) Scores at the Specified Timepoints

End point title	Best Corrected Visual Acuity (BCVA) Scores at the Specified Timepoints ^[1]
End point description: BCVA was measured using the set of three Precision Vision [^] TM or Lighthouse distance acuity charts (modified Early Treatment Diabetic Retinopathy Study [ETDRS] Charts 1, 2, and R) prior to dilating eyes by a trained and certified visual acuity (VA) examiner. The BCVA letter score ranges from 0 to 100. Higher scores and a gain in BCVA letter score from baseline indicated an improvement in VA. Intent-to-treat (ITT) population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.	
End point type	Primary
End point timeframe: nAMD: Baseline, Day 56 and Day 168; DME: Baseline, Day 112 and Day 168	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an exploratory study that was not designed for formal hypothesis testing. No comparisons were made between the nAMD and DME cohorts.

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	93		
Units: letters				
arithmetic mean (standard deviation)				
Baseline (n=114, 93)	57.78 (± 14.39)	61.76 (± 11.29)		
Day 56 (n=113,0)	62.93 (± 15.6)	9999 (± 9999)		
Day 112 (n=0, 84)	9999 (± 9999)	69 (± 11.03)		
Day 168 (n=112, 82)	64.12 (± 16.46)	68.67 (± 11.04)		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in BCVA Scores at the Specified Timepoints

End point title	Change From Baseline in BCVA Scores at the Specified Timepoints ^[2]
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End point description:

BCVA was measured using the set of three Precision Vision[^]TM or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R) prior to dilating eyes by a trained and certified VA examiner. The BCVA letter score ranges from 0 to 100. Higher scores and a gain in BCVA letter score from baseline indicated an improvement in VA. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Primary
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End point timeframe:

nAMD: Day 56 and Day 168;
DME: Day 112 and Day 168

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was an exploratory study that was not designed for formal hypothesis testing. No comparisons were made between the nAMD and DME cohorts.

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	84		
Units: letters				
arithmetic mean (standard deviation)				
Day 56 (n=112,0)	5.24 (± 7.52)	9999 (± 9999)		
Day 112 (n=0,84)	9999 (± 9999)	6.92 (± 6.68)		
Day 168 (n=111, 82)	6.19 (± 9.22)	6.61 (± 7.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in BCVA Scores Based on Mixed-effect Model of Repeated Measures (MMRM) Over Time

End point title	Change From Baseline in BCVA Scores Based on Mixed-effect Model of Repeated Measures (MMRM) Over Time
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End point description:

BCVA was measured using the set of three Precision Vision[^]TM or Lighthouse distance acuity charts (modified ETDRS Charts 1, 2, and R) prior to dilating eyes by a trained and certified VA examiner. The BCVA letter score ranges from 0 to 100. Higher scores and a gain in BCVA letter score from baseline indicated an improvement in VA. The analysis was performed using an MMRM. Adjusted mean is reported here. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Day 56, and Day 168;
DME: Day 112, Day 168, and Early Termination Visit

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	84		
Units: letters				
arithmetic mean (standard error)				
Day 56 (n = 112, 0)	5.0 (± 0.85)	9999 (± 9999)		
Day 112 (n = 0, 84)	9999 (± 9999)	6.4 (± 0.78)		
Day 168 (n = 111, 82)	5.9 (± 0.96)	6.2 (± 0.81)		
Early Termination (n = 0, 4)	9999 (± 9999)	13.6 (± 3.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Absence of Intraretinal Fluid (IRF) in the Central Subfield Over Time

End point title	Percentage of Subjects With Absence of Intraretinal Fluid (IRF) in the Central Subfield Over Time
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End point description:

The absence of IRF in the study eye (defined as IRF absent or definite outside center subfield only) was assessed by the central reading center using Spectral Domain-Optical Coherence Tomography (SD-OCT). The percentage of subjects with absence of IRF and a two-sided 95% Clopper-Pearson exact confidence interval (CI) was reported. ITT population included all subjects enrolled in the study. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Baseline, Day 56 and Day 168;
DME: Baseline, Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	93		
Units: percentage of subjects				
number (confidence interval 95%)				
Baseline	36.2 (27.5 to 45.6)	0.0 (0.0 to 3.9)		
Day 56	59.5 (50.0 to 68.5)	9999 (9999 to 9999)		
Day 112	9999 (9999 to 9999)	9.7 (4.5 to 17.6)		
Day 168	64.7 (55.2 to 73.3)	11.8 (6.1 to 20.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Absence of Subretinal Fluid (SRF) in the Central Subfield Over Time

End point title	Percentage of Subjects With Absence of Subretinal Fluid (SRF) in the Central Subfield Over Time
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End point description:

The absence of SRF in the study eye (defined as SRF absent or definite outside center subfield only) was assessed by the central reading center using SD-OCT. The percentage of subjects with absence of SRF and a two-sided 95% Clopper-Pearson exact CI was reported. ITT population included all subjects enrolled in the study. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Baseline, Day 56 and Day 168;

DME: Baseline, Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	93		
Units: percentage of subjects				
number (confidence interval 95%)				
Baseline	9.5 (4.8 to 16.3)	66.7 (56.1 to 76.1)		
Day 56	65.5 (56.1 to 74.1)	9999 (9999 to 9999)		
Day 112	9999 (9999 to 9999)	83.9 (74.8 to 90.7)		
Day 168	56.0 (46.5 to 65.2)	82.8 (73.6 to 89.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Central Subfield Thickness (CST) Assessed From Internal Limiting Membrane to Bruch's Membrane (ILM-BM) Over Time

End point title	Central Subfield Thickness (CST) Assessed From Internal Limiting Membrane to Bruch's Membrane (ILM-BM) Over Time
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End point description:

CST was defined as an objective measurement of retinal thickness in the central 1 millimeter (mm)

diameter of macula. It is the distance between the ILM (inner layer of retina) and the BM (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Baseline, Day 56 and Day 168;

DME: Baseline, Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	92		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n = 116, 92)	0.46 (± 0.2)	0.47 (± 0.11)		
Day 56 (n = 111, 0)	0.3 (± 0.11)	9999 (± 9999)		
Day 112 (n = 0, 82)	9999 (± 9999)	0.33 (± 0.07)		
Day 168 (n = 111, 81)	0.33 (± 0.12)	0.33 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CST Assessed From ILM-BM Over Time

End point title	Change From Baseline in CST Assessed From ILM-BM Over Time
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End point description:

CST was defined as an objective measurement of retinal thickness in the central 1 mm diameter of macula. It is the distance between the ILM (inner layer of retina) and the BM (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Day 56 and Day 168;

DME: Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	82		
Units: mm				
arithmetic mean (standard deviation)				

Day 56 (n = 111, 0)	-0.16 (± 0.15)	9999 (± 9999)		
Day 112 (n = 0, 82)	9999 (± 9999)	-0.13 (± 0.1)		
Day 168 (n = 111, 81)	-0.14 (± 0.17)	-0.13 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: CST Assessed From ILM to Retinal Pigment Epithelium (RPE) Over Time

End point title	CST Assessed From ILM to Retinal Pigment Epithelium (RPE) Over Time
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End point description:

CST was defined as an objective measurement of retinal thickness in the central 1 mm diameter of macula. It is the distance between the ILM (inner layer of retina) and the RPE (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Baseline, Day 56 and Day 168;

DME: Baseline, Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	93		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n = 115, 93)	0.34 (± 0.1)	0.44 (± 0.11)		
Day 56 (n = 110, 0)	0.23 (± 0.05)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	0.31 (± 0.07)		
Day 168 (n = 110, 81)	0.24 (± 0.07)	0.31 (± 0.09)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CST Assessed From ILM-RPE Over Time

End point title	Change From Baseline in CST Assessed From ILM-RPE Over Time
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End point description:

CST was defined as an objective measurement of retinal thickness in the central 1 mm diameter of macula. It is the distance between the ILM (inner layer of retina) and the RPE (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed

at the specified time point.

End point type	Secondary
End point timeframe:	
nAMD: Day 56 and Day 168;	
DME: Day 112 and Day 168	

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	83		
Units: mm				
arithmetic mean (standard deviation)				
Day 56 (n = 110, 0)	-0.12 (± 0.1)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	-0.13 (± 0.1)		
Day 168 (n = 110, 81)	-0.1 (± 0.11)	-0.13 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Center Point Thickness (CPT) Assessed From ILM-BM Over Time

End point title	Center Point Thickness (CPT) Assessed From ILM-BM Over Time
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End point description:

CPT was defined as the measurement of retinal thickness at the very center of the fovea. It is the distance between the ILM (inner layer of retina) and the BM (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
End point timeframe:	
nAMD: Baseline, Day 56 and Day 168;	
DME: Baseline, Day 112 and Day 168	

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	93		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n = 116, 93)	0.43 (± 0.21)	0.46 (± 0.13)		
Day 56 (n = 112, 0)	0.26 (± 0.11)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	0.3 (± 0.1)		
Day 168 (n = 112, 81)	0.28 (± 0.13)	0.3 (± 0.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CPT Assessed From ILM-BM Over Time

End point title	Change From Baseline in CPT Assessed From ILM-BM Over Time
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End point description:

CPT was defined as the measurement of retinal thickness at the very center of the fovea. It is the distance between the ILM (inner layer of retina) and the BM (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Day 56 and Day 168;

DME: Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	83		
Units: mm				
arithmetic mean (standard deviation)				
Day 56 (n = 112, 0)	-0.17 (± 0.17)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	-0.15 (± 0.12)		
Day 168 (n = 112, 81)	-0.15 (± 0.19)	-0.15 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: CPT Assessed From ILM-RPE Over Time

End point title	CPT Assessed From ILM-RPE Over Time
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End point description:

CPT was defined as the measurement of retinal thickness at the very center of the fovea. It is the distance between the ILM (inner layer of retina) and the RPE (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Baseline, Day 56 and Day 168;

DME: Baseline, Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	93		
Units: mm				
arithmetic mean (standard deviation)				
Baseline (n = 115, 93)	0.31 (± 0.13)	0.43 (± 0.13)		
Day 56 (n = 110, 0)	0.18 (± 0.06)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	0.28 (± 0.09)		
Day 168 (n = 110, 81)	0.19 (± 0.08)	0.28 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in CPT Assessed From ILM-RPE Over Time

End point title	Change From Baseline in CPT Assessed From ILM-RPE Over Time
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End point description:

CPT was defined as the measurement of retinal thickness at the very center of the fovea. It is the distance between the ILM (inner layer of retina) and the RPE (outer layer) and was assessed using SD-OCT by the central reading center. ITT population included all subjects enrolled in the study. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point. 9999 = No subjects were analyzed at the specified time point.

End point type	Secondary
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End point timeframe:

nAMD: Day 56 and Day 168;

DME: Day 112 and Day 168

End point values	nAMD-treatment Naive	DME-treatment Naive		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	83		
Units: mm				
arithmetic mean (standard deviation)				
Day 56 (n = 110, 0)	-0.13 (± 0.13)	9999 (± 9999)		
Day 112 (n = 0, 83)	9999 (± 9999)	-0.14 (± 0.12)		
Day 168 (n = 110, 81)	-0.12 (± 0.14)	-0.15 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of DME Subjects With ≥ 2 -Step Improvement From Baseline on the ETDRS-Diabetic Retinopathy Severity Scale (DRSS) Over Time

End point title	Percentage of DME Subjects With ≥ 2 -Step Improvement From Baseline on the ETDRS-Diabetic Retinopathy Severity Scale (DRSS) Over Time ^[3]
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End point description:

The ETDRS-DRSS classifies diabetic retinopathy into 12 severity steps ranging from absence of retinopathy to advanced proliferative diabetic retinopathy. The DRSS ranges from level 10 (no diabetic retinopathy) to level 85 (advanced diabetic retinopathy), where higher scores indicate a higher risk of vision loss. The ETDRS-DRSS score of each subject's study eye was assessed using fundus photography-7 modified fields (FP-7M) taken by trained personnel by the central reading center. The percentage of subjects with a ≥ 2 -step improvement from baseline was summarized along with a two-sided 95% Clopper-Pearson exact CI. ITT population included all subjects enrolled in the DME-treatment naïve arm.

End point type	Secondary
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End point timeframe:

At Day 168

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: percentage of subjects				
number (confidence interval 95%)	25.8 (17.3 to 35.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of DME Subjects With ≥ 3 -Step Improvement From Baseline on the ETDRS-DRSS Over Time

End point title	Percentage of DME Subjects With ≥ 3 -Step Improvement From Baseline on the ETDRS-DRSS Over Time ^[4]
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End point description:

The ETDRS-DRSS classifies diabetic retinopathy into 12 severity steps ranging from absence of retinopathy to advanced proliferative diabetic retinopathy. The DRSS ranges from level 10 (no diabetic retinopathy) to level 85 (advanced diabetic retinopathy), where higher scores indicate a higher risk of vision loss. The ETDRS-DRSS score of each subject's study eye was assessed using FP-7M taken by trained personnel by the central reading center. The percentage of subjects with a ≥ 3 -step improvement from baseline was summarized along with a two-sided 95% Clopper-Pearson exact CI. ITT population

included all subjects enrolled in the DME-treatment naïve arm.

End point type	Secondary
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End point timeframe:

At Day 168

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: percentage of subjects				
number (confidence interval 95%)	8.6 (3.8 to 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Volume Between ILM-BM Over Time in DME Subjects

End point title	Retinal Volume Between ILM-BM Over Time in DME Subjects ^[5]
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End point description:

The retinal volume between ILM and BM in the study eye was assessed using SD-OCT. Volume of retinal thickness within the central 3 mm radius is presented here. ITT population included all subjects enrolled in the DME-treatment naïve arm. n = number of subjects with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 112 and Day 168

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: mm ³				
arithmetic mean (standard deviation)				
Baseline (n=93)	8.38 (± 2.17)			
Day 112 (n=83)	6.86 (± 1.36)			
Day 168 (n=81)	6.91 (± 1.46)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Retinal Volume Between ILM-BM Over Time in DME Subjects

End point title	Change From Baseline in Retinal Volume Between ILM-BM Over Time in DME Subjects ^[6]
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End point description:

The retinal volume between ILM and BM, in the study eye, was assessed using SD-OCT. Change from baseline in volume of retinal thickness within the central 3 mm radius is presented here. ITT population included all subjects enrolled in the DME-treatment naïve arm. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Day 112 and Day 168

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naïve			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: mm ³				
arithmetic mean (standard deviation)				
Day 112 (n=83)	-1.51 (± 1.95)			
Day 168 (n=81)	-1.48 (± 2.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Volume Between ILM-RPE Over Time in DME Subjects

End point title	Retinal Volume Between ILM-RPE Over Time in DME Subjects ^[7]
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End point description:

The retinal volume between ILM and RPE in the study eye was assessed using SD-OCT. Volume of retinal thickness within the central 3 mm radius is presented here. ITT population included all subjects enrolled in the DME-treatment naïve arm. n = number of subjects with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Baseline, Day 112 and Day 168

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naive			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: cubic millimeters (mm ³)				
arithmetic mean (standard deviation)				
Baseline (n=93)	9.56 (± 1.71)			
Day 112 (n=83)	8.59 (± 1.2)			
Day 168 (n=81)	8.3 (± 1.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Retinal Volume Between ILM-RPE Over Time in DME Subjects

End point title	Change From Baseline in Retinal Volume Between ILM-RPE Over Time in DME Subjects ^[8]
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End point description:

The retinal volume between ILM and RPE, in the study eye, was assessed using SD-OCT. Change from baseline in volume of retinal thickness within the central 3 mm radius is presented here. ITT population included all subjects enrolled in the DME-treatment naïve arm. Number analyzed is the number of subjects with data available for analysis. n = number of subjects with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Day 112 and Day 168

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point was only applicable to the cohort of patients with DME.

End point values	DME-treatment Naive			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: mm ³				
arithmetic mean (standard deviation)				
Day 112 (n=83)	-0.99 (± 1.3)			
Day 168 (n=81)	-1.22 (± 1.32)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to approximately 8.5 months

Adverse event reporting additional description:

Safety population included all subjects enrolled in the study who performed at least one study assessment or had one sample taken on Day 1.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.1
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Reporting groups

Reporting group title	DME-treatment Naive
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Reporting group description:

Subjects received aflibercept, 2 mg, as an IVT injection, Q4W for the first 5 doses, and thereafter once Q8W up to Week 24.

Reporting group title	nAMD-treatment Naive
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Reporting group description:

Subjects received aflibercept, 2 mg, as an IVT injection, Q4W for the first 3 doses, and thereafter once Q8W up to Week 24.

Serious adverse events	DME-treatment Naive	nAMD-treatment Naive	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 93 (11.83%)	11 / 116 (9.48%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Leg amputation			

subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bradycardia			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash erythematous			

subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 93 (1.08%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	2 / 93 (2.15%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 93 (1.08%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	DME-treatment Naive	nAMD-treatment Naive	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 93 (19.35%)	14 / 116 (12.07%)	
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	2 / 93 (2.15%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 93 (0.00%)	3 / 116 (2.59%)	
occurrences (all)	0	3	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 93 (2.15%)	0 / 116 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
Dry Eye			
subjects affected / exposed	0 / 93 (0.00%)	3 / 116 (2.59%)	
occurrences (all)	0	6	
Cataract			
subjects affected / exposed	3 / 93 (3.23%)	2 / 116 (1.72%)	
occurrences (all)	4	2	
Vitreous floaters			
subjects affected / exposed	0 / 93 (0.00%)	3 / 116 (2.59%)	
occurrences (all)	0	3	
Vitreous detachment			
subjects affected / exposed	1 / 93 (1.08%)	3 / 116 (2.59%)	
occurrences (all)	1	4	
Eye pain			

subjects affected / exposed occurrences (all)	0 / 93 (0.00%) 0	3 / 116 (2.59%) 3	
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	0 / 116 (0.00%) 0	
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	2 / 116 (1.72%) 2	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	2 / 93 (2.15%) 2	0 / 116 (0.00%) 0	
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	4 / 93 (4.30%) 4	2 / 116 (1.72%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2021	The following updates were made as per the amendment, version 2: The Schedule of Activities for nAMD and DME was updated, anthropometric measures and a clarification on when to perform the pregnancy test were added; An inclusion criterion for all subjects was added to align female participation with the recommendation of the local prescribing information; Exclusion criteria for all subjects were updated to align with the recommendation of the local prescribing information with additional examples of excluded diseases and information about exclusion of COVID-19 positive subjects, and to exclude subjects with aphakia or implantation of intraocular lens outside of the capsular bag in the study eye; An exclusion criterion for nAMD population was updated with additional examples of excluded ocular diseases other than nAMD; Exclusion criteria for DME population were updated with a clarification that one rescreening is permitted and with additional examples of ocular diseases other than DME; Reporting of post-study AEs and serious adverse events (SAEs) were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported