Clinical trial results:
A randomized, double-masked, 48-week, parallel group, placebo-controlled, proof of concept study to investigate the efficacy and safety of RG7774 in patients with diabetes mellitus Type 1 or Type 2 with treatment naive diabetic retinopathy

Summary

EudraCT number	2019-002067-10
Trial protocol	GB SK PL
Global end of trial date	19 July 2023

Results information

Result version number	v1 (current)
This version publication date	01 August 2024
First version publication date	01 August 2024

Trial information

Trial identification

Sponsor protocol code	BP41321

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04265261
WHO universal trial number (UTN)	-
Other trial identifiers	CANBERRA: BP41321

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +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	28 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, tolerability, and effect of oral administration of RG7774 on the severity of diabetic retinopathy (DR) in participants with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and good vision

Protection of trial subjects:

All participants were required to sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 June 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	Australia: 2
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	United States: 107
Worldwide total number of subjects	139
EEA total number of subjects	20

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)	109
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with diabetes mellitus Type 1 or 2 with treatment-naive diabetic retinopathy

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received an oral dose of placebo matched to RG7774 once daily (QD)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received oral placebo once daily

Arm title	Vicasinabin 30 mg QD

Arm description:

Participants received 30 mg of oral RG7774 QD

Arm type	Experimental
Investigational medicinal product name	Vicasinabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 30 mg of oral vicasinabin once daily

Arm title	Vicasinabin 200 mg QD

Arm description:

Participants received 200 mg of oral RG7774 QD

Arm type	Experimental
Investigational medicinal product name	Vicasinabin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 200 mg of oral vicasinabin once daily

Number of subjects in period 1	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD
Started	47	48	44
Completed	37	43	36
Not completed	10	5	8
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	1	4
Physician decision	-	-	1
Non-Compliance with Study Drug	1	1	-
Adverse event, non-fatal	2	-	-
Protocol Deviation	-	2	-
Lost to follow-up	4	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received an oral dose of placebo matched to RG7774 once daily (QD)	
Reporting group title	Vicasinabin 30 mg QD
Reporting group description:	
Participants received 30 mg of oral RG7774 QD	
Reporting group title	Vicasinabin 200 mg QD
Reporting group description:	
Participants received 200 mg of oral RG7774 QD	

Reporting group values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD
Number of subjects	47	48	44
Age categorical Units: Subjects			
Adults (18-64 years)	35	39	35
From 65-84 years	12	9	9
Age Continuous Units: Years			
arithmetic mean	58.9	57.3	56.5
standard deviation	± 9.3	± 10.0	± 10.5
Sex: Female, Male Units: Participants			
Female	17	18	16
Male	30	30	28
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	14	18	15
Not Hispanic or Latino	32	30	29
Unknown or Not Reported	1	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	2	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	5	0	4
White	40	46	35
More than one race	0	0	0
Unknown or Not Reported	0	0	2

Reporting group values	Total		
Number of subjects	139		
Age categorical Units: Subjects			
Adults (18-64 years)	109		
From 65-84 years	30		

Age Continuous Units: Years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: Participants			
Female	51		
Male	88		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	47		
Not Hispanic or Latino	91		
Unknown or Not Reported	1		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	7		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	121		
More than one race	0		
Unknown or Not Reported	2		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received an oral dose of placebo matched to RG7774 once daily (QD)	
Reporting group title	Vicasinabin 30 mg QD
Reporting group description:	
Participants received 30 mg of oral RG7774 QD	
Reporting group title	Vicasinabin 200 mg QD
Reporting group description:	
Participants received 200 mg of oral RG7774 QD	

Primary: Proportion of Participants with >/= 2-Step Improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS) from Baseline at Week 36 Measured in the Study Eye

End point title	Proportion of Participants with >/= 2-Step Improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS) from Baseline at Week 36 Measured in the Study Eye
End point description:	
The ETDRS DRSS is a standardized grading test to measure diabetic retinopathy progression, where higher scores indicate a higher risk of vision loss. The DRSS ranges from level 10 (no diabetic retinopathy) to level 85 (advanced diabetic retinopathy)	
End point type	Primary
End point timeframe:	
Week 36	

End point values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	42	35	
Units: Percentage				
number (confidence interval 95%)	7.89 (2.72 to 20.8)	9.52 (3.77 to 22.07)	5.71 (1.58 to 18.61)	

Statistical analyses

Statistical analysis title	Placebo vs Vicasinabin 30 mg
Comparison groups	Placebo v Vicasinabin 30 mg QD

Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8586
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.86
upper limit	14.23

Statistical analysis title	Placebo vs Vicasinabin 200 mg
Comparison groups	Placebo v Vicasinabin 200 mg QD
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6388
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	-2.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.18
upper limit	9.31

Primary: Percentage of Participants with Adverse Events (AEs)

End point title	Percentage of Participants with Adverse Events (AEs)[1]

End point description:

End point type	Primary

End point timeframe:

Up to 1 year (baseline through follow-up period)

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: There was no formal statistical analyses deemed necessary for this endpoint.

End point values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	48	43	
Units: Percentage of participants				
number (not applicable)	72.3	64.6	81.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Time-to-Event for Vision-Threatening DR in the Study Eye

End point title	Time-to-Event for Vision-Threatening DR in the Study Eye

End point description:

Vision-threatening DR was defined as anterior segment neovascularization (ASNV), new proliferative diabetic retinopathy (PDR), new diabetic macular edema (DME), and pre-existing DME requiring treatment. Time-to-event was defined as the time where 50% of the population develops a DR vision-threatening event.

9999 indicates that either the Kaplan-Meier percentile time has not been achieved or that the percentile is at a boundary of the observed range and no upper or lower 95% CI can be found.

End point type	Secondary

End point timeframe:

Up to Day 277

End point values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	48	43	
Units: Days				
number (confidence interval 95%)	9999 (257.0 to 9999)	267.0 (254.0 to 9999)	9999 (260.0 to 9999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of new Anterior Segment Neovascularization (ASNV), new Proliferative Diabetic Retinopathy (PDR), new Diabetic Macular Edema (DME), and Pre-Existing DME Requiring Intervention in the Study Eye

End point title	Incidence of new Anterior Segment Neovascularization (ASNV), new Proliferative Diabetic Retinopathy (PDR), new Diabetic Macular Edema (DME), and Pre-Existing DME Requiring Intervention in the Study Eye

End point description:

This is a descriptive summary of the incidence of new ASNV, new PDR, and both new and pre-existing DME, all of which indicate disease progression.

End point type	Secondary

End point timeframe:

Week 36

End point values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	48	43	
Units: Percentage of participants				
number (confidence interval 95%)				
New ASNV	0 (0.0 to 9.4)	0 (0.0 to 9.2)	0 (0.0 to 10.2)	
New PDR	0 (0.0 to 9.4)	6.3 (1.6 to 18.2)	0 (0.0 to 10.2)	
New DME	0 (0.0 to 9.4)	4.2 (0.7 to 15.4)	0 (0.0 to 10.2)	
Pre-existing DME requiring treatment	4.3 (0.7 to 15.7)	10.4 (3.9 to 23.4)	6.8 (1.8 to 20.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 36

End point title	Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 36

End point description:

BCVA was measured by a qualified VA examiner prior to pupil dilation using modified ETDRS Charts 1, 2, and R. The adjusted mean is reported for each group.

End point type	Secondary

End point timeframe:

Baseline; Week 36

End point values	Placebo	Vicasinabin 30 mg QD	Vicasinabin 200 mg QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	48	43	
Units: Number of letters				
arithmetic mean (standard error)	0.12 (± 0.747)	-0.45 (± 0.697)	-0.22 (± 0.744)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 3 years

Adverse event reporting additional description:

All-cause mortality includes the entire study population.
SAE and NSAE reporting includes the safety population, which included all participants who gave informed consent and received at least one dose of study medication. Participants in the safety population were grouped according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received an oral dose of placebo matched to RG7774 once daily (QD)

Reporting group title	Vicasinabin 200 mg QD

Reporting group description:

Participants received 200 mg of oral RG7774 QD

Reporting group title	Vicasinabin 30 mg QD

Reporting group description:

Participants received 30 mg of oral RG7774 QD

Serious adverse events	Placebo	Vicasinabin 200 mg QD	Vicasinabin 30 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 47 (17.02%)	5 / 43 (11.63%)	3 / 48 (6.25%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Intermittent claudication			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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
Eye disorders			
Retinal tear			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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 retinopathy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Pancreatitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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			
Biliary colic			

subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	0 / 43 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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
Sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
Localised infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
Extradural abscess			
subjects affected / exposed	0 / 47 (0.00%)	1 / 43 (2.33%)	0 / 48 (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	1 / 47 (2.13%)	0 / 43 (0.00%)	0 / 48 (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
COVID-19			
subjects affected / exposed	1 / 47 (2.13%)	1 / 43 (2.33%)	0 / 48 (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

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

Non-serious adverse events	Placebo	Vicasinabin 200 mg QD	Vicasinabin 30 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 47 (27.66%)	15 / 43 (34.88%)	21 / 48 (43.75%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 47 (4.26%)	1 / 43 (2.33%)	3 / 48 (6.25%)
occurrences (all)	2	1	3
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 47 (6.38%)	2 / 43 (4.65%)	2 / 48 (4.17%)
occurrences (all)	5	2	2
Eye disorders			
Diabetic retinal oedema			
subjects affected / exposed	3 / 47 (6.38%)	6 / 43 (13.95%)	8 / 48 (16.67%)
occurrences (all)	3	7	13
Diabetic retinopathy			
subjects affected / exposed	3 / 47 (6.38%)	1 / 43 (2.33%)	5 / 48 (10.42%)
occurrences (all)	3	2	5
Vitreous haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	2 / 43 (4.65%)	3 / 48 (6.25%)
occurrences (all)	2	3	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 47 (6.38%)	0 / 43 (0.00%)	0 / 48 (0.00%)
occurrences (all)	4	0	0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 47 (2.13%)	5 / 43 (11.63%)	3 / 48 (6.25%)
occurrences (all)	1	5	3
Nasopharyngitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 43 (0.00%)	3 / 48 (6.25%)
occurrences (all)	4	0	3
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			

subjects affected / exposed occurrences (all)	1 / 47 (2.13%) 1	1 / 43 (2.33%) 1	4 / 48 (8.33%) 4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	- The exploratory assessments of contrast sensitivity and visual field were clarified to only be required from sites with appropriate capabilities. - An additional exploratory objective was added to explore the use of an advanced, artificial intelligence-based analytics tool to assess clinically relevant features. - An inclusion criterion was removed for consistency with the exclusion criteria. - It was clarified that the determination of natural progression of disease versus an adverse event (AE) was to be based upon Investigator opinion.
13 November 2020	- Operational procedures on Day 1 assessment were clarified. - An additional exploratory objective was added to explore potential effects of vicasinabin on glycemic status. - Operational updates related to COVID-19 were implemented, including a new assessment. - Clarifications and additional examples were added to both the inclusion and exclusion criteria. - The screen failure process was clarified. - Brolucizumab use was made to be an exception from permitted therapies and excluded as rescue treatment. - Disease-related AEs were further defined; clarifications were made to the number of assessments needed in case of rescue treatments for disease-related events; and follow up for disease-related AEs was specifically delineated. - Disease-related AEs (e.g., amputations, ulcers, diabetes-related surgery) and sight-threatening events (e.g., decrease of > 30 letters in visual acuity [VA] score, severe intraocular inflammation) were added as Adverse Events of Special Interest (AESIs); sight-threatening events were added under the definition of serious adverse events (SAEs). - Sample size and the efficacy analysis method were clarified, and a sensitivity analysis was added in case the amount of missing data exceeded 10% of all expected data.
03 February 2021	- An exclusion criterion regarding the location of an implantation of intraocular lens for the study eye was modified. - COVID-19 positive participants were added to the exclusion criteria. - The timing of additional visits for warfarin-taking participants was clarified.
15 June 2021	- The number of assessments and duration of patient visits were reduced. - Entry Criteria were modified to increase enrollment: an additional Diabetic Retinopathy Severity Scale (DRSS) rescreening was added, the glycosylated hemoglobin (HbA1c) threshold was increased to 12%, prior periocular pharmacological intervention was excluded, and participants without active hepatitis B virus or hepatitis C virus (HBC) and participants enrolled in other retinal/ovular clinical trials may be permitted in select circumstances. - The screen failure process was modified to allow participants who had previously failed according to outdated inclusion/exclusion criteria. - The process for evaluating ECG results was standardized. - Missing data treatment and the assessment of related efficacy estimates was clarified to be detailed in an external technical document.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported