Clinical trial results:
A Phase 2 randomized, placebo-controlled, double-masked proof-of-concept study to investigate the efficacy and safety off runcaciguat (BAY 1101042) in patients with moderately severe to severe non-proliferative diabetic retinopathy

Summary

EudraCT number	2020-002333-15
Trial protocol	DE PL CZ PT NL DK HU IT SK BG LV
Global end of trial date	22 April 2024

Results information

Result version number	v1 (current)
This version publication date	23 April 2025
First version publication date	23 April 2025

Trial information

Trial identification

Sponsor protocol code	20739

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04722991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	24 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the proof of concept for the efficacy of the soluble guanylyl cyclase (sGC) activator runcaciguat in the treatment of non-proliferative diabetic retinopathy (NPDR)

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects (or their legally authorized representative according to local legislation). Participating subjects (or their legally authorized representative according to local legislation) signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 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	Bulgaria: 7
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Denmark: 7
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 45
Worldwide total number of subjects	109
EEA total number of subjects	52

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)	77
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 39 study centers in Europe and US that randomized 109 participants from 17 MAR 2021 (first patient first visit) to 22 APR 2024 (last patient last visit).

Pre-assignment

Screening details:

Out of the 224 screened participants, 109 participants were randomized and started treatment. 115 participants did not pass screening. The primary reason for screen failure was that one or more inclusion or exclusion criteria were not met by the participant.

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, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Runcacigat (BAY1101042)

Arm description:

Participants received runcaciguat gastrointestinal therapeutic system (GITS) tablets and were treated following an intra-individual dose-titration design with three titration steps.

Arm type	Experimental
Investigational medicinal product name	Runcacigat
Investigational medicinal product code	BAY1101042
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received runcaciguat gastrointestinal therapeutic system (GITS) tablets and were treated following an intra-individual dose-titration design with three titration steps.

Arm title	Placebo

Arm description:

Participants received matching placebo GITS tablets.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received matching placebo GITS tablets.

Number of subjects in period 1	Runcacigat (BAY1101042)	Placebo
Started	56	53
Completed	38	44
Not completed	18	9
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	12	4
Non-compliance	-	1
Lost to follow-up	1	1
Withdrawal cirterion met	2	2
not specified	1	-

Baseline characteristics

Reporting groups

Reporting group title	Runcacigat (BAY1101042)
Reporting group description:	
Participants received runcaciguat gastrointestinal therapeutic system (GITS) tablets and were treated following an intra-individual dose-titration design with three titration steps.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo GITS tablets.	

Reporting group values	Runcacigat (BAY1101042)	Placebo	Total
Number of subjects	56	53	109
Age categorical Units: Subjects			
Adults (18-64 years)	40	37	77
From 65-84 years	16	16	32
Age Continuous Units: Years			
arithmetic mean	56.4	57.9	
standard deviation	± 12.7	± 11.5	-
Sex: Female, Male Units: Subjects			
Female	25	22	47
Male	31	31	62
Race (NIH/OMB) Units: Subjects			
Asian	0	1	1
Black or African American	2	2	4
White	54	50	104

Subject analysis sets

Subject analysis set title	FAS (Full Analysis Set)
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) included all randomized participants.	
Subject analysis set title	SAF (Safety Analysis Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set (SAF) included all participants who received at least one dose of study intervention, equalling all randomized participants.	

Reporting group values	FAS (Full Analysis Set)	SAF (Safety Analysis Set)	
Number of subjects	109	109	
Age categorical Units: Subjects			
Adults (18-64 years)	77	77	

From 65-84 years	32	32	

Age Continuous Units: Years			
arithmetic mean	57.1	57.1	
standard deviation	± 12.1	± 12.1	
Sex: Female, Male Units: Subjects			
Female	47	47	
Male	62	62	
Race (NIH/OMB) Units: Subjects			
Asian	1	1	
Black or African American	4	4	
White	104	104	

End points

End points reporting groups

Reporting group title	Runcacigat (BAY1101042)
Reporting group description:	
Participants received runcaciguat gastrointestinal therapeutic system (GITS) tablets and were treated following an intra-individual dose-titration design with three titration steps.	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo GITS tablets.	
Subject analysis set title	FAS (Full Analysis Set)
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) included all randomized participants.	
Subject analysis set title	SAF (Safety Analysis Set)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety analysis set (SAF) included all participants who received at least one dose of study intervention, equalling all randomized participants.	

Primary: Percentage of participants with improvement in DRSS by ≥ 2 steps at 48 weeks of treatment in the study eye

End point title	Percentage of participants with improvement in DRSS by ≥ 2 steps at 48 weeks of treatment in the study eye
End point description:	
DRSS (Diabetic Retinopathy Severity Scale) is measured on a 13-point scale and was graded centrally for the study.	
End point type	Primary
End point timeframe:	
At 48 weeks of treatment	

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 4.7)	1.9 (0.2 to 8.7)		

Statistical analyses

Statistical analysis title	Statistical analysis (final)
Comparison groups	Runcacigat (BAY1101042) v Placebo

Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Point estimate
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.029

Notes:

[1] - Bayesian inference with non-informative priors

Secondary: Percentage participants with vision threatening complications (VTC) at 48 weeks of treatment in the study eye

End point title	Percentage participants with vision threatening complications (VTC) at 48 weeks of treatment in the study eye

End point description:

VTC are defined as occurrence of any of the following AEs: • Proliferative diabetic retinopathy (PDR) (DRSS ≥61) • Any ocular neo-vascularization (retinal or anterior-segment neovascularization) • Center-involved (central Early Treatment Diabetic Retinopathy Study [ETDRS] subfield) DME • Drop of Best corrected visual acuity (BCVA) of 10 letters or more from baseline

End point type	Secondary

End point timeframe:

At 48 weeks

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of participants				
number (not applicable)	17.6	11.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with ≥ 2 steps improvement in DRSS at 24 weeks of treatment in the study eye

End point title	Percentage of participants with ≥ 2 steps improvement in DRSS at 24 weeks of treatment in the study eye

End point description:

DRSS (Diabetic Retinopathy Severity Scale) is measured on a 13-point scale and was graded centrally for the study.

End point type	Secondary

End point timeframe:

At 24 weeks of treatment

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 4.8)	0.0 (0.0 to 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with ≥ 3 steps improvement in DRSS at 48 weeks of treatment on the for persons scale

End point title	Percentage of participants with ≥ 3 steps improvement in DRSS at 48 weeks of treatment on the for persons scale

End point description:

DRSS (Diabetic Retinopathy Severity Scale) is measured on a 13-point scale and was graded centrally for the study.

End point type	Secondary

End point timeframe:

At 48 weeks of treatment

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of participants				
number (confidence interval 95%)	0.0 (0.0 to 4.7)	1.9 (0.2 to 8.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse event (TEAE)

End point title	Number of participants with treatment emergent adverse event (TEAE)

End point description:

End point type	Secondary

End point timeframe:

From first dosing up to 28 days after last dose of study intervention

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	53		
Units: number of participants	53	44		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of participants with < 3 steps deterioration in DRSS at 48 weeks of treatment on the for persons scale

End point title	Percentage of participants with < 3 steps deterioration in DRSS at 48 weeks of treatment on the for persons scale

End point description:

DRSS (Diabetic Retinopathy Severity Scale) is measured on a 13-point scale and was graded centrally for the study.

End point type	Other pre-specified

End point timeframe:

At 48 weeks of treatment

End point values	Runcacigat (BAY1101042)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	52		
Units: percentage of participants				
number (confidence interval 95%)	78.4 (65.8 to 88.0)	80.8 (68.5 to 89.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dosing up to 28 days after last dose of study intervention.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Runcaciguat (BAY1101042)

Reporting group description:

Participants received Runcaciguat 15 mg gastrointestinal therapeutic system (GITS) tablets and were treated following an intra-individual dose-titration design with three titration steps with four dose levels (30, 60, 90, 120 mg)

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo GITS tablets and were treated following an intra-individual dose-titration design with three titration steps with four dose levels

Serious adverse events	Runcaciguat (BAY1101042)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 56 (16.07%)	3 / 53 (5.66%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery thrombosis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry gangrene			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Plantar fasciitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic foot infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Septic shock			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 56 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 56 (1.79%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Runcaciguat (BAY1101042)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 56 (89.29%)	32 / 53 (60.38%)	
Investigations			
Glomerular filtration rate decreased			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Blood creatinine increased			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	2 / 53 (3.77%)	
occurrences (all)	4	2	
Aspartate aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Vascular disorders			
Hypertension			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 56 (3.57%)	4 / 53 (7.55%)	
occurrences (all)	2	4	
Hypotension			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			

subjects affected / exposed	6 / 56 (10.71%)	2 / 53 (3.77%)	
occurrences (all)	12	6	
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	6 / 56 (10.71%)	4 / 53 (7.55%)	
occurrences (all)	24	4	
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Erythropenia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Eye disorders			
Retinal haemorrhage			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Retinal exudates			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Dry eye			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Diabetic retinopathy			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Diabetic retinal oedema			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 56 (3.57%)	3 / 53 (5.66%)	
occurrences (all)	2	4	
Vision blurred			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 56 (3.57%)	3 / 53 (5.66%)	
occurrences (all)	3	3	
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	16 / 56 (28.57%)	10 / 53 (18.87%)	
occurrences (all)	28	17	
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Abdominal pain upper			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	2 / 53 (3.77%)	
occurrences (all)	5	2	
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	5 / 53 (9.43%)	
occurrences (all)	5	7	
Nausea			
alternative assessment type: Systematic			

subjects affected / exposed	6 / 56 (10.71%)	5 / 53 (9.43%)	
occurrences (all)	7	5	
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 56 (8.93%)	0 / 53 (0.00%)	
occurrences (all)	5	0	
Myalgia			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 56 (5.36%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Pain in extremity			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	0 / 53 (0.00%)	
occurrences (all)	4	0	
Arthralgia			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 56 (3.57%)	3 / 53 (5.66%)	
occurrences (all)	2	3	
Infections and infestations			
COVID-19			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 56 (8.93%)	4 / 53 (7.55%)	
occurrences (all)	5	4	
Tooth infection			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	1 / 53 (1.89%)	
occurrences (all)	4	1	
Urinary tract infection			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 56 (5.36%)	0 / 53 (0.00%)	
occurrences (all)	3	0	
Upper respiratory tract infection			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 56 (1.79%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 56 (7.14%)	0 / 53 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2020	Amendment 1- This amendment was implemented to follow requests from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and central Independent Ethics Committee (IEC). Changes were made to the following protocol sections: Run in, Exclusion criteria, Intra-individual dose-titration decisions, Stopping rules (study level), Permanent discontinuation, Vision threatening complications, Genetics, Biomarkers, Safety assessment group, Central reading centers
13 January 2021	Amendment 2 - This amendment was implemented to accommodate requests by Competent Authorities and Independent Ethics Committees on the use of the smartphone app to support drug adherence. In addition, endpoint assessments were specified and additional endpoints included. Changes were made to the following protocol sections: Electrocardiograms, Study intervention compliance, Color fungus photography (CFP), Optical coherence tomogrpahy angiography (OCT-A)
04 November 2021	Amendment 3 - Due to product development reasons, the study was restrucutred. The Terms Part A and Part B were retired. Part 1 now referred to the PK/PD substudy and Part 2 referred to the main part of the PoC study. Changes were made throughout the entire protocol, affecting all sections.
09 February 2023	Amendment 4 - Clarifications were made of dose-titration instructions changes to the primary endpoint assessment, making this amendment substantial. Changes were made to the following protocol sections: Synopsis, Schema, Objectives and endpoints, Overall design, Scientific rationale for study design, End-of-study definition, Study assessments and procedures, Statistical hypotheses, Primary endpoint, Efficacy, Risk assessment, Intra-individual dose-titration decisions, Part 2- Proof of concept, Pharmacokinetics, Interim analysis, Re-challenge / re-start of study intervention, Permanent discontinuation

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported