Clinical trial results:
An Exploratory, Prospective, Multi-Center, Open-Label, Single-Arm, Interventional, Phase IIB Study to Investigate Aqueous Humor and Multimodal Imaging Biomarkers in Treatment-Naïve Patients With Diabetic Macular Edema Treated With Faricimab (RO6867461) - ALTIMETER STUDY

Summary

EudraCT number	2020-001174-30
Trial protocol	DE PL IT HR
Global end of trial date	22 December 2022

Results information

Result version number	v1 (current)
This version publication date	02 December 2023
First version publication date	02 December 2023

Trial information

Trial identification

Sponsor protocol code	MR41926

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04597918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
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	22 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2022
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the associations over time between clinical assessments, multimodal imaging assessments, aqueous humor (AH) biomarker patterns, and genetic polymorphisms

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. All participants were required to read and sign an informed consent form prior to participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2020
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	Argentina: 24
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 52
Worldwide total number of subjects	99
EEA total number of subjects	9

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)	73
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 99 patients were enrolled in the study at 23 sites in 7 countries.

Period 1

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

Arms

Arm title	Faricimab

Arm description:

Participants received 6 doses of faricimab (one 6-mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Participants returned for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment.

Arm type	Experimental
Investigational medicinal product name	Faricimab
Investigational medicinal product code	RO6867461
Other name	Vabysmo
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Patients were to receive 6 doses (one 6-mg faricimab intravitreal [IVT] injection once every 4 weeks [Q4W]) starting at Day 1 and ending on the Day 140 visit.

Number of subjects in period 1	Faricimab
Started	99
Completed	89
Not completed	10
Adverse event, serious fatal	1
Consent withdrawn by subject	6
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Faricimab
Reporting group description:	
Participants received 6 doses of faricimab (one 6-mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Participants returned for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment.	

Reporting group values	Faricimab	Total	
Number of subjects	99	99	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	73	73	
From 65-84 years	26	26	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	59.5		
standard deviation	± 9.8	-	
Sex: Female, Male Units: Participants			
Female	38	38	
Male	61	61	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	25	25	
Not Hispanic or Latino	73	73	
Unknown or Not Reported	1	1	
Race/Ethnicity, Customized Units: Subjects			
Black or African American	7	7	
White	86	86	
Asian	5	5	
Unknown	1	1	
Region of Enrollment Units: Subjects			
US and Canada	62	62	
Rest of the World	37	37	
Central Subfield Thickness (CST) in the Study Eye at Baseline			
Central subfield thickness (CST) was defined as the distance between the internal limiting membrane			

(ILM) and the retinal pigment epithelium (RPE) using Spectral Domain-Optical Coherence Tomography (SD-OCT).			
Units: microns arithmetic mean standard deviation	 464.0 ± 149.5	 -	
Best-Corrected Visual Acuity (BCVA) in the Study Eye at Baseline			
Best Corrected Visual Acuity (BCVA) was measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters. The BCVA letter score ranges from 0 to 100 (best score).			
Units: ETDRS Letters arithmetic mean standard deviation	 62.5 ± 11.8	 -	

End points

End points reporting groups

Reporting group title	Faricimab

Reporting group description:

Participants received 6 doses of faricimab (one 6-mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Participants returned for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment.

Primary: Percentage of Participants with a ≥2-Step Improvement from Baseline on the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) in the Study Eye at Week 24

End point title	Percentage of Participants with a ≥2-Step Improvement from Baseline on the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) in the Study Eye at Week 24[1]

End point description:

The ETDRS DRSS score of each participant's study eye was assessed using ultra-wide field color fundus photography (UWF-CFP) taken by trained personnel at the study sites. Analysis of the fundus photographs was performed by the central reading center, and the percentage of participants with a ≥2-step improvement from baseline was summarized along with a two-sided 95% Clopper-Pearson exact confidence interval. Baseline was defined as the participant's last observation prior to initiation of study drug. Participants in the modified intent-to-treat (mITT) Population with missing baseline assessments were excluded from the analysis. The number analyzed indicates participants with assessments at both Baseline and Week 24.

End point type	Primary

End point timeframe:

Baseline and Week 24

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, open-label, single-arm study. The results were summarized using descriptive statistics.

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: Percentage of participants				
number (confidence interval 95%)	50.0 (37.2 to 62.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Absence of Intraretinal Fluid in the Study Eye at Week 24

End point title	Percentage of Participants with Absence of Intraretinal Fluid in the Study Eye at Week 24

End point description:

The absence of intraretinal fluid (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 participants with absence of IRF and a two-sided 95% Clopper-Pearson exact confidence interval are reported. Participants in the modified intent-to-treat (mITT) Population with non-missing Week 24 assessments were included in the analysis.

End point type	Secondary

End point timeframe:

Week 24

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Percentage of participants				
number (confidence interval 95%)	26.1 (17.3 to 36.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to First Absence of DME in the Study Eye During the Study

End point title	Median Time to First Absence of DME in the Study Eye During the Study

End point description:

An event was defined as the first absence of diabetic macular edema (DME) in the study eye, defined as first time reaching central subfield thickness (CST; ILM-RPE) <305 microns, after baseline. Baseline was defined as the participant's last observation prior to initiation of study drug. The time to first absence of DME was a Kaplan-Meier estimate. The 95% confidence interval (CI) for the median was computed using the method of Brookmeyer and Crowley. Participants without an event and discontinued from treatment were censored at the last CST assessment. Participants with absence of DME at Baseline were excluded from the analysis.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: Weeks				
median (confidence interval 95%)	8.0 (8.0 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change from Baseline in Best-Corrected Visual Acuity (BCVA) in the Study Eye at Week 24

End point title	Adjusted Mean Change from Baseline in Best-Corrected Visual Acuity (BCVA) in the Study Eye at Week 24

End point description:

Best Corrected Visual Acuity (BCVA) was measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters. The BCVA letter score ranges from 0 to 100 (best score), and a gain in BCVA letter score from baseline indicates an improvement in visual acuity. For the Mixed Model for Repeated Measures (MMRM) analysis, the model adjusted for visit, age (continuous), baseline BCVA (continuous), and region (US and Canada and the rest of the world). An unstructured covariance structure was used. In case of convergence issues with the model, an AR (1) covariance structure was used. Treatment policy strategy (i.e., all observed values used) and hypothetical strategy (i.e., all values censored after the occurrence of the intercurrent event) were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: ETDRS Letters				
arithmetic mean (confidence interval 95%)	9.2 (7.5 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted Mean Change from Baseline in Central Subfield Thickness in the Study Eye at Week 24

End point title	Adjusted Mean Change from Baseline in Central Subfield Thickness in the Study Eye at Week 24

End point description:

Central subfield thickness (CST) was defined as the distance between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE) using Spectral Domain-Optical Coherence Tomography (SD-OCT), as assessed by the central reading center. For the Mixed Model of Repeated Measures (MMRM) analysis, the model was adjusted for visit, age (continuous), baseline CST (continuous), and region (US and Canada and the rest of the world). An unstructured covariance structure was used. In case of convergence issues with the model, an AR (1) covariance structure was used. Treatment policy strategy (i.e., all observed values used) and hypothetical strategy (i.e., all values censored after the occurrence of the intercurrent event) were applied to non-COVID-19 related and COVID-19 related intercurrent events, respectively. Missing data were implicitly imputed by MMRM.

End point type	Secondary

End point timeframe:

From Baseline to Week 24

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: microns				
arithmetic mean (confidence interval 95%)	-200.2 (-214.1 to -186.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Absence of Subretinal Fluid in the Study Eye at Week 24

End point title	Percentage of Participants with Absence of Subretinal Fluid in the Study Eye at Week 24

End point description:

The absence of subretinal fluid (SRF) in the study eye (defined as SRF 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 participants with absence of SRF and a two-sided 95% Clopper-Pearson exact confidence interval are reported. Participants in the modified intent-to-treat (mITT) Population with non-missing Week 24 assessments were included in the analysis.

End point type	Secondary

End point timeframe:

Week 24

End point values	Faricimab			
Subject group type	Reporting group			
Number of subjects analysed	88			
Units: Percentage of participants				
number (confidence interval 95%)	98.9 (93.8 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until ≥28 days to <35 days after the last dose of study drug (up to 24 weeks)

Adverse event reporting additional description:

Adverse events (AEs) are reported for the safety population, which includes all participants who received at least one injection of faricimab in the study eye. For ocular AEs, the number of participants and events reported per term are combined totals of AEs that occurred in the study eye or the fellow eye.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Faricimab

Reporting group description:

Participants received 6 doses of faricimab (one 6-mg faricimab intravitreal [IVT] injection every 28 days [Q4W]) starting at Day 1 and ending on the Day 140 visit. Participants returned for a safety follow-up visit (SFV) after ≥28 days and within <35 days following their last study treatment.

Serious adverse events	Faricimab		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 99 (8.08%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Spinal operation			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Toe amputation			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Sepsis			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Faricimab		
Total subjects affected by non-serious adverse events subjects affected / exposed	21 / 99 (21.21%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	5 / 99 (5.05%) 5		
Eye disorders Diabetic retinal oedema subjects affected / exposed occurrences (all) Retinal exudates subjects affected / exposed occurrences (all)	6 / 99 (6.06%) 6 5 / 99 (5.05%) 10		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	7 / 99 (7.07%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2021	Protocol version 2: •The AC paracentesis-associated risk of cataract induction was added as requested in the list of grounds for non-acceptance in the EU; •The bulbar tension was to be assessed manually after the AH tap. If the bulbar tension was deemed too low to be able to perform a safe IVT injection, as per the treatment administrator's discretion, a re-toning with saline solution was to be performed through a paracentesis; •Correction that ultra-wide field fundus fluorescein angiography was to also be collected for the non-study eye at the Day 140 visit; •Clarification that ocular assessments at the screening visit were to be performed for both eyes at the time of screening, as it was not confirmed yet which eye would be the study eye; •Inclusion of the option of continued access to faricimab based on primary endpoint results of the faricimab DME Phase III study data; •Clarification that patients with ocular disease other than DME, which could preclude in the opinion of the investigator acquisition
05 May 2021	Protocol version 3: •Inclusion criterion 8 (ETDRS DRSS) was removed; •Exclusion criterion 22 (ETDRS DRSS) was modified; •Clarification that patients screen failed solely due to the DRSS criteria in protocol versions 1 and 2 that met all of the inclusion criteria in protocol version 3 could be re-screened
18 February 2022	Protocol version 4: •Benefit-risk assessment was updated to align with the faricimab Investigator's Brochure; •Clarification was added to the sample size of study population to compensate for those patients that do not have a complete set of analyzable AH samples; •The responsibilities of the investigator and the role of the medical monitor in determining patient eligibility was clarified; •Total length of the study was extended; •Language was added to indicate that systemic corticosteroids also included inhaled corticosteroids from inhalers used regularly (eg, pulmonary disease, asthma, or seasonal allergy); •Additional guidance regarding patients using inhaled corticosteroids occasionally (PRN) was added; •Exclusion criterion #29 was clarified to also exclude some laser procedures that could interfere with AH production; •Additional guidance regarding the fellow (non-study) eye treatment with anti-vascular endothelial growth factor therapy was added; •Clarification that continuous usage of topical ophthalmic corticosteroids for 100 days or more was considered prohibited therapy, and added the medications claiming to have an effect on macular pathology to the list of prohibited therapies; •Clarification added that the same device must be used to assess the patient's pre-treatment IOP and their post-treatment IOP; •Language was added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest were to be reported within 24 hours

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported