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

Protocol title:

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

Protocol number: 20739

Protocol Version: 5.0

Amendment Number: 4

Compound number: BAY 1101042 / Runcaciguat

Brief title: Non-proliferative diabetic retinopathy treated with runcaciguat

Study phase: 2

Acronym: NEON-NPDR

Sponsor name and legal registered address:

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Name: PPD Role: PPD

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Protocol amendment summary of changes table

Document history		
Document	**Date**	**Applicable documents**
Amendment 4	09 FEB 2023	Clinical study protocol
Amendment 3	04 NOV 2021	Master Protocol Protocol Part A Protocol Part B
Amendment 2	13 JAN 2021	Master Protocol Protocol Part A Protocol Part B
Amendment 1	23 NOV 2020	Master Protocol Protocol Part A Protocol Part B
Original protocol	24 AUG 2020	Master Protocol Protocol Part A Protocol Part B

Amendment 4 (09 FEB 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for Amendment 4:

A description of changes and a brief rationale is outlined in the table at the end of this section. An overview is given below.

Clarification of dose-titration instructions

Clear blood pressure limits were added to the titration instructions to provide more precise guidance on when to maintain and not increase the dose. This amendment is expected to improve participant's safety and to result in more consistent titration decisions across sites.

In addition, two dose reductions are now permissible instead of a single dose reduction.

This change is considered substantial as it has effects on participant's safety.

Primary endpoint after 48 weeks instead of after 24 weeks of treatment

2-step DRSS improvement is the main efficacy endpoint in this clinical study. Assessments are planned after 12, 24, and 48 weeks of treatment. The assessment after 24 weeks was initially defined as the primary endpoint. However, information was received from other clinical trials in non-proliferative diabetic retinopathy, that achieving 2-step DRSS improvement in a sufficient number of study participants may take longer than 24 weeks for most drugs not administered by intravitreal injection (e.g. ROBIN trial NCT03238963, discussed in (Boyer et al. 2021). To provide sufficient time for the treatment effect, the primary assessment of this endpoint is moved to 48 weeks of treatment. Up to the date of this amendment, on-treatment DRSS assessments were not transferred from the central reading center into the study database, they were not seen by the sponsor nor by the independent data monitoring committee, in agreement with study procedures. No interim assessment was performed until now. Thus, no efficacy data from the present study were reviewed and the decision for this amendment was solely driven by general considerations triggered by

information received from other clinical trials in diabetic retinopathy. Based on these considerations, a power adjustment is not deemed necessary.

This change to the primary endpoint assessment is considered substantial.

A full overview of changes is provided in the two tables below.

Key changes in study design and other substantial changes

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 1.2 Schema Section 3 Objectives and endpoints Section 4.1 Overall design Section 4.2 Scientific rationale for study design Section 4.4 End-of-study definition Section 8 Study assessments and procedures Section 9.1 Statistical hypotheses Section 9.4.2 Primary endpoint Section 9.4.3.1 Efficacy	The primary DRSS assessment was moved to 48 weeks of treatment.	Information was received from other clinical trials in non-proliferative diabetic retinopathy, that achieving 2-step DRSS improvement in a sufficient number of study participants may take longer than 24 weeks for most drugs not administered by intravitreal injection (e.g. ROBIN trial NCT03238963, discussed in (Boyer et al. 2021). To increase the probability of a successful clinical trial, the primary assessment of this endpoint is moved to 48 weeks of treatment
Section 2.3.1 Risk assessment	Safety information from CONCORD study was updated.	Update of new information included in the IB
Section 6.5.1 Intra-individual dose-titration decisions	Minimum treatment interruption in case of pertinent adverse event extended to 48 hours.	Correction and extension of minimum temporary discontinuation interval
Section 4.1.2 Part 2 – Proof of concept Section 8.4 Pharmocokinetics Section 9.5 Interim analysis	No interim analysis is planned. DMC oversight will continue as planned.	With the primary endpoint moved to the end of the treatment period, the interim assessment is no longer deemed useful.
Section 6.5.1 Intra-individual dose-titration decisions Section 7.1.3 Re-challenge / re-start of study intervention	The dose-titrations instruction was specified by providing minimum blood pressure requirements for dose titration.	This amendment is expected to improve participant's safety and to result in more consistent titration decisions across sites. (substantial amendment)
Section 6.5.1 Intra-individual dose-titration decisions	Up to two (instead of only one) dose reductions are permissible	Allowing only a single dose reduction and imposing permanent treatment discontinuation in case a single dose reduction does not sufficiently improve tolerability may result in undue early treatment discontinuations and reduce the power of the clinical trial
Section 7.1.1 Permanent discontinuation	If study intervention is permanently discontinued, an End-of-Treatment visit should be performed in line with Visit 15. The participant remains in the study for continued assessment of study outcomes following the visit schedule in section 1.3.	Clarification of the visit schedule for study intervention permanent discontinuation

Section # and Name	Description of Change	Brief Rationale
Section 7.1.1 Permanent discontinuation	Withdrawal from trial is no longer mandatory, in case of vision threatening complication or progression to PDR, but to be decided case by case by the investigator.	There is no safety concern with continuing treatment after a vision threatening complication. Continued treatment may be beneficial. Therefore, treatment discontinuation is not mandatory in general but to be considered case by case by the investigator.

Clarifications and corrections (non-substantial)

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SoA)	Footnotes were added to clarify the timepoints for safety, blood sampling and ophthalmology examinations.	Clarification of sequence of activities
Section 1.3 Schedule of activities (SoA)	Administer study intervention (after blood draws) was removed at Visit 15 EoT. Dispensation of urine pregnancy test was added at Visit 12. 7-field color fundus photography (DRSS) was removed at Visit 8.	Corrections of mistakes: Assessing DRSS assessment after 8 weeks of treatment in addition to after 12 weeks of treatment cannot be expected to provide relevant additional data.
Section 7.1.2 Temporary discontinuation	If the re-assessed laboratory result indicates a decrease in eGFR <40% from baseline, study intervention may be re-started at the same dose as before this temporary discontinuation, in line with section 7.1.3.	Clarification on re-starting study intervention

Table of contents

Table of tables

Table of figures

1. Protocol summary

1.1 Synopsis

Protocol title:

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

Brief title: Non-proliferative diabetic retinopathy treated with runcaciguat

Overall study plan:

Study 20739 is a Phase 2 proof-of-concept study that includes a subpart with PK/PD assessments (Part 1). Part 1 enrolls a subset of patients at a more intense investigation in specific study sites. Part 2 is the main PoC part, to be conducted in ophthalmology sites, that enrolls the majority of participants. PoC will be based on the evaluation of outcomes in participants from both parts.

Rationale:

Results from previous Phase 1 studies in healthy as well as renally impaired patients as well as a phase 2 study with patients with chronic kidney disease have demonstrated that runcaciguat given as modified-release oral tablets was well tolerated and support the start of further studies in patients.

Due to the mode of action of sGC activators, and based on preclinical data, it is assumed that sGC activators, administered to NPDR patients, can positively influence retinal perfusion and thereby improve fundus morphology and reduce the progression of retinal ischemia and vision-threatening later stages like PDR and/or DME.

The present study is to be conducted to obtain information on sGC activators by investigating

1. whether runcaciguat improves the diabetic retinopathy score in patients with moderately severe to severe NPDR

   and to

2. explore the pharmacokinetic - pharmacodynamic relationship of runcaciguat on retinal perfusion

The results are intended to provide useful information to improve the design of clinical studies with subsequent sGC activators, for example by supporting the choice of the appropriate dose and treatment duration.

Objectives and endpoints:

Table 1-1 Study objectives and endpoints

Objectives	Endpoints
Primary objective: Efficacy Establish the proof-of-concept for the efficacy of the sGC activator runcaciguat in the treatment of NPDR.	**Primary endpoint:** • DRSS improvement ≥ 2 steps at 48 weeks of treatment in the study eye **Secondary endpoints for primary objective:** • Vision threatening complications at 48 weeks of treatment in the study eye • DRSS improvement ≥ 2 steps at 24 weeks of treatment in the study eye **Other endpoints (for primary objective):** • Change in visual acuity from baseline • Change in leakage area on Fluorescein Angiography • DRSS changes from baseline in the study and fellow eye • Vision threatening complications in any eye up to 48 weeks of treatment
Secondary objective: Safety Investigate the safety and tolerability of runcaciguat in patients with NPDR	**Secondary endpoints for secondary objective:** • Frequency of treatment-emergent adverse events • **Other endpoints (for secondary objective):** • Laboratory parameters • Vital signs • Electrocardiography
Other objectives Characterize pharmacodynamic effects of runcaciguat in patients with NPDR	**Other endpoints** • Central retinal thickness • HbA1c • Serum lipoproteins
Characterize pharmacokinetics of runcaciguat in patients with NPDR	• Population pharmacokinetics • Pre-dose (trough) plasma concentrations of runcaciguat by visit

DRSS = Diabetic Retinopathy Severity Scale; NPDR = Non-proliferative diabetic retinopathy;

Overall design:

This is a randomized, double-masked parallel study with two study arms enrolling N=98 patients with non-proliferative diabetic retinopathy. The study is conducted as a placebo-controlled study, for details see Section 6.3.

Total treatment duration is 48 weeks. The primary endpoint will be the number of participants with a ≥ 2-step improvement (reduction) in the DRSS after 48 weeks of treatment in the study eye.

A steering committee consisting of ophthalmologists and diabetologists (masked) is put in place to provide scientific and operational recommendations to the study protocol and may be consulted to support decisions in study conduct. An independent Data Monitoring Committee is set up to provide recommendations based on unmasked review of data, if needed.

Brief summary:

This Phase 2 study is conducted to determine whether runcaciguat, administered at once daily oral doses of a modified-release formulation, is more effective in treating NPDR than placebo.

The study comprises two subparts, 1 (PK/PD) and 2 (proof of concept); both subparts will be conducted in parallel.

To assess the efficacy, the retinal morphology will be investigated by 7-field color fundus photography (CFP) supported by 7 Field FA images for the assessment of the DRSS by a central reading center. Two-step DRSS improvement at 48 weeks of treatment will be the primary efficacy endpoint. Additional DRSS assessments are done after 12 and 24 weeks of treatment. In addition, vision-threatening complications will be recorded throughout the study and assessed as secondary efficacy endpoint.

During the course of the study, 16 visits are planned, including the screening visit (Visit 1) and the end-of-study visit (Visit 16). Visit intervals are weekly during the first 4 weeks, while the dose of runcaciguat (or placebo) is titrated to the target dose, then fortnightly for the next 4 weeks and then every 4 weeks up to Week 25 (Visit 12). The subsequent visits, up to end of treatment in Week 49 (Visit 15), will be at 8-week intervals. The end-of-study visit, Visit 16, will take place 4 weeks later.

Number of participants:

A combined total of approximately 98 participants for Part 1 and 2 will be randomly assigned for an estimated total of ≥ 40 participants per intervention group evaluable for primary endpoint assessment, as defined in Section 9.2. The estimated screen failure rate is approximately 50%.

Intervention groups and duration:

Participants are randomly assigned to one of two study arms. Assignment will be masked, as detailed in Section 6.3. After providing informed consent, participants will be screened (Visit 1) and within up to 4 weeks, eligible participants will be randomized and treatment will be initiated at Visit 2. During the initial four weeks, treatment will be titrated to the target dose of 120 mg runcaciguat or matching placebo. Treatment will start at 30 mg runcaciguat or placebo once daily for the first week. If well tolerated, the dose will be increased to 60 mg runcaciguat or placebo at Visit 3 in the second week of treatment, then to 90 mg runcaciguat or placebo at Visit 4 in the third week of treatment, and finally to 120 mg runcaciguat or placebo at Visit 5.

In case of intolerability (see Section 6.5.1) treatment may continue without up-titration or the dose may be reduced by one titration step.

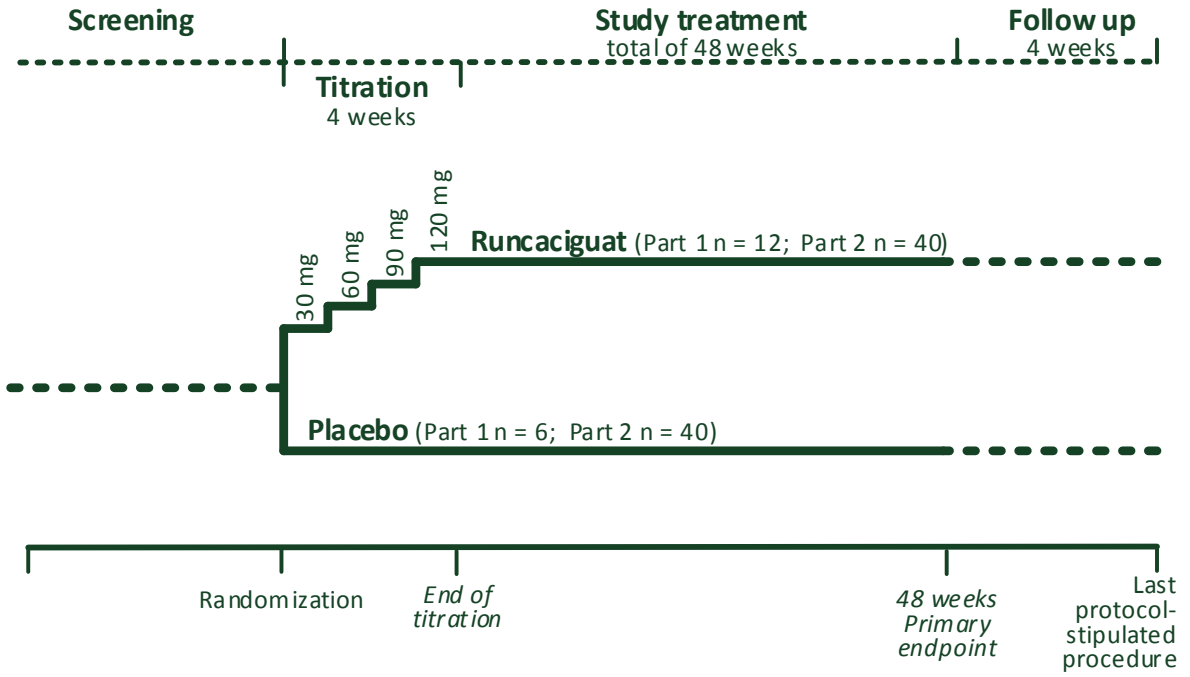
Treatment will continue at the highest tolerated dose until completion of 48 weeks of treatment if tolerated, or until development of a vision threatening complication or development of PDR.

An end-of-study visit will be performed 4 weeks after end of treatment. This includes both participants who complete the planned treatment period, and participants who discontinue treatment early including treatment discontinuation due to vision threatening complications.

Data monitoring / Other committee: **Yes**

1.2 Schema

Figure 1–1 Schematic study design



1.3 Schedule of activities (SoA)

Table 1-2 Schedule of activities: Part 1 – Screening (Visit 1) and titration phase (Visits 2 to 6)

		Screen	Titration								
	Visit number	**1**	**2**			**3, 4, 5**			**6**		
	Study week	***-1***	***1***			***2, 3, 4***			***5***		
	Study day	**-2**	**1**			**8, 15, 22**			**29**		
	Permissible time window (days)	-28 to -2	n/a			±1			±2		
	Time (hours relative to dose)		**pre**	**1-2**	**2-4**	**pre**	**1-2[2]**	**2-4**	**pre**	**1-2[2]**	**2-4**
Initiation	Written informed consent	●									
	Allocation of screening number	●									
	Demographic data	●									
	Medical/surgical history (general and cardiological)	●									
	Previous medication (medication history)	●									
	History on use of caffeine, alcohol, tobacco	●									
	Check of in-/exclusion criteria	●	●								
	Determination of study eye		●								
Study intervention	Randomization		●								
	Dose titration decision					●					
	Administration of study intervention (time 0)			●			●			●	
	Collection of unused study intervention					●			●		
	Dispensation of study intervention				●			●			●
Safety[4]	Recording of AEs, concomitant medication	→	→	→	→	→	→		→	→	
	Physical examination, height, weight	●									
	Checking fasting / feeding state	●	●			●			●		
	Blood pressure, pulse rate [1]	●	●	●[2]	●	●	●[2]	●	●	●[2]	●
	12-lead ECG (triplicate) [1]	●	●	●[2]	●	●	●[2]	●	●	●[2]	●
	Urine pregnancy test (women)		●			●			●		
Blood sampling[3,4]	Hematology, biochemistry	●	●			●			●		
	Hormones	●									
	Biomarker (plasma, serum)		●			●					●
	Pharmacogenetics (optional)		●								
	Serum pregnancy test (women)	●	●			●			●		
	Pharmacokinetics		●	●[2]	●	●	●[2]	●	●	●[2]	●
Ophthalmology examinations[4] (bilateral)	Visual acuity test (BCVA)	●	●								
	Tonometry	●	●			●			●		
	Structural OCT	●	●			●			●		
	Anterior and posterior segment examination	●									
	OCT angiography	●	●		●	●		●	●		●
	7-field color fundus photography (DRSS)	●									
	Fluorescein angiography (DRSS)	●									

AE = adverse event; BCVA = best corrected visual acuity; DRSS = used for assessment of diabetic retinopathy severity score; ECG = electrocardiogram; OCT = optical coherence tomography

1 Blood pressure, pulse rate and ECG always to be measured in supine or semi-supine position after ≥ 5 minutes rest and before any blood draws

2 Minimum interval of 1 hour to prior and subsequent examinations

3 Blood sampling to be performed before fluorescein angiography, to avoid interferences with analytics

4 To be done before study intervention administration, except for Visit 7 taking place in the afternoon

Table 1-3 Schedule of activities: Part 2 - Screening (Visit 1) and titration phase (Visits 2 to 6)

		Screen	Titration				
	Visit number	**1**	**2**	**3**	**4**	**5**	**6**
	Study week	***-1***	***1***	***2***	***3***	***4***	***5***
	Study day	**-2**	**1**	**8**	**15**	**22**	**29**
	Permissible time window (days)	-28 to -2	0	±1	±2 [2]	±2 [2]	±2
Initiation	Written informed consent	●					
	Allocation of screening number	●					
	Demographic data	●					
	Medical/surgical history (general and cardiological)	●					
	Previous medication (medication history)	●					
	History on use of caffeine, alcohol, tobacco	●					
	Check of in-/exclusion criteria	●	●				
	Determination of study eye		●				
Study intervention	Randomization		●				
	Dose titration decision by investigator			●	●	●	
	Administration of study intervention (time 0, after blood draws)		●	●	●	●	●
	Collection of unused study intervention			●	●	●	●
	Dispensation of study intervention		●	●	●	●	●
Safety[4]	Record AEs and concomitant medication	→	→	→	→	→	→
	Physical examination, height, weight	●					
	Blood pressure, pulse rate [1]	●	●	●	●	●	●
	12-lead ECG [1]	●	●	●	●	●	●
	Urine pregnancy test (women)		●	●	●	●	●
Blood sampling[3,4]	Hematology, biochemistry	●	●	●	●	●	●
	Hormones	●					
	Biomarker (plasma, serum)		●	●	●	●	●
	Pharmacogenetics (optional)		●				
	Serum pregnancy test (women)	●	●	●	●	●	●
	Pharmacokinetics (pre dose)			●	●	●	●
Ophthalmology examinations[4] *(bilateral)*	Visual acuity test (BCVA)	●	●				
	Tonometry	●	●	●	●	●	●
	Structural OCT	●	●	●	●	●	●
	Anterior and posterior segment examination	●					
	OCT angiography (optional)	●	●	●	●	●	●
	7-field color fundus photography (DRSS)	●					
	Fluorescein angiography (DRSS)	●					

AE = adverse event; BCVA = best corrected visual acuity; DRSS = used for assessment of diabetic retinopathy severity score; ECG = electrocardiogram; OCT = optical coherence tomography

1 Blood pressure, pulse rate and ECG always to be measured in supine or semi-supine position after ≥ 5 minutes rest and before any blood draws
2 Visit windows are wider than in Part 2 due to difference in PK/PD assessments
3 Blood sampling to be performed before fluorescein angiography to avoid interferences with analytics
4 To be done pre-dose before study intervention administration, except for Visit 7 taking place in the afternoon

Table 1-4 Schedule of activities: Parts 1 and 2 - Visits 7 to 16

	Visit number	7 [1]	8	9	10	11	12	13	14	15 EoT	16 EoS
	Study week	*7*	*9*	*13*	*17*	*21*	*25*	*33*	*41*	*49*	*53*
	Study day	43	57	85	113	141	169	225	281	337	365
	Permissible time window (days)	±2	±2	±7	±7	±7	±7	±7	±7	±7	±7
Study interv.	Dispensation of study intervention	●	●	●	●	●	●	●	●		
	Administer study intervention (after blood draws)		●	●	●	●	●	●	●		
	Collection of unused study intervention	●	●	●	●	●	●	●	●	●	
Safety [4]	Record AEs and concomitant medication	→	→	→	→	→	→	→	→	→	→
	Physical examination, weight									●	
	Blood pressure, pulse rate [2]	●	●	●	●	●	●	●	●	●	●
	12-lead ECG [2]	●	●		●		●	●	●	●	
	Dispensation of urine pregnancy test [3]						●	●	●		
Blood sampling [4,5]	Hematology, biochemistry	●	●	●	●	●	●	●	●	●	●
	Biomarker samples: plasma, serum	●	●	●	●	●	●			●	
	Serum pregnancy test (women)	●	●	●	●	●	●	●	●	●	●
	Pharmacokinetics	●	●	●	●	●	●				
Ophthalmolog examinations [4] *(bilateral)*	Visual acuity test (BCVA)		●		●		●	●	●	●	●
	Tonometry	●	●	●	●	●	●	●	●	●	●
	Structural OCT	●	●	●	●	●	●	●	●	●	●
	Anterior and posterior segment examination			●			●			●	
	OCT angiography (optional in Part 2)	●	●	●	●	●	●	●	●	●	●
	7-field color fundus photography (DRSS)			●			●			●	
	Fluorescein angiography (DRSS)						●			●	

AE = adverse event; BCVA = best corrected visual acuity; DRSS = used for assessment of diabetic retinopathy severity score; ECG = electrocardiogram; EoS = End of study; EoT = end of treatment; OCT = optical coherence tomography

1 Visit 7 should take place in the afternoon, PK and biomarker samples to be taken at 4 to 8 hours after dosing

2 Blood pressure, pulse rate and ECG always to be measured in supine or semi-supine position after ≥ 5 minutes rest and before any blood draws

3 Additional urine pregnancy test to be provided to women for use off-site 4 weeks after the respective visit

4 To be done pre-dose before study intervention administration, except for Visit 7 taking place in the afternoon

5 Blood sampling to be performed before fluorescein angiography to avoid interferences with analytics

2. Introduction

As of amendment 3, this Section and its sub-sections were integrated from Master Protocol.

Runcaciguat (BAY 1101042) is a representative from a new class of drugs, the soluble guanylate cyclase (sGC) activators. The sponsor is developing sGC activators for the treatment of microangiopathies, namely chronic kidney disease (CKD) and non-proliferative diabetic retinopathy (NPDR). For both indications, proof-of-concept studies are currently ongoing, one being the NEON-NPDR study.

For the NPDR indication, the treatment is intended to

- Prevent progression of diabetic retinopathy and vision-threatening complications
- Reverse retinal changes attributed to diabetic retinopathy
- Maintain visual acuity.

Runcaciguat will be investigated in a formulation of modified-release (MR) tablets, which result in peak plasma concentrations at approximately 10 hours post dose and a peak-to-trough concentration ratio of 2:1. The terminal half-life of runcaciguat in plasma ranged from approximately 14 to 21 hours in healthy study participants.

Runcaciguat, given as MR tablets, showed vasodilatory effects at doses from 20 mg to 90 mg once daily without clinically relevant signs of hemodynamic intolerance. Once-daily doses up to the highest investigated dose of 90 mg administered over 7 days were safe and well tolerated by healthy participants.

Other indications under development for runcaciguat include chronic kidney disease. A clinical study in patients with chronic kidney disease (CONCORD study 18748; EudraCT: 2019-003297-53) started in 2020 and is ongoing in parallel. In that study, patients are treated with once-daily doses of runcaciguat titrated up to 120 mg. The current recruitment status is summarized in Section 2.3.1.

Further information on pre-clinical and available clinical data relevant in the context of this study are provided and discussed in Section 2.3. Additional information is given in the most recent version of the IB.

2.1 Study rationale

The clinical development of runcaciguat so far has shown that the compound is well tolerated. However, formulation challenges lead to an inconvenient dosing regimen and a difficult to manage supply chain. CCI [redacted]

The Sponsor plans to run the NEON-NPDR study with runcaciguat as a PoC trial for sGC activators in NPDR. Although the sGC activator runcaciguat will not be further developed, the results from this trial will generate a general PoC for sGC activation in NPDR using a investigational compound that has proven its activity in nonclinical and in phase 1 clinical trials and that has been shown to be well tolerated.

In addition, detailed pharmacokinetic and pharmacodynamic assessments will be performed on a subset of participants enrolled in Part 1. The resulting improved PK/PD understanding will facilitate the translation of the results obtained with the runcaciguat to other sGC activators.

Therefore, this trial will be the basis for a general decision on the suitability of sGC activators for treatment of NPDR. In the positive case, this may optimize the development of subsequent sGC activators. In particular the data will facilitate the choice of the appropriate dose-range and the choice of the most appropriate treatment duration. This knowledge will result in safer and more focused clinical trials with the follow-up compound.

2.2 Background

2.2.1 Disease background

The prevalence of diabetic retinopathy (DR) approximates 35% among people with diabetes worldwide (Yau et al. 2012). Diabetic retinopathy ranks fifth among common causes for blindness or severe vision impairment, and the prevalence of DR-related blindness will increase due to increasing prevalence of diabetes (Leasher et al. 2016).

Diabetic retinopathy is characterized by progressive changes in the retinal microvasculature with accompanying neuroglial damage (Santiago et al. 2018). Pathognomonic changes consist of microaneurysms and soft exudates, macular edema, and neovascularization. In addition, other retinal cell types are affected by diabetes and may compromise or contribute to visual impairment.

Predicting progression of mild- and moderate- NPDR to PDR has been evaluated at the group level but is still not well established at the individual level (ETDRS report number 10 1991). HbA1c, hypertensive status and hyperlipidemia are all factors routinely used in screening in many European countries (Aspelund et al. 2011, Lund et al. 2016, van der Heijden et al. 2014), they poorly predict progression of non-proliferative retinopathy. According to Sato et al (Sato et al. 2001), baseline severity of diabetic retinopathy is a better predictor of clinical outcomes. Cunha-Vaz et al. (Cunha-Vaz et al. 2017) proposed an evolution model to PDR which is based on microaneurysms and retinal features, classifying patients into 3 risk phenotypes, disregarding HbA1c or other metabolic parameters.

Oxidative stress plays a key role in the pathogenesis of diabetic retinopathy. Reactive oxygen species (ROS) are increased in the retina in diabetes, at the same time the antioxidant defense system is also compromised. Increased ROS stimulate the release of pro-inflammatory cytokines, promoting a chronic low-grade inflammation involving various signaling pathways. An excessive production of ROS can lead to retinal endothelial cell injury, increased microvascular permeability, and recruitment of inflammatory cells at the site of inflammation (Santiago et al. 2018).

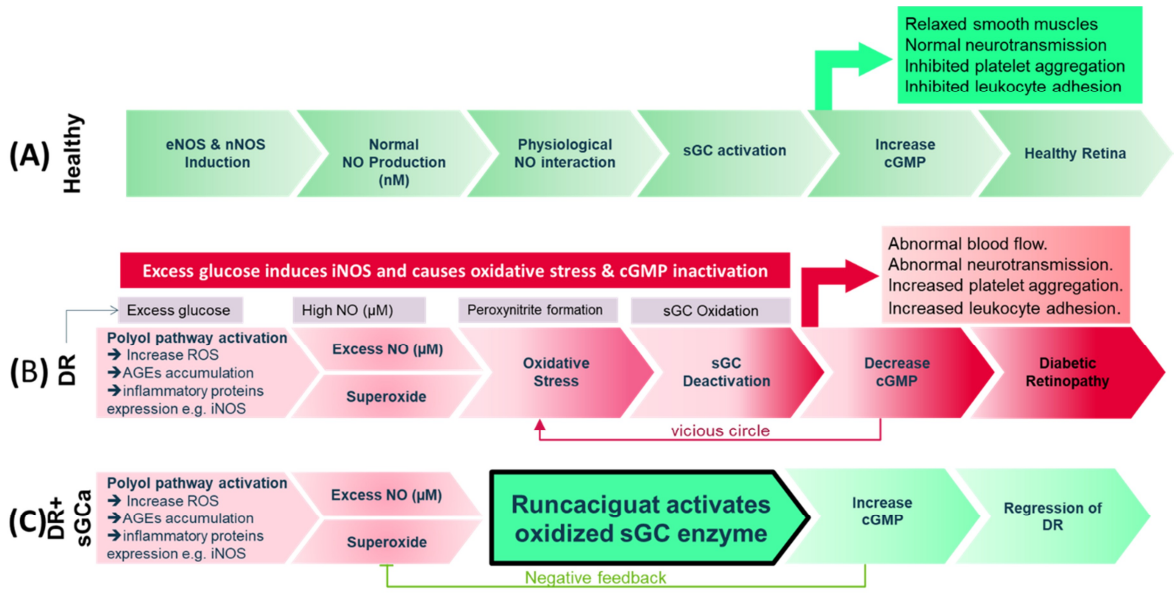
2.2.2 The role of soluble guanylyl cyclase in diabetic retinopathy

Under physiological conditions (Figure 2–1 A), endothelial (eNOS) and neuronal nitric oxide synthase (nNOS) are expressed by retinal cells and produce nitric oxide (NO) in small (nanomolar) amounts to activate the soluble forms of guanylyl cyclase (sGC). Active sGC catalyzes the synthesis of cGMP from GTP. The classical effects of the NO-sGC-cGMP axis are vasodilation, regulation of blood flow, inhibition of platelet aggregation and suppression of leukocyte adhesion and migration (Lehners et al. 2018).

Under pathological conditions, such as DR, (Figure 2–1 B), cytokine-inducible NOS (iNOS) is expressed. iNOS is expressed in macrophages, microglia, glial cells, neurons, and vascular cells of the retina. iNOS differs from eNOS and nNOS as it produces NO in large (micromolar) amounts. Excess NO binding to superoxide results in peroxynitrite formation. Peroxynitrite oxidizes the sGC enzyme, which loses its heme-moiety, making it unresponsive to NO (Stasch et al. 2011). As a result, cGMP production is reduced and a vicious circle of oxidative stress within the retina is initiated that drives the progression of diabetic retinopathy (Förstermann 2010).

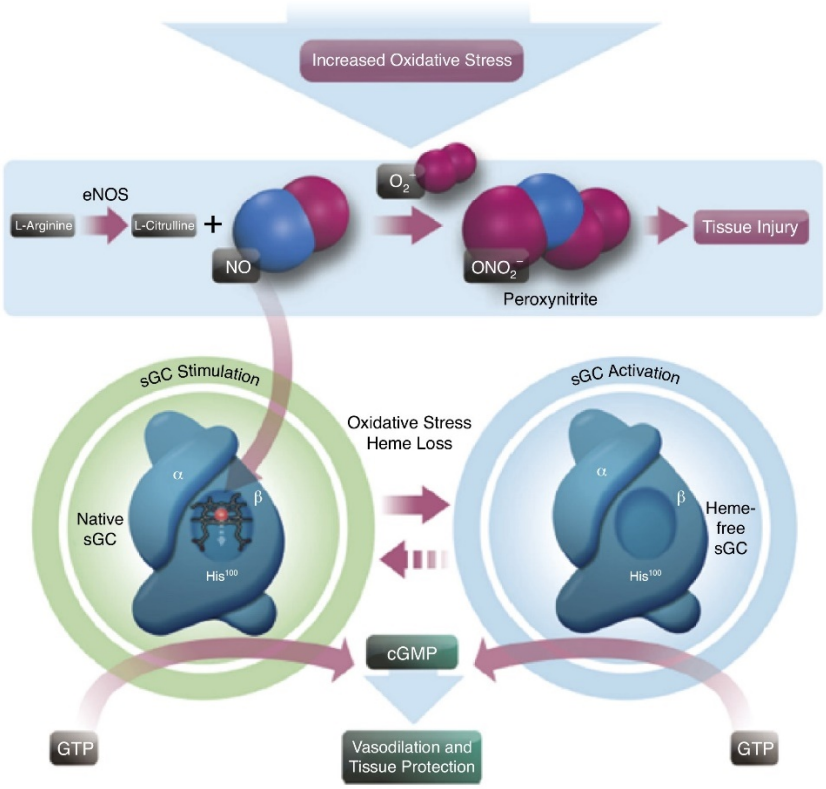
Figure 2–1 C illustrates that the sGC activator runcaciguat (BAY 1101042) targets the nitric oxide-insensitive states of the sGC enzyme. Runcaciguat binds to the unoccupied heme-binding complex or displaces the prosthetic heme of sGC and produces an additive effect with NO. In certain cases, sGC activators also protect sGC from proteasomal degradation. This restores the NO-sGC-cGMP axis functions. It improves retinal blood flow by vascular vasodilation through relaxation of smooth muscles, inhibits platelet aggregation and inhibited leukocyte adhesion. This leads to better neurovascular unit function neurotransmission and, subsequently, slows the disease progression.

Figure 2–1 The role of sGC activator in diabetic retinopathy



AGE = advanced glycation endproduct; cGMP = cyclic guanosine monophosphate; DR = diabetic retinopathy; eNOS = endothelial nitric oxide synthase; iNOS = cytokine-inducible nitric oxide synthase; nNOS = neuronal nitric oxide synthase; NO = nitric oxide; ROS = reactive oxygen species; sGC = soluble guanylyl cyclase ; sGCa = soluble guanylyl cyclase A

Figure 2–2 sGC stimulators and activators target different redox states of the enzyme



cGMP = cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GTP = guanosine triphosphate; NO = nitric oxide; sGC = soluble guanylyl cyclase
Source : (Stasch et al. 2015).

2.2.3 Runcaciguat

Runcaciguat is a sGC activator that improved function and retinal structure in pre-clinical DR models. In patients with NPDR, runcaciguat is expected to improve retinal perfusion and thereby reverse changes in fundus morphology attributable to diabetic retinopathy and reduce the incidence of vision-threatening events and lower the risk of progression to proliferative diabetic retinopathy.

2.3 Benefit/risk assessment

Based on the expected low risk of study participation, discussed below in Section 2.3.1, and in view of the potential benefit that may result from successful development of a drug improving NPDR and preventing complications as discussed below in Section 2.3.2, the benefit-risk assessment of this study with runcaciguat is considered positive and supportive of the participation of patients with NPDR in this clinical trial.

Emerging safety issues affecting the benefit/risk assessment of the study will be communicated as soon as possible between the sponsor, all study sites and investigators and trial participants according to the requirements of the EMA guideline on strategies to identify risks for early clinical trials and including first in human studies.

2.3.1 Risk assessment

Risks associated with study interventions – Runcaciguat

Runcaciguat was well tolerated by healthy male participants up to a single oral dose of 20 mg given as IR tablet. This IR tablet resulted in maximum plasma concentrations at approximately 30 minutes post dose (t_{max} 0.5 hours). A 30 mg IR tablet dose was not well tolerated based on the exaggerated vasodilative effects. These findings were attributed to the fast increase in plasma concentrations, as reflected by a high peak-to-trough ratio of > 8:1.

When administering as MR tablets with a t_{max} of approximately 10 hours, as planned in this clinical trial, mild vasodilative effects, indicated by a compensatory heart rate increase were observed at doses of 20 mg and above in healthy study participants. A consistent decrease of blood pressure was observed at doses of 50 mg and above and no signs of hemodynamic intolerance were apparent up to 90 mg once daily, the highest dose investigated. Therefore, the MR-tablet formulation was chosen for further clinical development. Hence, unless specified otherwise, any further mention of runcaciguat tablets in this document refers to the MR formulation.

Different drug classes introduced in clinical practice increase cGMP concentrations. This group of drugs includes nitrates, phosphodiesterase inhibitors, and sGC stimulators. Nitrates, in particular, have an excellent safety track record in patients with coronary heart disease. This is a population that includes patients with diabetes and DR, indicating that targeting cGMP in the patient population of this study is safe in principle. Runcaciguat was shown to have vasodilatory effects in healthy subjects, with consecutive decreases in diastolic blood pressure and compensatory increases in heart rate.

Concomitant treatment with other drugs acting on the NO-sGC-cGMP system has the potential to result in synergistic and excessive pharmacodynamic activity with the relative adverse effects. Therefore, these medications must not be co-administered to the patients enrolled in this study.

When runcaciguat was investigated in healthy participants at once-daily doses of 10 to 90 mg over 7 days, increased heart rate was observed at doses of 20 mg and higher. Consistent systolic and diastolic blood pressure decreases were observed at once-daily doses of 50 mg and above, as shown in Table 2-1. Overall, the effects on heart rate and blood pressure were higher after the first administration than after 7 days of once-daily dosing, suggestive of an adaptation to vasodilative effects. Orthostatic reactions in testing standing blood pressure considered drug-related by the investigator, were reported after single dose only in the dose steps 75 and 90 mg but were not provoked on testing on the last dosing day (7 days of once daily dosing).

Table 2-1 Placebo-corrected change in blood pressure and heart rate from baseline after once-daily runcaciguat administration over 7 days (ANCOVA, pre-dose adjusted, 90%CI)

	Heart rate (min^{-1})		Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
	ANCOVA	90%CI	ANCOVA	90%CI	ANCOVA	90%CI
10 mg	*1.8*	*-2.0 – 5.5*	*-2.1*	*-6.1 – 1.9*	*0.9*	*-2.2 – 4.0*
20 mg	*4.8*	*1.1 – 8.5*	*-0.3*	*-4.3 – 3.7*	*2.5*	*-0.5 – 5.6*
30 mg	5.5	1.8 – 9.3	*1.8*	*-2.2 – 5.8*	*0.6*	*-2.5 – 3.6*
40 mg	2.3	*-1.4 – 6.0*	*2.5*	*-1.5 – 6.5*	*0.9*	*-2.1 – 4.0*
50 mg	4.0	1.1 – 7.0	-4.3	-7.4 – -1.1	-2.5	-4.9 – -0.0
75 mg	2.8	*-1.1 – 6.7*	-5.6	-9.8 – -1.5	*-2.2*	*-5.4 – 1.0*
90 mg	2.3	*-1.5 – 6.2*	-5.6	-9.8 – -1.5	-4.0	-7.2 – -0.8

Changes with 90% CI inclusive of zero (0) shown in *italic*
ANCOVA = analysis of covariance; CI = confidence interval
Source: PH-41225, Tables 9-4, 9-6 and 9-10

In a study investigating the effects of a single oral dose of 30 mg runcaciguat in participants of different age and gender in comparison with placebo, runcaciguat was well tolerated without clinically relevant effects on heart rate or blood pressure.

The clinical phase 2 study of runcaciguat in patients with chronic kidney disease was completed and final data are available (CONCORD study 18748; EudraCT: 2019-003297-53). The CONCORD study was a randomized, placebo-controlled, double-masked study with 243 patients randomized 3:1 to runcaciguat (n=184) and to placebo (n=59). The study used the same titration regimen as in the present NEON-NPDR study. The treatment duration was 8 weeks.

Peripheral oedema, dizziness, diarrhea, headache, and hypotension occurred at an incidence of over 4% in participants treated with runcaciguat and at a lower incidence in placebo-treated participants. They can all be plausibly explained by the mechanism of action, resulting in relaxation of smooth muscles and lower BP. The incidence of SAEs was similar in the runcaciguat and the placebo arms.

Five cases of syncope were reported only in the runcaciguat arm, at doses of 60 mg, 90 mg, and 120 mg per day. Three of the syncopes occurred after alcohol intake, in one instance in combination with additional sildenafil. Another case was related to dehydration and the remaining case occurred in a participant who had prior hypotension and dizziness and whose dose was therefore not titrated beyond 60 mg.

In the runcaciguat arm, a slight reduction in mean eGFR from baseline was observed, that could be explained by a transient SBP reduction. Six cases of acute kidney injury were observed including one case in placebo arm. The observed incidence was higher in the runcaciguat arm (2.7%) than in the placebo arm (1.7%). Except for two cases, the events observed from runcaciguat arm were confounded by dehydration, infection, or cardiac arrhythmia. All patients fully recovered.

There was no evidence for hepatic toxicity in this study in patients with chronic kidney disease.

Taken together, the safety data from this study indicate that runcaciguat was well tolerated. AEs were predominantly mild to moderate, driven by mode of action, amenable to the monitoring as defined for the present clinical trial, and raised no safety concern.

Further detail on the safety data from the CONCORD study is presented in the current Investigator's Brochure (Version 8.0, Section 5.3.3.2).

In view of these results from the CONCORD study, and taking into consideration that the characteristics of the patient populations enrolled in the NEON-NPDR and the CONCORD studies are similar, it can be concluded that the weekly titration and administration of runcaciguat up to 8 weeks of treatment can be considered as safe also for the NEON-NPDR study.

In this study, dose titrations will be confirmed by the investigator after confirmation that the prior dose level was well-tolerated. These confirmations are supported by clear decision criteria, which are provided in Section 6.5.

The risk associated with once-daily treatment of diabetic patients with NPDR with runcaciguat in this study is assessed as low, considering the conservative dose titration regimen. In addition, safety investigations and assessments are in place to support prompt reaction to any potential adverse event, in particular during the early but also during the later period of treatment.

Mild liver enzyme increases (reversible, without bilirubin increase) were reported in the single/multiple dose escalation study in two healthy participants administered once daily doses of 50 mg runcaciguat (Study 18747). The observed serum enzyme increases started prior to study drug administration, were not dose-dependent and potential alternative etiologies were identified (physical activity, viral infection). As a precaution, however, study participants will be monitored for laboratory changes indicating potential adverse effects on the liver (see Sections 8.2.4 and 10.5) and relative stopping criteria are defined in Section 6.5.2.

Taken together, once-daily doses up to 90 mg without initial titration were well tolerated by healthy study participants. Therefore, the target dose of 120 mg, which is to be reached over a 4-step titration spanning 4 weeks, is considered to be appropriate, as discussed in detail in Section 4.3 and confirmed by the experience of the CONCORD study. Potential risks of runcaciguat treatment and implemented mitigation activities are described in Table 2-1.

Table 2-2 Risk assessment for the study intervention runcaciguat

Potential risk of clinical significance	Summary of data / Rationale for risk	Mitigation strategy
Hypotension, blood pressure decrease with compensatory tachycardia	Study 18747 in healthy participants: Dose-dependent heart rate increases at single doses ≥ 20 mg interpreted as compensatory heart rate increase in response to vasodilation. Dose-dependent decrease in diastolic and systolic blood pressure after single and multiple doses ≥ 50 mg	Risk communication in IB / ICF Clinical Study design: Individual up-titration schedule incl. modification/discontinuation criteria Monitoring of blood pressure, heart rate Document and assess adverse events closely as AESI
Liver enzyme elevation	Study 18747 in healthy participants: Transient asymptomatic transaminase increases observed in two participants (ALT peak 8.6 x ULN, AST peak 3.6 x ULN, GLDH) without increase of bilirubin. Fully recovered without specific therapeutic intervention Concomitant CRP increase suggestive of infection as potential alternative cause	Risk communication in IB / ICF Clinical Study design: Exclusion of participants with liver failure Monitoring of liver function and definition of stopping criteria Document and assess adverse events closely as AESI
Impairment of renal function	Nonclinical pharmacology Decrease in arterial blood pressure may result in transient decrease in renal perfusion and consecutive glomerular filtration rate. In rats, a transient reduction of urine volume, and urine electrolytes was observed	Risk communication in IB / ICF Clinical Study design: Exclusion of participants with severe renal impairment (eGFR < 30 mL/min) Monitoring of blood pressure Monitoring of serum chemistry for renal function (creatinine, eGFR), serum electrolytes Individual dose titration

AESI = adverse event of special interest; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = c-reactive protein; eGFR = estimated glomerular filtration rate; GLDH = glutamate dehydrogenase ; IB = investigator's brochure; ICF = informed consent form; ULN = upper limit of normal.

Risks associated with study procedures

The only procedures in this study which may qualify as invasive are fluorescein angiography and blood draws.

The blood volumes drawn at any visit (< 25 mL) are low and generally considered as safe.

Fluorescein angiography is a routine diagnostic intervention in ophthalmology for patients with advanced DR. The main risks of fluorescein angiography include nausea, hypersensitivity reactions and local reactions on the injection site that are mostly mild. Severe hypersensitivity reactions are extremely rare (approximately 1 : 200,000), but have a potential to be fatal. Clinical sites which examine DR patients are experienced with the use of fluorescein angiography and the management of adverse reactions.

In summary, the risks associated with the study procedures can be viewed as low.

Risks associated with assignment to the placebo arm

At present, ranibizumab and aflibercept are approved therapies for DR of any stage in the US, including moderate to severe NPDR. In the EU, no pharmacologically active product is presently approved for treatment of NPDR. Both ranibizumab and aflibercept are invasive treatment options, administered by intravitreal injection. As NPDR is often asymptomatic, the inconvenience of such an invasive approach results in a low acceptance by patients and physicians, even in territories where it is approved. Consequently, regular ophthalmologic monitoring remains the standard of care for NPDR, even where intravitreal anti-VEGF treatment is available. Therefore, assignment of patients in this study with frequent ophthalmology examinations to the placebo arm does not represent a deviation from the standard of care.

Risks associated with inclusion of women of child-bearing potential

The reproductive toxicity of runcaciguat was investigated in rats and rabbits. In embryofetal development studies in both species, maternal toxicity was observed at exposures similar to the anticipated human exposure. At the corresponding doses, increased rates of embryonal loss (resorptions) were noted in rats and malformations were observed in rabbits.

Women of child-bearing potential may participate in this clinical study if they have a negative pregnancy test at screening, are not breast feeding and if they consent to use highly effective contraception, as specified in the inclusion and exclusion criteria (Sections 5.1 and 5.2). If, despite these precautions, a female study participant becomes pregnant, study intervention will be permanently discontinued (Section 7.1).

With the use of highly effective contraception, i.e. methods that can achieve a failure rate of less than 1% per year when used consistently and correctly (CTFG 2014), together with regular pregnancy testing, the risk of inadvertent pregnancy in the participants is considered to be low. Therefore, in line with ICH guidance M3(R2) (ICH 2009) and with the CTFG recommendations on contraception and pregnancy testing in clinical trials (CTFG 2014). inclusion of women of child-bearing potential in this clinical study is justified.

Risks associated with the COVID-19 pandemic situation

This clinical study is conducted as an outpatient study at sites that have procedures in place to minimize the risk of contagion at sites, in line with institutional and governmental guidelines and regulations. In this setting, the risk of contagion attributable to study participation is considered similar to other activities of daily living, depending on the current local pandemic situation.

Diabetes and cardiovascular disease are conditions that are likely to predispose patients to a higher risk of severe course of infection (Ciceri et al. 2020, Robert Koch Institut 2020). On this basis, careful adherence to hygienic standards during study related activities is of high importance.

Based on current knowledge, runcaciguat is not known to interact with the immune system. Therefore, there is currently no indication that incidental infection of study participants with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) would change the individual risk for a severe course of infection. Based on the mechanism of cGMP increase, treatment with runcaciguat may have anti-thrombogenic effects and improve perfusion of the microvasculature. Whether this may result in a beneficial effect in severe courses of

COVID-19 is currently unknown. Based on these considerations, a general withdrawal of participants intercurrently tested positive for SARS-CoV-2 does not seem to be warranted. As for other infectious diseases, individual decisions by the Investigator are more appropriate.

2.3.2 Benefit assessment

Treatment duration of 48 weeks is probably insufficient to result in a meaningful individual benefit, such as a significant decrease in vision-threatening complications. However, obtaining a 2-step DRSS improvement may be associated with an improvement in disease status shown to be beneficial in clinical trials such as the PANORAMA study and Protocol W (Maturi et al. 2021, Wykoff 2020). Whether such change results in an individual functional benefit is yet to be demonstrated.

All patients, including those assigned to the placebo arms, will be under close surveillance with regards to their diabetic retinopathy while participating in this study. The 8-week visit intervals in the study are shorter than the standard intervals for ophthalmology monitoring of patients with moderately severe to severe diabetic retinopathy (Berufsverband der Augenärzte Deutschlands e.V. and Deutsche Ophthalmologische Gesellschaft e.V. 2011, Flaxel et al. 2020, Nationale VersorgungsLeitlinie 2020, Ophthalmologists TRCo 2012). Since the standard therapeutic approach to NPDR without DME consists of regular monitoring, patients assigned to placebo are ensured to have timely surveillance during their participation in the study, similar to the highest levels of standard of care. Progression of DR, including development of DME, would be promptly identified in these patients. This represents a relevant benefit, as it expedites the treatment of vision threatening complications.

3. Objectives and endpoints

The objectives and endpoints for the study are summarized in Table 3-1.

Table 3-1 Study objectives and endpoints

Objectives	Endpoints
Primary objective: Efficacy Establish the proof-of-concept for the efficacy of the sGC activator runcaciguat in the treatment of NPDR.	**Primary endpoint:** • DRSS improvement ≥2 steps at 48 Weeks of treatment in the study eye **Secondary endpoints for primary objective:** • Vision threatening complications at 48 weeks of treatment in the study eye • DRSS improvement ≥2 steps at 24 weeks of treatment in the study eye **Other endpoints for primary objective:** • Change in visual acuity from baseline • Change in leakage area on Fluorescein Angiography • DRSS changes from baseline in the study and fellow eye • Vision threatening complications in any eye up to 48 weeks of treatment
Secondary objective: Safety Investigate the safety and tolerability of runcaciguat in patients with NPDR	**Secondary endpoints for secondary objective:** • Frequency of treatment emergent adverse events **Other endpoints for secondary objective:** • Laboratory parameters • Vital signs • Electrocardiography
Other objectives	**Other endpoints**
Characterize pharmacodynamic effects of runcaciguat in patients with NPDR	• Central retinal thickness • HbA1c • Serum lipoproteins
Characterize pharmacokinetics of runcaciguat in patients with NPDR	• Population pharmacokinetics • Pre-dose (trough) plasma concentrations of runcaciguat by visit
Further investigate the study intervention and similar drugs (e.g. mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to NPDR, (cardio)vascular diseases and associated health problems	• Various biomarkers (e.g. diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

DRSS = Diabetic Retinopathy Severity Scale; HbA1c = Hemoglobin A1c (glycated hemoglobin); NPDR = Non-proliferative diabetic retinopathy

4. Study design

4.1 Overall design

The study is subdivided into two components, as shown in Table 4-1. Part 1 is conducted to provide data for PK/PD analyses in diabetic patients with NPDR and to explore the value of different OCT-A assessments as PD marker in diabetic retinopathy. Part 2 is the main part of this proof of concept study and will be conducted in parallel. Both components follow a similar design – except for the randomization ratio and additional examinations in Part 1. Both study subparts will be evaluated together, to the extent that common data are available and at the same time.

A steering committee consisting of ophthalmologists and diabetologists (masked) is put in place to provide scientific and operational recommendations to the study protocol.

An independent Data Monitoring Committee (DMC) is set up to provide recommendations based on unmasked review of data, if needed.

Table 4-1 Overall study plan

Study part	Main purpose	Overall design
Part 1 PK/PD	PK/PD assessment	Placebo-controlled, double-masked, 2-arm parallel-group design with 2:1 randomization. Total n = 18 Intra-individual weekly dose escalation in 30-mg increments up to 120 mg once daily. Each participant will continue treatment at the individual maximum dose for a total treatment duration of 48 weeks.
Part 2 Proof of concept	Demonstration of proof of concept based on efficacy outcome after 48 weeks of treatment	Placebo-controlled, double-masked, 2-arm parallel-group design with 1:1 randomization. n = 40 per treatment arm Intra-individual weekly dose escalation in 30-mg increments up to 120 mg once daily. Each participant will continue treatment at the individual maximum dose for a total treatment duration of 48 weeks.

4.1.1 Part 1 – PK/PD

In Part 1, the randomized participants will be titrated at weekly visits in 30-mg increments to the target dose of 120 mg QD, or the maximum individually tolerated dose. After the titration period, the individually reached highest dose will be maintained until the end of treatment, for the total treatment duration of 48 weeks, followed by a 4-week safety follow-up period. A total of 18 participants are planned to be randomized into Part 1 (12 active; 6 placebo). A schematic study design for Part 1 is provided in Figure 1–1.

In Part 1, additional safety, PK and PD investigations will be performed during the titration phase as described in Table 1-3. On Visits 2 to 6, participants will remain at sites for 4 hours post-dose. During this time, the pulse rate and the blood pressure will be checked and OCT-A will be used to assess retinal perfusion as PD markers. Blood samples will be drawn for population PK and for PK/PD analyses pre-dose and in two post-dose windows.

4.1.2 Part 2 – Proof of concept

Recruitment, screening, and randomization of participants for Part 2 of the study is independent from Part 1.

Part 2 of the study is planned to follow the same titration and dosing scheme as Part 1.

In Part 2, the participants will be randomized to either placebo (n = 40) or runcaciguat (n = 40). The participants are planned to be titrated at 30-mg increments to the maximum tolerated dose or sham titrated. Each participant will continue treatment for a total treatment duration of 48 weeks, followed by a 4-week follow-up period.

The 24-week and 48-week data together are intended to derive proof-of-concept and may provide information on the durability of the effect.

4.2 Scientific rationale for study design

As of amendment 3, this section was integrated from the Master protocol.

Results from previous Phase 1 studies in healthy as well as renally impaired study participants and from a phase 2 study in patients with chronic kidney disease have demonstrated that runcaciguat given as MR tablets was well tolerated, and support the start of further studies in patients.

Due to the mode of action of sGC activators, and based on preclinical data, it is assumed that sGC activators administered to patients with NPDR can positively influence retinal perfusion and thereby improve fundus morphology and reduce the progression of retinal ischemia and prevent vision-threatening later stages like proliferative diabetic retinopathy (DR) and/or diabetic macular edema (DME).

Efficacy is to be assessed based on the Diabetic Retinopathy Severity Scale (DRSS), the widely accepted standard to assess disease severity and to stage diabetic retinopathy in clinical trials. This scale is based on the presence or absence of disease-specific phenotypes in a defined set of highly standardized 7-field color fundus photographs. The scale was introduced by the Early Treatment of Diabetic Retinopathy Study research group (ETDRS report number 10 1991). A commonly accepted efficacy endpoint in clinical trials is an improvement in DRSS ratings by more than one severity level or step, i.e. so-called DRSS two-step improvement. This has been used as an endpoint in previous diabetic retinopathy development programs resulting in regulatory acceptance (FDA 2019).

Progression rates to vision-threatening events have consistently been shown to be lower in patients with lower DRSS severity (ETDRS report number 12 1991, Maturi et al. 2021, Wykoff 2020). Therefore, an improvement in DRSS indicates a regression of diabetic retinopathy and is associated with a clinically relevant risk reduction of progression towards proliferative retinopathy and other vision threatening complications (Klein et al. 2001).

In previous studies of intra-vitreal anti-VEGF treatments, 2-step DRSS improvements were detected as early as 8 weeks after treatment initiation and reached a maximum after 6 to 12 months of treatment. However, recent clinical trials of oral agents in NPDR failed after treatment periods of up to 24 weeks (e.g. NCT03238963). Therefore, the primary endpoint assessment is planned after 48 weeks of treatment. Additional assessments are planned for DRSS assessment at 12 and 24 weeks of treatment.

Assessment of vision threatening complications as secondary endpoint is planned in addition, to correlate the DRSS-change with a clinical outcome parameter in support of the efficacy assessment in this study.

Participant input into design

A patient advisory board was conducted to

- Identify potential hurdles in the plans for the clinical trial to recruitment, adherence with the study procedures, and patient retention
- Confirm the relevance of the investigated endpoints for patients with diabetic retinopathy (DR)
- Seek input on medical need and relevant study outcomes in NPDR from the perspective of patients with DR

The feedback from the advisory board was duly integrated in the study protocol.

4.3 Justification for dose

As of amendment 3, this section was integrated from Master Protocol.

All study medication will be administered as modified-release formulation, as discussed in Section 2.3.1.

A randomized placebo-controlled double-masked study in patients with chronic kidney disease is currently ongoing and recruiting patients (CONCORD study 18748, EudraCT: 2019-003297-53). This study is exposing participants to the same titration regimen and target dose as the present NEON study, and ongoing safety reviews indicate that this regimen and target dose are well tolerated, as discussed in Section 2.3.1.

Starting dose

As this study is conducted in patients, the number of patients assigned to dose levels that are expected to have no or only marginal effect should be avoided. Therefore, the lowest dose to be tested is a low dose for which consistent PD effects on the cardiovascular system were observed in prior studies(see Section 2.3.1). The 30 mg dose was identified as minimal effective dose with regards to vasodilatory effects (study 18747). At the same time, this dose was very well tolerated in healthy subjects and it is anticipated to be safe and well tolerated in patients with NPDR participating in this study. Therefore, the dose of 30 mg was chosen for the lowest dose of continuous treatment in this study.

The starting dose of 30 mg was confirmed to be well tolerated in the ongoing study of runcaciguat in patients with chronic kidney disease, the CONCORD study 18748.

Dose titration

Daily doses are titrated up to three times by 30-mg increments, to the target dose. Titration is expected to minimize potential cardiovascular adverse effects, based on a pharmacokinetic / pharmacodynamic correlation analysis. In this PK/PD analysis including data from healthy participants taking the MR-formulation of runcaciguat, the changes in diastolic blood pressure

and heart rate were 2.5 times and 3.5 times higher on the first day of dosing compared with repeated dosing, indicating an attenuation to these acute hemodynamic effects. This indicates that titration can be expected to safely achieve higher, presumably more efficacious doses.

The investigator will take an individual decision prior to each titration in each participant after approximately 7 days of treatment at the prior dose level. At this point, steady-state plasma levels should have been reached, considering the plasma half-life of approximately 20 hours. Depending on the safety and tolerability observed, the decision may be to either titrate as planned, to maintain, or to reduce the daily dose. Clear guidance to support the investigator's decisions is provided in Section 6.5.

Weekly dose increments of 30 mg were confirmed to be well tolerated in the ongoing study of runcaciguat in patients with chronic kidney disease, the CONCORD study 18748.

Highest dose

The dose of 120 mg/day was selected to increase potential treatment efficacy with a higher exposure, while keeping the safety profile similar to the previous dose level. Pharmacokinetic modeling and pre-clinical pharmacology data support this hypothesis. The following aspects related to the PK and PD properties of runcaciguat were carefully considered in the selection of the highest dose of 120 mg:

In prior studies in healthy participants, doses up to 90 mg were safe and well tolerated, even when administered without dose-titration. Based on the experience with the sGC stimulators riociguat (Merck Sharp and Dohme 2019) and vericiguat tolerability will likely be significantly improved with a dose titration design, as implemented in this clinical trial. Such a titration design should allow to safely reach higher doses and to fully exploit the pharmacologic activity of runcaciguat.

While the dose-exposure relationship was approximately dose proportional up to a daily dose of 75 mg in healthy participants, $C_{max,ss}$ values were overlapping at daily doses of 75 mg and 90 mg (Study 18747). The observation based on a group comparison with small sample size (n=8 participants per dose step) remains to be confirmed, but it suggests that the risk for over-proportional increases of runcaciguat concentrations at the planned maximum dose of 120 mg per day is very low. With the dose-titration design, appropriate interim evaluations, involving an independent Data Monitoring Committee, are in place for timely detection of any potential residual risk. Based on the results from the renal impairment study 18745, no relevantly higher exposure is to be expected in participants with moderate impairment of renal function (eGFR range 30 to 60 ml/min). Considering the lower permissible eGFR limit of 30 ml/min defined in exclusion criterion 18, the individual dose titration up to a target dose of 120 mg is considered to be appropriate.

The selection of the highest target dose for runcaciguat in this study (120 mg) is further supported by PK/PD modeling performed for the runcaciguat POC study in patients with chronic kidney disease (Study 18748) utilizing the reduction of the urinary albumin-creatinine ratio (uACR) as an efficacy marker. For that study, a translational PK/PD analysis for runcaciguat was performed, linking a population PK/PD model built on the basis of Phase 1 data, to model derived hemodynamic response and efficacy observations, e.g. uACR reduction in the ZSF-1 rat disease model (Petersson and Voelkner 2019). Dose-dependent uACR changes were extrapolated for runcaciguat indicating that with a dose of 120 mg, a slightly higher percentage of patients will achieve the efficacy target of >30% reduction in uACR compared to the dose of 90 mg (Table 4-2).

Table 4-2 CONCORD Study 18748 (CKD): Simulated median outcome in % of treated patients [90% CI]

Dose (steady-state)	**30 mg**	**60 mg**	**90 mg**	**120 mg**
MAP 24 h decrease Percentage < 3 mmHg decrease	61.5 [54-68]	56.5 [47-64]	53.5 [44-63]	52 [42-61]
uACR decrease Percentage > 30 % decrease	61 [52-72]	69 [60-78]	73 [64-82]	75 [65-84]
Percentage >30% uACR decrease AND < 3 mmHg MAP	32.5 [24-40]	33 [24-40]	33 [24-42]	33 [22-42]

CKD = chronic kidney disease; CI = Confidence interval; MAP = mean arterial pressure; uACR = urinary albumin-creatinine ratio
Source: (Petersson and Voelkner 2019)

To substantiate the doses to be used in this clinical study in patients suffering from NPDR, it should be noted that similar efficacious exposures were measured in preclinical CKD and DR disease models, as shown in Table 4-3. Lower EC50 in DR models may partially be attributed to usage of C_{trough} in the STZ DR model vs. $C_{average\ (AUC(0\text{-}24)/24h)}$ in the ZSF-1 CKD model, owing to animal model-related PK-sampling limitations. Similar changes in triglycerides, an established biomarker for sGC-modulation and which were used in both models, support the bridging (Hoffmann et al. 2015). A dose dependent increase of the ERG b wave amplitude values was observed in the STZ DR model. Similarly, a dose-dependent decrease in urinary protein-creatinine ratio was observed in the in the ZSF-1 CKD model.

Table 4-3 PK/PD relationship in animal models of CKD and DR
Model estimates of EC50 with 90% CI

Model	**Observation**	**Day**	**EC50** (mg/l)	**90%CI**
Rat ZSF-1	UPCR	48, 93	13	5.8-27
CKD model	Triglycerides	48, 93	6.2	3.0-13
Rat STZ	ERG b wave amplitude	60	4.7	2.5-9.0
DR model	Triglycerides	60	2.4	1.4-4.1

CI = confidence interval, CKD = chronic kidney disease, DR = diabetic retinopathy, EC50 = plasma concentration of runcaciguat causing half-maximal effect, ERG = electroretinogram, PD = pharmacodynamics, PK = pharmacokinetics, UPCR = urinary protein-creatinine ratio

Based on these nonclinical experiments, the efficacy of runcaciguat is anticipated to be higher at the target dose of 120 mg once daily than at 90 mg once daily, but still tolerable in terms of cardiovascular effects.

Conclusion

Overall, the selected dose range from 30 mg to 120 mg is expected to deliver significant efficacy while being safe and well tolerated under individual titration dosing. Early signs and symptoms of e.g. hypotension will be closely monitored during the titration phase and overall safety will be assessed during the whole study duration with additional review by the DMC.

A placebo-treated reference group is included in order to allow a more reliable evaluation of efficacy and safety.

4.4 End-of-study definition

As of amendment 3, this section was integrated from Master Protocol.

The end of the study as a whole is defined as the date of the last visit of the last participant globally.

A participant is considered to have completed the study if he/she has completed the last visit of the study .

5. Study population

The study will be performed in a representative NPDR study population reflecting the composition of study populations in later development stages. Specifically, participants should show typical fundus alterations as described in the DRSS criteria for moderately severe and severe NPDR without DME in need of treatment and no previous experience of anti-VEGF treatment. This corresponds to DRSS Levels 47 and 53, which need to be confirmed by an independent reading center, in at least one eye.

Treatment of NPDR with runcaciguat targets the retina, which is being investigated for signs of efficacy in this clinical trial. In order to be able to examine the retina appropriately at screening and during the study, participants whose eyes have anomalies that interfere with protocol-required examinations are excluded.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥ 18 of age inclusive, at the time of signing the ICF.

Type of participant and disease characteristics

2. Moderately severe to severe NPDR in the study eye: DRSS levels 47 or 53
3. Diabetes type 1 or 2
4. BCVA ETDRS letter score in the study eye of ≥ 69 letters (approximate Snellen equivalent of 20/40 or better)
5. Refraction with a spherical equivalent from -6 dpt to +5 dpt

Sex and contraceptive/barrier requirements

6. Male and/or female

   Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Male participants must agree to use condoms from signing of ICF signature until the end of the study period. Female participants must be either of non-child bearing potential or using a highly effective method of contraception (See Section 10.4). This applies from the time of ICF signature until the end of the study period.

Informed consent

7. Capable of giving signed informed consent as described in Section 10.1.3 which includes compliance with the requirements and restrictions listed in the informed consent form and in this protocol

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Uncontrolled diabetes mellitus as defined by HbA1c > 11.0% at screening
2. Eye disease that significantly interferes with fundus examinations in the study eye
3. Glaucoma in the study eye
4. Dilatation of the pupil < 5 mm in the study eye
5. Ocular inflammation (including trace or above) or conjunctivitis at screening, or history of uveitis in the study eye
6. Presence or history of macular edema involving the center of the macula (defined as the area of the center subfield on OCT) in the study eye with visual impairment or in need of treatment with anti-VEGF, immediately or anticipated within the next 3 months, by judgement of the investigator or with OCT central subfield thickness above gender specific thresholds, measured including Bruch's membrane, ≥305 µm in women, ≥ 320 µm in men, as provided by the central reading center
7. Any kind of neovascular growth in the study eye, including anterior segment neovascularization
8. History of or current retinal vascular or neurodegenerative disease in the study eye, including hypertensive retinopathy Grade III or IV
9. Only one functional eye
10. Symptomatic arterial occlusive disease, including peripheral artery occlusive disease, coronary heart disease (e.g. angina pectoris, myocardial infarction), cerebrovascular disease (e.g. transient ischemic attack, stroke), clinically significant aortic stenosis, or renal artery stenosis, within 6 months before the screening visit
11. Deep venous thrombosis within 6 months before the screening visit

12. Thromboembolic events (e.g. acute arterial embolism, pulmonary embolism or stroke) within 6 months before the screening visit
13. Heart failure New York Heart Association class III or IV
14. History of clinically relevant cardiac arrhythmia (e.g. atrial fibrillation, atrioventricular block grade II and III, Wolf-Parkinson-White Syndrome, Sick Sinus Syndrome, bradycardia < 45 bpm at rest, tachycardia > 100 bpm at rest)
15. Arterial hypotension with systolic blood pressure < 100 or diastolic blood pressure < 60mmHg;
16. Uncontrolled arterial hypertension, defined as systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg
17. ALT or AST above 3 x ULN or bilirubin ≥ 1.5 ULN at screening, known ascites
18. Estimated glomerular filtration rate (eGFR CKD-EPI) below 30 ml/min/1.73 m^2 at screening
19. Known pulmonary hypertension associated with idiopathic interstitial pneumonia
20. Relevant allergy or hypersensitivity to drugs or excipients administered as part of this study, e.g. hereditary galactose intolerance, complete lactase deficiency or glucose-galactose malabsorption, iodine allergy
21. Any finding in the medical examinations or medical history giving, in the opinion of the Investigator, reasonable suspicion of a disease or condition that makes treatment with the investigational drug unadvisable, or that might affect interpretation of the results of the study or render the patient at high risk for treatment complications

Prior/concomitant therapy

22. Any prior systemic anti-VEGF treatment or IVT anti-VEGF treatment in the study eye
23. Any prior intraocular steroid injection in the study eye
24. Any prior grid or focal laser photocoagulation within 500 microns of the foveal center or any prior PRP in the study eye
25. Any intraocular eye surgery within a period of 3 months prior to randomization in the study eye
26. Yttrium-Aluminum-Garnet laser treatment performed within 28 days before screening, in the study eye
27. Continued use of any prohibited medication during the exclusion period from one to two weeks before first study drug administration throughout the treatment period (see Table 6-3)
28. Use of nitrates or NO donors (such as amyl nitrate) in any form including topical; PDE5 inhibitors, non-specific PDE inhibitors within 1 week or less than 5 half-lives (whichever is longer) before first study drug administration
29. Use of sGC stimulators such as riociguat within 1 week or less than 5 half-lives (whichever is longer) before first study drug administration
30. Combination use of angiotensin converting enzyme-inhibitor together with angiotensin receptor blocker

Prior/concurrent clinical study experience

31. Participation in an interventional clinical study within 30 days prior to screening visit that involved treatment with any drug (excluding vitamins and minerals) or medical device
32. Previous assignment to treatment or randomization during this study

Other exclusion criteria

33. Breastfeeding or positive pregnancy test (ß-hCG in serum or urine)
34. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site), employee of Bayer AG or affiliates

5.3 Lifestyle considerations

No study specific lifestyle restrictions are required. Participation in this study does not require modifications of lifestyle. Participants should follow their usual lifestyle, as part of their diabetes management plan.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once. In any case, the investigator must ensure that the repeated screening procedures do not expose the participant to an unjustifiable health risk. For re-screening, the participant must re-sign the ICF, even if it was not changed after the participant's previous screening.

Participants who failed screening before protocol Amendment 3 was implemented may be re-screened in view of the changes in inclusion/exclusion criteria.

Rescreened participants will be assigned a new participant number.

In case of abnormal or implausible results, which may be caused by intercurrent diseases, short-term treatable conditions, other temporary health disorders (e.g. acute infection, laboratory changes, blood pressure outside defined range), or inappropriate circumstances (e.g. inadequate rest when required, hemolysis) the investigator may decide to repeat the respective screening parameter(s) twice.

5.5 Criteria for temporarily delaying randomization / study intervention administration

If a participant is otherwise eligible, acute intercurrent conditions may allow to postpone start of study intervention in a participant to a time when the condition has resolved. Under these circumstances, the screening period may be extended to 6 weeks.

5.6 Selection of the study eye

Only one eye will be designated as the study eye in every participant. For participants who meet eligibility criteria in both eyes during the screening phase, the eye without DME and with the higher DRSS should be selected. If both eyes have the same score, the eye with the clearest lens and ocular media will be selected. If there is no objective basis for selecting the study eye, factors such as ocular dominance (better focus ability), other ocular pathology and participant preference should be considered in making the selection. The final selection will be done by the investigator at baseline and must not be changed during the course of the study.

6. Study intervention(s) and concomitant therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study interventions administered

6.1.1 Study interventions

In this study, several doses of runcaciguat or placebo, will be given to the NPDR participants, as shown in Table 6-1. Participants will be treated following an intra-individual dose-titration design with three titration steps.

Tablets containing runcaciguat and corresponding placebo are identical in appearance (size, color, shape). In order to remain masked, study interventions will be packaged in bottles labeled with a unique number which will be pre-printed on each bottle.

The following doses are envisaged for the intra-individual dose titration steps with four dose levels.

Table 6-1 Study interventions

Arm name	Runcaciguat (BAY 1101042)	Placebo
Intervention name	Runcaciguat (BAY 1101042)	Placebo
Type	Active drug	Placebo
Dose formulation	Modified-release tablets	Tablet
Unit dose strength(s)	15 mg	*not applicable*
Dose levels (once daily)	30 mg 60 mg 90 mg 120 mg	*not applicable*
Route of administration	Oral	Oral
Use	Experimental	Placebo
Packaging and labeling	Study intervention will be provided in high-density polyethylene bottles closed with child-resistant screw cap. Each bottle will be labeled as required per country requirement.	

Titrated oral doses of runcaciguat or matching placebo will be given once a day on top of respective standard of care treatment before, during or closely after the first meal in the morning. The study intervention (tablets) are not to be broken, halved or crushed, they should be swallowed whole with a glass of water. If a participant has missed a dose or forgotten to take the medication and > 16 hours have passed from the regular scheduled time, the dose should be skipped and the next dose should be taken promptly the next day in the morning.

- On Visit days (except Visit 7) study intervention is to be administered at site after blood draws.
- On non-visit days and on the day of Visit 7 study intervention is to be taken in the morning at home.

6.1.2 Medical devices

No sponsor manufactured devices or devices manufactured for the sponsor are used in this study. Other medical devices (not manufactured by or for sponsor) provided for use in this study are:

- ECG machine for central ECG reading

Instructions for medical device use are provided in the corresponding manual. All device deficiencies (including malfunction, use error and inadequate labelling) that caused or could have caused a SAE to a study participant shall be documented and reported by the investigator throughout the clinical investigation and appropriately managed by the sponsor.

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

For any device deficiencies related to a study participant AE or SAE: the investigator should complete the AE CRF and safety reports (complementary pages) in addition to the Medical Device Incident (MDI) CRF.

6.2 Preparation / handling / storage / accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants randomized in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or the head of the institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records). Drug receipt, reconciliation and destruction information on the study sites will be captured in the IWRS.

Further guidance and information for the final disposition of unused study interventions are provided in the Investigator Site File.

6.3 Measures to minimize bias: Randomization and masking

All participants will be centrally assigned to randomized study intervention using IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Participants will be randomized to either Placebo or Runcaciguat. Randomization will be stratified by baseline DRSS score (47 or 53). In Part 1, the randomization ratio will be 2:1 runcaciguat : placebo and in Part 2 it will be 1:1.

Potential bias will be reduced by the use of central randomization via the IWRS. The level of masking is presented in Table 6-2.

Table 6-2 Level of masking – Part 1 and 2

	Masked	Unmasked
Participant	●	
Care provider	●	
Investigator	●	
Outcomes assessor	●	
Sponsor study team (except Bioanalytical / PK group)	●	
Sponsor Bioanalytical / PK group		●

PK = pharmacokinetics

The IWRS will be programmed with instructions on how to break / unmask a participant's randomized treatment. In case of an emergency, the investigator has the responsibility for determining if unmasking of a participant's intervention assignment is warranted. If the investigator is unavailable, and a treating physician not associated with the study requests emergency unmasking, the emergency unmasking requests are forwarded to the emergency medical advice 24 hours / 7 day service. Participant safety must always be the first

consideration in making such a determination. If the investigator decides that unmasking is warranted, the investigator should make every effort to contact the sponsor prior to unmasking a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unmasked, the sponsor must be notified within 24 hours after the unmasking. Date and reason for the unmasking must be recorded in the source documentation and case report form, as applicable.

Bioanalytics and pharmacometrics staff will be unmasked according to Sponsor's standard operating procedures. Pharmacometrics analysis and report will be done under a separate cover. Bioanalysis and pharmacometrics evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain masking of the study team, e.g. data will be stored separately, and members of the study team will not have access to the unmasked data.

The primary outcome measure, DRSS, will be assessed centrally by a masked reading center, in order to have a standardized assessment throughout study sites and in order to minimize potential bias.

6.4 Study intervention compliance

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets during the site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded. Unopened and undamaged bottles of returned study intervention may be re-dispensed to the same participant.

A record of the quantity of tablets dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

A system to remind the participants of study intervention self-administration and to document the intake may be used. Such a system may consist of a mobile application and web portal components. Study drug intake may be documented by the participants by scanning a barcode with a mobile phone using a dedicated smartphone application. These scans are recorded via a web-portal. An alternative methodology, e.g. a paper based diary, may be used for documenting study intervention intake. If study intervention intake has not yet been documented, the participants may be reminded to take the study intervention, e.g. by telephone, email, push-notification, text message, at defined time points prior and after the scheduled time of study intervention intake.

IWRS will be used for drug accountability on a patient basis. Drug returns, reconciliation and destruction information will be captured in the IWRS.

On all visit days during the treatment period, plasma samples will be taken to determine the concentrations of the study intervention.

Taken together, these measures are deemed appropriate to support participants adherence and to detect participants that are systematically non-adherent.

6.5 Dose modification

The doses to be administered are provided in Table 6-1.

In exceptional cases, participants may request to reschedule visits. Visits 3, 4, and 5 may be shifted by no more than one day to an earlier or later timepoint. Actual dates of dose titrations may be shifted as a result. The treatment duration at the subsequent dose level may be shortened or extended by one day to compensate the effect on the total treatment duration.

6.5.1 Intra-individual dose-titration decisions

Doses will be titrated on a weekly basis from 30 mg to 60 mg to 90 mg and to 120 mg once daily. The decision to titrate to the next higher dose will be taken by the investigator upon availability of all relevant safety data on study days 8, 15, and 22. The decision to increase the dose should not be taken in presence of any condition where dose titration is deemed unadvisable by the investigator.

The investigator should not confirm the dose titration but, instead, **maintain** the dose if systolic blood pressure (SBP)

- SBP ≥ 90 and <105 mmHg, or
- >30 mmHg decrease from previous visit (even if SBP ≥ 105)

The investigator should not confirm the dose titration but rather **reduce** the dose if the participant previously experienced:

- A serious adverse event considered to be related to treatment with runcaciguat.
- A severe adverse event considered to be related to treatment with runcaciguat.
- Relevant hypotension (e.g. symptoms of hypotension or SBP < 90 mmHg or both).

Restart with last well-tolerated dose after ≥48 hours if SBP recovers above 90 mm Hg and symptoms resolve within 24 hours.

If there is evidence for clinically relevant side effects (e.g. dizziness, diarrhea), the investigator can decide to maintain the dose at its current level or, if side-effects are considered as sustained intolerability or safety risk, even lower the dose back to the previous dose level (the dose modification and the reason for it have to be captured accordingly in the eCRF).

For each participant, up to two dose reductions are permissible with continued study participation at any point of the clinical study. The final reduced dose level should be maintained until the end of the study.

Please refer to Section 7.1.2 for temporary treatment discontinuations.

6.5.2 Stopping rules (study level)

In addition to the general criteria as listed in Section 10.1.9, the following criteria result in an immediate stop of dosing and will result in a temporary halt of the study:

- Any relevant information, from this trial or from outside of this trial, indicating a relevant deterioration of the benefit-risk ratio. In particular, consistently observed SAEs or severe drug-related AEs will be thoroughly assessed.
- Safety findings observed by DMC which indicate unacceptable pharmacological effects, reasonably attributable to runcaciguat

Resuming the trial after a temporary halt requires an approved substantial amendment.

For discontinuation of study intervention for individual study participants see Section 7.1.

6.6 Continued access to study intervention after the end of the study

No treatment with study medication will be provided after the end of the planned treatment period or after early withdrawal of treatment.

6.7 Treatment of overdose

An overdose is defined as any occasion when participants have been exposed to more tablets than the maximum number foreseen per intake and/or per day in the protocol (accidentally or intentionally).

There is no known specific treatment or antidote for an overdose with runcaciguat. Accordingly, overdose of the study intervention should be treated as clinically indicated based on symptoms and signs. Due to the pharmacological profile of runcaciguat, cardiovascular effects are to be expected in case of overdose. If symptoms develop after the overdose, any therapy that becomes necessary has to be guided by the predominant symptoms. Participants have to remain under medical supervision until all relevant adverse effects have subsided.

Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent, or if this resulted in clinical signs or symptoms diagnosed as AE/SAE by the investigator.

In the event of an overdose, the investigator should:

- Contact the sponsor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until runcaciguat can no longer be detected systemically (at least 3 days).
- Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator based on the clinical evaluation of the participant. The investigator may consult the Medical Monitor as needed.

6.8 Concomitant therapy

Only drugs prescribed by a health care professional are permitted while the study is ongoing. Exceptionally, short-term intake of paracetamol/acetaminophen ≤ 2000 mg/day is acceptable. Such intake is to be recorded (see below).

Concomitant medications are to be recorded in the eCRF, in particular international non-proprietary names, dosing frequency, individual dose, route, indication are to be documented. This includes anti-diabetic treatments.

Participants are requested to record the dose of antidiabetic treatments that are dosed variably, e.g. insulin, in a diary along with glycemia test results. Other concomitant medications taken intermittently should be documented in the same diary.

Participants with HbA1c concentrations outside of the recommended corridor should be instructed to contact their diabetologist to seek support in achieving better diabetic control.

The medications provided in Table 6-3 are not allowed for use during treatment with the study intervention and one or two weeks prior to start of treatment.

Table 6-3 List of prohibited medications

Drug class	Drug	Last permissible intake before start of study medication
Inducers of metabolizing enzymes	Artemisinin	>2 weeks
	Avasimibe	>2 weeks
	Bosentan	>2 weeks
	Carbamazepine	>2 weeks
	Enzalutamide	>2 weeks
	Efavirenz	>2 weeks
	Etravirine	>2 weeks
	Mitotane	>2 weeks
	Modafinil	>2 weeks
	Nafcillin	>2 weeks
	Phenobarbital	>2 weeks
	Phenytoin	>2 weeks
	Primidone	>2 weeks
	Rifabutin	>2 weeks
	Rifampicin	>2 weeks
	St. John's Wort *Hypericum perforatum*	>2 weeks
Inhibitors of metabolizing enzymes	Fluconazole	>2 weeks
	Fluvoxamine	>2 weeks
	Fluoxetine	>2 weeks
	Probenecid	>1 week
	Ticlopidine	>2 weeks
	Valproic acid	>1 week
PDE inhibitors (non-specific, PDE5)	Theophylline	>1 week
	Dipyridamole	>1 week
	Sildenafil	>1 week
	Vardenafil	>1 week
	Tadalafil	>1 week
sGC stimulators	Riociguat	>1 week
	Vericiguat	>1 week
Nitrates or NO donors	Amyl nitrate	>1 week

NO = nitric oxide; PDE = phosphodiesterase; PDE5 = phosphodiesterase 5; sGC = soluble guanylyl cyclase

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. Discontinuation of study intervention and participant discontinuation/withdrawal

7.1 Discontinuation of study intervention

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, an End-of-Treatment visit should be performed in line with Visit 15. The participant remains in the study for continued assessment of study outcomes following the visit schedule in section 1.3.

Unscheduled visits may be performed as deemed appropriate by the investigator, in particular in case of withdrawal because of an adverse event.

Participants *must* be withdrawn from the *study intervention* for any of the following reasons:

- Increases in transaminases as described in Table 10-3 (confirmed by analysis of two blood samples; additional laboratory examinations may be performed if necessary):
- Safety concerns for a participant by the investigator or the sponsor, e.g. due to obvious non-compliance.
- Pregnancy (see Section 8.3.5 for details)
- Temporary discontinuation exceeding 14 consecutive days or 21 days overall

Participants *may* be withdrawn from the *study intervention* for any of the following reasons:

- Repeated incidents of relevant hypotension or tachycardia
- Repeated temporary discontinuation of study intervention
- Vision threatening complication or progression to PDR

Necessity to withdraw the participant from the study will be assessed case by case by the investigator.

7.1.2 Temporary discontinuation

Treatment should be withheld temporarily if any of the following conditions apply:

- Relevant hypotension or tachycardia considered to be related to treatment with runcaciguat, e.g. SBP < 90 mmHg with symptoms of hypotension persisting > 24 hours, or AE indicating non tolerability with regard to mode of action (e.g. severe dizziness, orthostatic dysregulation, syncope). In case of additional, subsequent temporary discontinuation(s), the investigator should consider whether a permanent discontinuation of the study intervention is appropriate.
- Temporary discontinuation for drop in eGFR from baseline:
  If the participant presents a decrease of eGFR ≥ 40% compared with baseline, the investigator should temporarily discontinue study intervention and perform confirmatory laboratory examinations. If eGFR decrease by ≥ 40% is confirmed, study intervention should be discontinued permanently (see Section 7.1.1). If the re-assessed laboratory result indicates a decrease in eGFR <40% from baseline, study intervention may be re-started at the same dose as before this temporary discontinuation, in line with section 7.1.3. The investigator should consider a close observation of the case (e.g. repeated laboratory investigation of renal function).
- The investigator may decide to temporarily discontinue treatment for other reasons if deemed appropriate for the safety and well-being of the participant.

A temporary discontinuation exceeding 14 consecutive days or 21 days overall results in a permanent discontinuation (see section 7.1.1)

7.1.3 Re-challenge / re-start of study intervention

Participants who permanently discontinue the study intervention must not be re-challenged.

After a temporary discontinuation, study intervention intake may be resumed as follows:

- ≤ 48 hours since last intake:
  resume intake at same dose as prior discontinuation
- > 48 hours to < 7 days (168 hours) since last intake:
  resume intake at one titration step below dose prior to discontinuation. Titration to target dose at the discretion of the investigator, as described in Section 6.5.
- > 7 days (168 hours) since last intake:
  resume intake with complete re-titration of study intervention, as described in Section 6.5.

The dose-titrations after temporary discontinuation should follow the same procedures as described for the initial dose titrations. This may result in conducting one or more unscheduled visit/s, analogously to Visit 4. Additional assessments and examinations may be performed, depending on the reason for the temporary discontinuation. Titration steps may be extended, e.g. for operational reasons, to the next scheduled visit.

The final dose at the end of re-titration should not exceed the dose at which the decision for temporary discontinuation was taken, but the dose may be lower than prior to the temporary discontinuation. This also includes cases of prior dose reduction.

7.2 Participant discontinuation / withdrawal from the study

Participants *must* be withdrawn from the s*tudy* for any of the following reasons:

A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This includes cases where, in the investigator's opinion, continued participation in the study would be harmful to the participant's well-being. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, Visit 15 should be conducted as early discontinuation visit, followed by safety follow-up (Visit 16) as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Participants *may* be withdrawn from the *study* for the following reasons:

- Non-compliance with the study conditions or instructions from the study team.

7.3 Lost to follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1, Appendix 1.

8. Study assessments and procedures

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Individual pharmacokinetic results could unmask the study and will not be reported to investigative sites or other masked personnel until the study has been unmasked.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

After signing an informed consent, participants will be invited to a screening visit, Visit 1, to evaluate their eligibility for this study. Eligible patients with NPDR who meet all of the inclusion criteria and none of the exclusion criteria, will be randomized to treatment with either runcaciguat or placebo. During the treatment period, participants will be monitored for adverse events and concomitant medication, and undergo the assessments outlined in the SoA, Section 1.3.

The treatment period comprises Visits 2 to 15 (Week 1 to Week 49), the End-of-Treatment visit.

An End-of-Study visit, Visit 16, is planned approximately 28 days after last administration of study drug.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 300 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.1.1 Ophthalmology assessments

Unless specified otherwise, ophthalmology examinations will be done for both eyes.

Source data of all ophthalmology examinations will be archived at the site. This includes data and images sent to the central reading center for evaluation.

8.1.1.1 Color fundus photography (CFP)

The anatomical state of the retinal vasculature will be evaluated by an ophthalmologist from posterior segment (Section 8.1.1.6) examination and CFP. All digital CFP images need to be taken by a certified technician following an acquisition protocol for ETDRS 7-Fields of the central reading center at the visits indicated in the SoA.

All CFPs will be transmitted to the **central reading center** for ETDRS diabetic retinopathy severity scale (DRSS, Table 8-1) grading and storage. The images of the screening visit of both eyes will be used as part of the eligibility assessment regarding the severity of diabetic retinopathy.

CFPs may, in addition, be evaluated for additional, exploratory, endpoints. This may include assessment of microaneurysm turnover (Nunes et al. 2009) or measurement of diameters of retinal vessels as described previously (Lundberg et al. 2013). This may involve transmission of CFP to additional central reading centers.

Table 8-1 ETDRS final retinopathy severity scale (for individual eyes)

Level	Severity
10	DR absent
20	Microaneurysms only
35	Mild NPDR
43	Moderate NPDR
47	Moderately severe NPDR
53	Severe NPDR
61	Mild PDR
65	Moderate PDR
71	High-risk PDR
75	High-risk PDR
81	Advanced PDR: fundus partially obscured, center of macula attached
85	Advanced PDR: posterior fundus obscured, or center of macula detached
90	Cannot grade, even sufficiently for level 81 or 85

ETDRS = Early Treatment Diabetic Retinopathy Study; DR = diabetic retinopathy; NPDR = non-proliferative DR; PDR = proliferative DR;
Modified from (Staurenghi et al. 2018)

8.1.1.2 Best corrected visual acuity (BCVA)

Visual function will be assessed using a modified ETDRS protocol starting at 4 meters (AREDS 1999). Visual Acuity examiners must be certified to ensure consistent measurement of BCVA.

8.1.1.3 Fluorescein angiography (FA)

The anatomical state of the retinal vasculature of the study eye (transit eye) and the fellow eye (non-transit eye) will be evaluated by FA. All FAs will be conducted by a certified technician following an acquisition protocol of the reading center. The angiographic images will be evaluated by a study ophthalmologist for individual safety decisions, and by the central reading center to support the DRSS assessment. All FA images will be sent to the central reading center for evaluation.

At screening a standardized set of FA images with the study eye as transit eye will be sent to the reading center for evaluation and eligibility assessment.

8.1.1.4 Optical coherence tomography (OCT)

Structural OCT will be performed preferably by using spectral domain devices. The specific device models accepted for the study will be defined by the reading center. OCTs will be performed by certified technicians following an acquisition protocol of the reading center as scheduled in the SoA for local safety assessment. Newly found clinically relevant pathologies should be reported as adverse event. All obtained images will be sent to the reading center for evaluation at the visits stated in the SoA.

At screening a standardized set of OCT images will be sent to the reading center for evaluation and eligibility assessment.

OCT Central Subfield Thickness (CST) will be analyzed by the reading center to guide the investigator relating to Exclusion criterion 6, which excludes participants with macular edema requiring treatment. The thresholds depend on gender (+15 µm in men) and on the inclusion or exclusion of Bruch's membrane by the OCT-devices segmentation algorithm.

The reference threshold for the CST will be determined by the central reading center using the Heidelberg-Engineering segmentation algorithm as a standard, which includes Bruch's membrane. For other OCT-devices, equivalent CST values will be provided by the central reading center.

The CST thresholds used are:

- ≥305 µm in women, ≥ 320 µm in men

8.1.1.5 Optical coherence tomography angiography (OCT-A)

For Part 1, OCT-A is mandatory, for Part 2, OCT-A is optional. In any case, the OCT-A needs to be performed by a certified technician following an acquisition protocol of the reading center as scheduled in the SoA. The specifications of this OCT-A can be found in the acquisition protocol of the Reading center. Images obtained via OCT-A will be sent to the Central Reading Center for evaluation.

The following parameters will be quantified and assessed prior to start of treatment with the study intervention, after the first study intervention administration and at steady state treatment with each of the dose levels as shown in the SoA (Section 1.3). For the following vascular regions in the central 3 mm x 3 mm will be assessed separately to the extent feasible:

- Superficial retinal layer
- Intermediate retinal layer
- Deep retinal layer
- Retina (cumulative, all layers combined)

The following parameters will be assessed for these vascular regions, as applicable:

- Perfusion density
- Vessel density
- Foveal avascular zone

Cross-sectional macular full depth line scans acquired with an experimental software used for positioning the scan lines and to average the information obtained for each scan will be analyzed for

- Total perfusion
- Vessel density

8.1.1.6 Slit lamp biomicroscopy (anterior and posterior segment)

The slit lamp examination (anterior and posterior segment) will be performed according to local medical practice and applicable medical standards at the site as stated in the SoA. Abnormal findings are to be recorded in the eCRF as either medical history or adverse event as applicable.

8.1.1.7 Tonometry (intraocular pressure (IOP) measurement)

Intraocular pressure is to be measured with any locally approved non-contact tonometer.

In case that there is no non-contact tonometer available at the site, applanation tonometry (Goldmann, Tonopen or other locally approved alternatives) may be used. In any case, where both methods are available the non-contact method is to be used.

The same method of IOP measurement must be used throughout the study for each individual participant. Values and measuring type are to be recorded in the eCRF.

8.1.2 Vision-threatening complications

Vision-threatening complications are defined as occurrence of any of the following adverse events:

- PDR
- Any ocular neo-vascularization

- Center-involved (ci) (central ETDRS subfield) DME
- Drop of BCVA of 10 letters or more from baseline

The assessment will be continued after treatment discontinuation if possible.

Treatment of the vision threatening complication should follow local standards and guidelines, i.e. treatment of ci DME with anti-VEGF or other appropriate measures, at the discretion of the investigator.

8.1.3 Albuminuria

Albuminuria evaluations were removed from the protocol via Amendment 3.

8.1.4 Visual function questionnaire (VFQ-25)

VFQ-25 evaluations were removed from the protocol via Amendment 3.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examination

A physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the study site and will cover at least the organs of the cardiovascular, respiratory and abdominal systems. Measuring the body temperature will be included.

Abnormal physical examination findings are recorded either as medical history or as AEs in the eCRF.

Body weight will be measured by a member of the investigator's team under the following conditions:

- Participant in light clothing without shoes after having emptied the bladder
- Analogue or digital scale physician scale, measurement precision 0.1 kg

Height will be taken at screening only.

The BMI will be calculated by Data Management on the eCRF based on weight and height.

8.2.2 Vital signs

Pulse rate and systolic / diastolic blood pressure will be measured repeatedly pre-dose, and on the time points provided in the SoA (Section 1.3) after the initial dose and at steady state of each dose-level.

Vital signs will be measured in a supine or semi-supine position after ≥ 5 minutes rest. Vital signs should always be measured before blood draws when scheduled at the same time point. Blood pressure and pulse rate measurements will be performed with a completely automated device.

8.2.3 Electrocardiograms

ECGs are recorded with a computerized 12-lead ECG device after the participants rested for at least 5 minutes in supine position (small pillow under head allowed). These ECGs are evaluated by the investigator for safety signals. ECGs will be transferred to central reading center for evaluation.

During Part 1 up to study Visit 6 (inclusive), triplicate ECG tracings are to be recorded. These triplicate tracings may be transferred to a central ECG reading center for later QT evaluation. The results of the QT evaluations may be reported separately.

For part 2 single ECGs will be recorded and transferred to a central ECG reading center for evaluation.

The following ECG parameters will be determined and transferred to the database:

- Ventricular rate, PR interval, QRS-duration, QT interval.

The QT interval will also be corrected for the heart rate using QTcB and Fridericia's method, i.e. by dividing the observed QT interval by the cube-root of RR:

$$\mathrm{QTcF} = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}$$

8.2.4 Clinical safety laboratory assessments

See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within one month after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or the medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded.

Clinically relevant changes, especially when resulting in a decision against dose titration, are to be documented as AE, with details on the respective lab results provided in the comment field of the AE page in the eCRF.

In case of clinically relevant abnormal laboratory results, the investigator has the discretion to perform unscheduled repeat laboratory examinations earlier than at the intervals provided in the SoA in Section 1.3. These unscheduled examinations should be processed by the central lab to ascertain that the data will be included in the database. At the investigator's discretion, additional laboratory parameters may be investigated and samples may be processed by the local lab. In case of relevant liver enzyme elevation (see also Section 10.5), the investigator should perform a repeat serum chemistry panel 2 times per week (including serum transaminases [AST and ALT] and serum bilirubin), frequency of retesting can decrease to once a week if laboratory abnormalities decrease and participant is asymptomatic.

Estimation of glomerular filtration rate (eGFR)

eGFR will be calculated using CKD-EPI formula, using the serum creatinine concentration measured at screening (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013). The calculation will be done by the central laboratory. In case of a decrease by ≥ 40%, a critical alert will be provided to the investigator, as it may represent a reason for treatment discontinuation, as described in Section 7.1.2.

8.2.5 Pregnancy testing

During the initial treatment phase, both urine and serum ß-hCG pregnancy tests are planned to be conducted in women enrolled in this clinical study. Dip stick urine pregnancy tests allow the investigator to take action while the participant is at site in case of a positive test. Serum pregnancy tests are intended to confirm negative test results with higher reliability than urine tests. Later during the study, urine pregnancy tests do not need to be performed at visits where blood is drawn for a serum pregnancy test.

Pregnancy tests are to be performed in all female study participants, unless anatomically sterile, at all study visits, regardless of age and fertility status. When visit intervals are extended to 8 weeks after completion of 24 weeks of treatment (Visit 12), additional urine pregnancy tests are to be performed four weeks after each visit up to Visit 15, in line with the CTFG contraception guidance (CTFG 2014).

8.3 Adverse events (AEs), serious adverse events (SAEs) and other safety reporting

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs/SAEs will be collected from the signing of the ICF until 28 days after end-of treatment or until the follow-up visit (whichever comes later) at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours of learning of the event, as indicated in Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

TEAEs will be defined as those AEs that occurred after first dosing and those existing pre-dose AEs that worsened severity post-dose during the main treatment period until 28 days after the last dose of the study drug.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation / the End-of-Study visit. However, if the investigator learns of any AE/SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- For all studies except those using medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until the end-of study visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours after obtaining the necessary signed informed consents from the parents.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs, and will be reported as such.
- The participant /pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant / pregnant female partner and the neonate and the information will be forwarded to the sponsor.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants /pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.3.6 Adverse events of special interest (AESI)

Adverse events of special interest have to be reported to the sponsor along the timelines set for serious adverse events (even though they may not be classified as serious), i.e. within 24 hours of the investigator´s awareness, as described in Section 10.3.4.

Adverse events of special interest are:

- Adverse events suggestive of hepatic injury (please refer to Section 10.5)
- Syncope/loss of consciousness
- Acute kidney injury suggested by 2.0 fold increase in serum creatinine or > 50% decrease in eGFR

8.4 Pharmacokinetics

- Plasma samples will be collected for measurement of plasma concentrations of runcaciguat and its metabolites M1, M6 and M7 as specified in SoA. Instructions for the collection and handling of biological samples will be provided by the sponsor. At visits with pre-dose (trough, before intake of study intervention) sampling, study intervention will be administered at the study center by study personnel and the exact time of study intervention intake on the day before the visit and on the day of the visit and the exact sampling time will be recorded in the eCRF. Ideally the study personnel should contact the participant prior to these visits to remind them not to take the study intervention as usual in the morning at home and to document the exact time of study intervention intake on the days before the visit. For Visit 7, the participants should be advised to take their drug as usual in the morning at home and document the time of drug intake.
- The actual date and time (24-hour clock time) of each sample will be recorded. In addition, the actual date and time of study intervention intake on the day prior to the visit day and the actual date and time of study intervention intake on the visit day will be documented.in the eCRF.
- Concentration data will be summarized descriptively. These data are trough (pre-dose) plasma concentrations of runcaciguat by visit at Visits 3-6, and 815. Further details will be specified in the statistical analysis plan.

- Pharmacokinetic data for runcaciguat collected during the study will be analyzed at the end of study using nonlinear mixed effects models. Mixed effects models, or population type models, describe the relationship between e.g. dose, time and pharmacological observations such as plasma drug concentrations. Both structural and random effects are involved in this relationship. A population PK model may be developed to characterize the PK of runcaciguat over the entire treatment period using individual runcaciguat concentration data. Individual PK parameters of runcaciguat may be calculated. PK/PD models may be developed to relate parameters of clinical safety and efficacy response with runcaciguat plasma concentrations. The details of the analyses will be described in a separate M&S Analysis Plan, and the results will be reported in a separate M&S Report separately from the main clinical study report.
- Drug concentration information that would unmask the study will not be reported to investigative sites or blinded personnel until the study has been unmasked.
- Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or laboratory manual).

8.5 Genetics

Genetic analyses may be part of the biomarker investigations in this study. Genetic analyses are primarily done to address altered drug metabolism, in particular genetic variants that may influence runcaciguat exposure and factors predisposing to cardiovascular and/or eye diseases. The exact genetic variant may arise during the clinical program.

Genetic analyses relate to gene variants such as single nucleotide polymorphisms of drug transporters and/or drug metabolizing enzymes including enzymes of the cytochrome P450 system, the Solute Carrier Family or uridine 5′-diphosphate-glucuronosyltransferase. Different variants predispose to altered metabolization of drugs and may result in differences in runcaciguat exposure. Genetic analyses may be pivotal to understanding the pharmacology of runcaciguat and support its safe and efficacious use resulting in an improved benefit/risk ratio.

Genetic factors predisposing to cardiovascular and/or eye disease may be variants which effect oxidative stress and/or the NO pathway. Oxidative stress and a dysfunctional NO pathway are hallmarks of diabetic retinopathy and other (cardio-)vascular diseases. The study drug acts on soluble guanylate cyclase to produce cGMP in the absence of sufficient NO. Therefore, it is conceivable that certain genetic variants encoding components of the NO-cGMP pathway or genetic variants associated with oxidative stress may influence a participants response to treatment with runcaciguat. In addition, genetic variants may influence the course of disease. For example, asymmetric dimethyl arginine inhibits endogenous NO production. Its breakdown is mainly governed by two enzyme isoforms for which several genetic variants exist. Studies have demonstrated that different variants are associated with different asymmetric dimethyl arginine levels and therefore NO and cGMP bioavailability.

The genetic sample may be used to test for individual single nucleotide polymorphisms deemed relevant to better understand observations related to pharmacokinetics, mode-of-action-related and / or safety of runcaciguat and to further investigate pathomechanisms

deemed relevant to diabetic retinopathy, cardiovascular disease, and associated health problems. Whole genome sequencing is excluded.

8.6 Biomarkers

In this study, genetic as well as non-genetic biomarkers will be investigated.

8.6.1 Laboratory biomarkers

Biomarkers will be evaluated in samples collected before, during and after treatment in order to determine the impact of runcaciguat. These markers fall into the following categories:

A. **Biomarkers which may be related to the mode-of-action of the study drug:** e.g. vasoactive agents such as cGMP, Kynurenines or other tryptophan metabolites
B. **Functional markers of the cardiovascular system and cardiometabolic markers:** e.g. B-type natriuretic peptide, Kidney Injury Molecule-1, neutrophil gelatinase-associated lipocalin, clusterin, osteopontin, cystatin-C, uromodulin, heart-fatty acid binding protein, markers of inflammation and/or fibrosis, metabolic markers (e.g. adiponectin, apolipoproteins, HbA1c, glucose, (gluco)corticoids), or markers reflecting the oxidative stress status.
C. **OMICS / Untargeted Multiplex Analysis:** A sample may be collected for (untargeted) analysis (e.g. untargeted metabolomics) in order to identify '*de novo*' pharmacodynamic biomarkers, biomarkers which support the understanding of the mode-of-action and/or biomarkers which may indicate disease progression.
D. **Further biomarkers related to the mode of action or the safety** of runcaciguat and similar drugs may be examined. The same applies to further biomarkers deemed relevant to NPDR, (cardio)vascular diseases and associated health problems. These investigations may include e.g. diagnostic, safety, PD, monitoring, or potentially predictive biomarkers.

The following sample types will be collected for biomarker analysis:

- Plasma
  PK or safety lab samples (leftovers) may be used for biomarker investigations. Generally, plasma is collected for biomarker analysis. Refer to sample handling sheets for further details as some laboratories may request serum for particular tests.
- Serum (optional)
- Whole blood

Timing – The planned time points of sample collection are provided in the SoA in Section 1.3. If deemed necessary, the sampling time points or frequency according to the SoA may be adjusted.

Sample handling and storage – details on the collection, processing, shipment and storage of samples will be provided in separate documents (e.g. sample handling sheets or lab manual).

Samples may be stored for a maximum of 15 years (or according to local regulations) following the end of the study at a facility selected by the Sponsor to enable further analyses.

Reporting – Biomarker investigations may be reported separately (e.g. in a biomarker evaluation report) except for biomarkers of Category A above, and serum lipoprotein(s).

8.6.2 Ambulatory blood pressure monitoring (ABPM) – only in Part 1

ABPM evaluations were removed from the protocol via Amendment 3.

8.7 Immunogenicity assessments

Not applicable.

8.8 Health economics

Health Economics/Medical Resource Utilization parameters are not evaluated in this study.

9. Statistical considerations

As of amendment 3, this Section and its sub-sections were integrated from Master Protocol.

In this section, the following terminology will be used:

- 'Clinical activity' will be used as a synonym for 'superiority of runcaciguat vs placebo'.
- 'Clinical relevance' will be used with its usual meaning (i.e. an effect that is sufficiently high to be of clinical interest).

9.1 Statistical hypotheses

The primary endpoint is the proportion of patients with "≥ 2-step improvement in DRSS at 48 weeks of treatment in the study eye". This proportion will be denoted as π_{ACT} within the runcaciguat treatment arm and as π_{PLC} within the Placebo treatment arm.

The study will be evaluated using a Bayesian approach with non-informative prior distribution. Using this approach for inference it is possible to base decisions directly on the posterior probabilities of the hypotheses of interest. Therefore, in a Bayesian setting it is not necessary to specify an alternative hypothesis.

The hypotheses of interest are the following:

- Hypothesis of clinical activity: $\pi_{ACT} > \pi_{PLC}$
- Hypothesis of clinical relevance: $\pi_{ACT} > 0.25$

9.2 Sample size determination

The overall planned sample size is displayed in Table 9-1.

Table 9-1 Planned sample size

	Target dose	Part 1	Part 2	Total		
Randomized	Placebo	6	40	46		
	30 mg	-	-	-		
	60 mg	-	-	-		
	90 mg	-	-	-		
	120 mg	12	40	52		
	Overall	18	80	98		
Evaluable*				80		

*minimum evaluable for primary endpoint

The relative contribution of Part 1 and Part 2 to the combined total of N = 98 randomized participants may vary. The assessment of the primary endpoint will include the combined total of all evaluable participants.

If unexpectedly high dropout rates occur (e.g. due to COVID-19), the number of randomized participants may be increased by up to 20%.

The study will use a Bayesian concept for inference, which is based on the posterior probabilities that the research hypotheses are true. Proof of concept shall be defined as fulfillment of the following criteria:

- ≥ 90% posterior probability for the hypothesis of clinical activity (i.e. $Pr(\pi_{ACT} > \pi_{PLC}|data) \geq 0.9$)
- ≥ 50% posterior probability for the hypothesis of clinical relevance (i.e. $Pr(\pi_{ACT} > 0.25|data) \geq 0.5$).

The sample size has been chosen to provide at least 90% probability to obtain proof of concept.

The following assumptions have been used

- True response probability for placebo: 10%
- True response probability for runcaciguat 120 mg: 35%

The response criterion is assumed to be binomially distributed. For the Bayesian evaluation, a Jeffries' prior (i.e. a Beta (0.5;0.5)-prior) has been used. Sample size was determined with a simulation approach using the R environment.

To be able to declare both clinical activity and clinical relevance ≥ 40 evaluable patients are needed in both groups.

98 participants will be randomly assigned to the study intervention such that approximately 80 evaluable participants complete the study. Of 98 participants, 18 participants will be randomized with a ratio of 2:1 to highest runcaciguat dose and placebo for Part 1 (PK/PD). 80 participants will be randomized with a ratio of 1:1 to placebo and runcaciguat for Part 2 (Table 9-1).

9.3 Analysis sets

For the purposes of analysis, the following analysis sets are defined in Table 9-2.

Participants will be analyzed by their actual treatment (i.e. placebo or runcaciguat, irrespective of the actual dose they were titrated to). It is planned to pool the data of participants from Part 1 and Part 2 for analysis.

Table 9-2 Analysis sets

Participant analysis set	Assignment rule
Full analysis set (FAS)	All participants of the respective study part randomized to treatment who fulfilled the relevant selection criteria.
Per protocol set (PPS)	All FAS participants of the respective study part without validity finding.
Pharmacokinetic analysis set (PKS)	All participants of the respective study part without validity findings affecting the PK analysis and with ≥ 1 valid PK samples who received at least one dose of study intervention.
Safety analysis set (SAF)	All participants of the respective study part who took ≥ 1 dose of study intervention.

9.4 Statistical analyses

The statistical analysis plan will be finalized prior to unmasking and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General considerations

All data will be listed and study summary tables as well as graphical illustrations will be provided where appropriate. Summary statistics will be presented per dose step for the participants treated with runcaciguat and for all participants treated with placebo for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data.

For handling of missing data for the primary endpoint, see Section 9.4.2. Statistical analysis will be based on the available data. Analysis will be performed considering all valid data observed for the respective analysis sets. All missing or partial data will be presented in the subject data listing as they are recorded on the case report form.

Baseline is defined as the last pre-dose assessment before first study intervention.

Statistical analysis will be performed using Statistical Analysis System (SAS). The version used will be specified in the statistical analysis plan.

9.4.2 Primary endpoint

The primary endpoint is "≥ 2-step improvement in DRSS at 48 weeks of treatment in the study eye".

Missing data for this endpoint will be imputed using the last measured DRSS score prior to this.

If the last measured DRSS score already showed an improvement by ≥ 2 steps at the last measurement prior to the missing assessment, the participant will be considered a responder for the primary endpoint. Otherwise, the participant will be considered a non-responder.

Participants that had a vision-threatening complication as defined in Section 8.1.2 prior to the missing assessment will be considered non-responders.

The primary analysis will be conducted using a Bayesian framework. This decision depends upon the following criteria:

(a) there is ≥ 90% posterior probability for superiority vs placebo and

(b) if there is ≥ 50% posterior probability that the proportion of patients with DRSS ≥ 2-step improvement exceeds 25%.

The response criterion is assumed to be binomially distributed within each treatment arm. For the Bayesian evaluation, a Jeffries' prior (i.e. a Beta (0.5;0.5)-prior) will be used. Under these assumptions, the posterior distribution for the parameter π will be a Beta (k+0.5,n-k+0.5)-distribution, where

- k is the number of patients with DRSS ≥ 2step improvement within the respective study arm and
- n is the number of participants within the respective study arms.

In order to demonstrate criterion (a), the posterior distribution of $\pi_{ACT} - \pi_{PLC}$ will be used to establish the posterior probability that $\pi_{ACT} - \pi_{PLC} > 0$ (e.g. by using a Monte-Carlo-approach).

The posterior distribution for criterion (b) can be directly evaluated from the Beta (k+0.5,n-k+0.5)- distribution in the runcaciguat arm.

This primary analysis will be conducted on the PPS. A sensitivity analysis will be performed on the FAS. Further sensitivity analyses will include a separate analysis for each runcaciguat dose level that was reached during titration (on the PPS), as well as an analysis in the subpopulation of participants without major changes in vital signs (i.e. systolic blood pressure and pulse rate). Another sensitivity analysis will be conducted using multiple imputations for missing data. This analysis will be described in the SAP in a more detailed way.

9.4.3 Secondary endpoint(s)

9.4.3.1 Efficacy

The secondary endpoints for primary objective (efficacy) of study are

- "≥ 2step improvement in DRSS in the study eye" at 24 weeks of treatment: These endpoints will be analyzed descriptively with a similar methodology described for the primary endpoints.
- Vision-threatening complications in study eye up to 48 weeks of treatment. These endpoints will be analyzed by the Kaplan-Meier-method. Participants dropping out from the study without a vision-threatening complication will be censored at the last visit with evidence of no event.

9.4.3.2 Safety

The secondary objective of the study is to investigate the safety and tolerability of runcaciguat in patients with NPDR. The secondary endpoints in the safety of runcaciguat are treatment-emergent adverse events (TEAEs) from first dosing up to 28 days after last dose of study intervention.

The incidence of TEAEs and drug-related TEAEs, respectively, will be summarized by treatment and total using MedDRA terms. AEs are considered to be treatment-emergent if they have started or worsened after first application of study intervention up to 28 days after end of treatment with study intervention.

9.4.4 Other efficacy analyses

For further addressing the primary objective (efficacy) of the study, the following additional endpoints will be analyzed descriptively:

- DRSS change in study and fellow eye by ≥ 1, ≥ 2, or ≥ 3 steps over time
- Change in visual acuity from baseline (study and fellow eye)
- Vision-threatening complications in any eye up to 48 weeks of treatment
- Change in leakage area on fluorescein angiography

9.4.5 Other safety analysis

All safety analyses will be made on the Safety Population. A detailed description will be given in the statistical analysis plan.

For the secondary objective (safety) of the study, the following additional endpoints will be considered and analyzed:

- Laboratory parameters
- Vital signs
- Electrocardiography

Quantitative data will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum and maximum. These summary statistics will be presented by treatment for the original data as well as for the difference to baseline. Frequency tables will be provided for qualitative data. Laboratory data outside the reference

range will be listed and flagged with 'L' for low and 'H' for high. Additional tables with all abnormal values will be presented.

Graphical displays of individual data as well as mean values with standard deviation will be included.

9.4.6 Other analysis

Other objectives of the study are to assess pharmacodynamics and pharmacokinetics of runcaciguat. Pharmacodynamics analyses include following endpoints:

- Change in central retinal thickness
- Change in HbA1c
- Change in serum lipoproteins

Pharmacokinetic analyses will be performed on the population valid for pharmacokinetics and pharmacodynamic analyses will be performed on the population valid for pharmacodynamics. Summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented and frequency tables for qualitative data will be provided.

For demographic and baseline characteristics summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) will be presented for total and each treatment group in the FAS. Frequency tables for qualitative data will be provided. Medical history findings will be summarized using MedDRA terms. Prior and concomitant medication will be summarized by World Health Organization Drug Dictionary using the latest effective version of the dictionaries.

9.5 Interim analysis

No interim analysis is planned.

10. Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. Any substantial modification of the protocol will be submitted to the competent authorities as substantial amendments for approval, in accordance with ICH Good Clinical Practice and national and international regulations.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations

10.1.2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The investigator or his/her representative will explain the nature of the study to the participants and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants.
- Participants who are rescreened are required to sign a new ICF.

10.1.4 Data protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or biological samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5 Committees structure

10.1.5.1 Central reading centers

The digital retinal images, OCT scans, fluorescence angiographies, and ECG print-outs will be assessed by independent central reading centers.

10.1.5.2 Steering committee

A steering committee consisting of experts in the field is created to provide scientific and operational recommendations to the study protocol and to potential day to day decisions in study conduct. The composition of the committee, the functional roles, and responsibilities can be found in the Steering Committee charter.

10.1.5.3 Data monitoring committee (DMC)

An independent DMC is set up to provide recommendations based on unmasked review of data if needed. The DMC consists of a combination of experts in the clinical field and statistical analysis.

10.1.5.4 Safety assessment group

An internal safety assessment group will perform masked reviews of the safety and tolerability data from the study at the request by any of its members. The safety assessment group may call for an unmasked review of study data by the DMC, if deemed appropriate.

- The internal safety assessment group consists of Study medical expert (chair), Early clinical lead, Global clinical lead, Global safety lead and PK expert.
- The safety assessment group will review severe adverse reactions, SAEs, and AESIs, AEs resulting in treatment interruption or discontinuation, as well as other AEs deemed relevant by any of its members.
- In particular, it will support the safety review by the DMC in case stopping criteria are met (see Sections 6.5.2, 7.1)

10.1.6 Dissemination of clinical study data

Result Summaries of Sponsor's sponsored clinical trials in drug development Phases 2, 3 and 4 and Phase 1 studies in patients are provided in the Sponsor’s Trial Finder application after marketing authorization approval in line with the position of the global pharmaceutical industry associations laid down in the "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases". In addition, results of clinical drug trials will be provided on the publicly funded website www.ClinicalTrials.gov and EU Clinical Trials Register in line with the applicable regulations.

The Sponsor commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and

European Union (EU) on or after 01 JAN 2014 as necessary for conducting legitimate research.

All of the Sponsor sponsored clinical trials are considered for publication in the scientific literature irrespective of whether the results of the clinical trials are positive or negative.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined in the Integrated Data Review Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (e.g. risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g. Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the Source Data Location List.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first patient first visit and will be the study start date.

Study/site termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 will be performed by a central laboratory apart from urine pregnancy test, that will be performed locally.

Investigators must document their review of each laboratory safety report.

The laboratory parameters to be analyzed are defined in Table 10-1. The time points of analysis are defined in the schedule of activities.

Additional laboratory tests (see Table 10-4 for examples) may be performed as deemed appropriate by the Investigator, e.g. in case of signs of liver toxicity.

Table 10-1 Protocol-required laboratory tests

		Parameters (by category)	Sample destination
Blood / plasma / serum	**Hematology**	Leukocytes, Erythrocytes, Hemoglobin, Hematocrit, HbA1c, Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Platelets, Neutrophils, Eosinophils, Basophils, Lymphocytes, Monocytes	Central laboratory
	Biochemistry	Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (AP), Total bilirubin (if elevated: differentiation of direct bilirubin), Lactate dehydrogenase (LDH), Creatinine, Urea, Creatine kinase, Chloride, Potassium, Sodium, Calcium, Phosphate, Glucose, Total protein, Albumin, Triglycerides, Cholesterol (total, LDL, HDL), ß-hCG (women)	Central laboratory
	Plasma PK	BAY 1101042 and its metabolites M1, M6 and M7	Central laboratory
	Biomarkers in plasma/serum	See Section 8.6.1 for details	Central laboratory
	Hormones	Thyroid stimulating hormone (TSH)	Central laboratory
Urine		ß-hCG pregnancy test (women)	Local evaluation

HDL = high-density lipoprotein, LDL = low-density lipoprotein; PK = pharmacokinetics; HbA1c= hemoglobin A1c (glycated hemoglobin); ß-hCG = β-subunit of human chorionic gonadotropin

10.3 Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g. ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e. not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g. endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any AE that, at any dose:	
a.	**Results in death**
b.	**Is life-threatening** • The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c.	**Requires inpatient hospitalization or prolongation of existing hospitalization** • In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d.	**Results in persistent or significant disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e.	**Is a congenital anomaly/birth defect**
f.	**Other situations:** • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to sponsor in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:
- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission** of the SAE data to sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to sponsor will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data transmission (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's Medical Monitor by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File.

SAE reporting to sponsor via paper data collection tool

- Email transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and if email transmission is not feasible, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions:

Woman of childbearing potential

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered women of childbearing potential

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g. mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception guidance:

Female participants of child bearing potential must use a highly effective method of contraception, as shown in Table 10-2. Male participants must agree to use condoms. This applies from the time of ICF signature until the end of the study period.

Table 10-2 Highly effective contraception methods

• Implantable hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion	• Hormonal contraception with inhibition of ovulation, either estrogen and progestogen containing or progesterone-only • Vasectomized partner if sole sexual partner • Sexual abstinence

Modified from: Clinical Trial Facilitation Group 2014: Recommendations related to contraception and pregnancy testing in clinical trials (CTFG 2014).

Collection of pregnancy information:

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5: Liver safety: Suggested actions and follow-up assessments

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Table 10-3 or if the investigator believes that it is in best interest of the participant.

Table 10-3 Liver-safety-related monitoring and discontinuation criteria

Laboratory result	Measures
ALT or AST > 3 x ULN after start of study intervention	'Close observation' as defined below
ALT or AST > 3 x ULN and TBL > 2 x ULN	Withdraw study intervention and close observation as outlined below
ALT or AST > 3 x ULN and INR > 1.5 x ULN in the absence of anti-coagulants	Withdraw study intervention and close observation as outlined below
ALT or AST > 3 ULN with appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)	Withdraw study intervention and close observation as outlined below
ALT or AST > 5 x ULN for more than 2 weeks	Withdraw study intervention and close observation as outlined below
ALT or AST > 8 x ULN	Withdraw study intervention and close observation as outlined below

ALT = alanine aminotransferase; AST = aspartate aminotransferase; INR= international normalized ratio, TBL = total bilirubin, ULN = upper limit of normal (all referring to serum/plasma)

In participants fulfilling one of the criteria listed in Table 10-3, investigators and participants should be alerted regarding non-specific symptoms which may be associated with liver dysfunction, including anorexia, nausea, fatigue, right upper abdominal discomfort, vomiting, malaise, jaundice, fever, and rash. Information on these symptoms should be asked for. The study participants should be reminded to contact the study site immediately, if they are concerned about such symptoms and unscheduled liver parameters should be considered. A close observation has to be initiated if any of the criteria listed in Table 10-3 occurs.

Close observation includes:

- Repeat serum chemistry panel (including serum transaminases and serum bilirubin) up to two times per week. Frequency of retesting can decrease to once a week or less if laboratory abnormalities decrease and participant is asymptomatic.
- Obtaining a more detailed history of the symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Investigation of potential alternative causes of liver disease. This may include ruling out liver injury by acute viral infection, autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy and biliary tract disease. This may require performing additional procedures, e.g. ultrasound examinations or laboratory examinations, including but not limited to those listed in Table 10-4. If requested, tests will be done retrospectively using residual blood/serum samples collected at visits before laboratory abnormalities occurred.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function as required, as outlined in a separate liver injury follow-up questionnaire.

Table 10-4 Laboratory examinations for workup of liver safety findings

Parameters
Albumin
Alkaline phosphatase (AP)
Alanine-aminotransferase (ALT)
Aspartate-aminotransferase (AST)
Bilirubin : total, direct
Complete blood count including differentials
Cholesterol (total, LDL, HDL)
Cholinesterase
Conjugated (direct) bilirubin
Creatine kinase (CK)
Gamma-glutamyltransferase (γ-GT = GGT)
Glutamate dehydrogenase (GLDH)
Hemoglobin
International normalized ratio (INR)
Lactate dehydrogenase (LDH)
Prothrombin time (Quick) (PT)
Triglycerides
Anti-Hepatitis A virus Antibodies
Hepatitis B virus (HB): surface antigen (HBs), anti-HBs, anti-HB core antibodies (IgM, IgG), HB PCR
Anti-Hepatitis C virus (HCV) antibodies, HCV PCR
Anti-Hepatitis D virus (HDV) antibodies (if positive, automatically test HDV RNA)
Anti-Hepatitis E virus (HEV) IgM (if positive, automatically test HEV RNA)
Anti-Cytomegalovirus (CMV) IgM Antibodies
Anti-Epstein-Barr Virus (EBV) IgM Antibodies
Herpes simplex IgM (anti HSV IgM)
SARS-COV-2 antibodies
Immunoglobulins: (Ig) G level (gamma globulins), IgA, IgM
Antineutrophil cytoplasmic antibodies (c-ANCA, p-ANCA)
Anti-mitochondrial antibodies
Anti-native double-stranded DNA Antibodies
Anti-Smith Antibodies
Alpha-1 antitrypsin (A1AT) level
Ceruloplasmin
Ferritin
Iron
Total iron binding capacity (TIBC)

HDL = High density lipoprotein; IgA = Immunoglobulin A; LDL = Low density lipoprotein; IgM = Immunoglobulin M; PCR = Polymerase chain reaction; RNA = Ribonucleic acid

10.6 Appendix 6: Standardized meal

Standardized meals were removed from the protocol via Amendment 3.

10.7 Appendix 7: Abbreviations

ABPM	Ambulatory blood pressure measurement
AE(s)	Adverse event(s)
AESI(s)	Adverse event(s) of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCVA	Best corrected visual aquity
ß-hCG	β-subunit of human chorionic gonadotropin
BMI	Body mass index
BP	Blood pressure
CFP	Color fundus photography
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
cGMP	Cyclic guanosine monophosphate
CRF(s)	Case report form(s)
CST	Central subfield thickness
CTFG	Clinical trial facilitation group
DMC	Data Monitoring Committee
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ECG(s)	Electrocardiogram(s)
eCRF(s)	Electronic case report form(s)
eGFR	Estimated glomerular filtration rate
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FA	Fluorescein angiography
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GLDH	Glutamate dehydrogenase
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HRT	Hormonal replacement therapy
IB	Investigator's brochure
ICF(s)	Informed consent form(s)
ICH	International conference on harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IOP	Intraocular pressure
IRB	Institutional review board
IVT	Intra-vitreal drug treatment
IWRS	Interactive Web Response System
NO	Nitric oxide
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
OCT-A	Optical coherence tomography angiography
PD	Pharmacodynamics
PDE	Phosphodiesterase
PDE 5	Phosphodiesterase 5
PDR	Proliferative diabetic retinopathy
PK	Pharmacokinetics
PoC	Proof of Concept
PRP	Pan-retinal photocoagulation
QD	*Quaque die*, daily
QTLs	Quality tolerance limits
SAE(s)	Serious adverse event(s)
SBP	Systolic blood pressure
sGC	Soluble guanylyl cyclase
SoA	Schedule of activities
TEAE(s)	Treatment emergent adverse event(s)
TMF	Trial master file
uACR	Ratio of urinary albumin and creatinine concentrations
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

10.8 Appendix 8: Protocol amendment history

10.8.1 Amendment 4

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.8.2 Amendment 3

As of Amendment 3 and in line with the change in overall development strategy, Part B of the study is obsolete and has been removed from the protocol previously consisting of 3 modules (Master, Part A, Part B). At the same instance, for ease of documentation and to enhance readability a single protocol document was created integrating the relevant information from the Master- and Part A documents.

Amendment 3 (04 NOV 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for Amendment 3:

A description of changes and a brief rationale is outlined in the table at the end of this section. An overview is given below.

Parallel start of Part 1 and 2 of former Part A

The sponsor's clinical development program for runcaciguat comprises two currently ongoing Phase 2a studies in different indications: Study 20739 (NEON) in patients with NPDR and Study 18748 (CONCORD; EudraCT: 2019-003297-53) in patients with chronic kidney disease (CKD). Initially, both studies were planned to start at the same time which is why the NEON-NPDR study had been designed to start with the safety-data-generating Part 1 before initiation of the subsequent study parts. Runcaciguat, in the two proposed indications, is planned to be studied in the same doses, 30, 60, 90 and 120 mg OD orally administered, with the same up-titration schedule. However, the CONCORD study started earlier and generated safety data from 147 randomized participants before randomization of the first NEON-NPDR participant. DMC reviews of these data confirm the tolerability of the planned dosing schedule of runcaciguat in a similar patient population. Details are provided in the master protocol Section 2.3.1.

In view of the above considerations, Part 1 is no longer considered to be a prerequisite to initiate the main study Part 2. Therefore, both study parts are initiated independently from each other and will be conducted in parallel. Also, the focus of the 18 patients to be enrolled

in study Part 1 was shifted from generating safety data to obtaining pharmacodynamic data, mainly OCT-A, for PK/PD analyses.

Study population

After initiation of the NEON study, 12 out of 16 screened patients were found to be ineligible.

Since the initial conception of the NEON-NPDR protocol, two landmark studies in treatment of NPDR with intravitreal aflibercept have been published. The first is Protocol W (Maturi et al. 2021) sponsored by the DRCR Retina Network providing important new insights. The second is the PANORAMA study (Brown et al. 2021), investigating intravitreal injection of aflibercept as compared to sham, in a similar population with moderately-severe to severe NPDR as in Protocol W. In addition, the CONCORD study investigating runcaciguat in renal disease provided preliminary safety data indicating that runcaciguat is well tolerated by participants with HbA1c up to 11% and renal impairment with eGFR as low as 25 mL/min/1.73 m^2.

The eligibility criteria were, therefore, more closely aligned with other recent studies in similar diabetic patient populations with NPDR or renal disease. This included the CONCORD study investigating runcaciguat in renal disease, the PANORAMA study and DRCR Protocol W both investigating aflibercept in NPDR. Based on these studies it was deemed safe to include patients with HbA1c up to 11% and renal impairment with eGFR of at least 30 mL/min/1.73 m^2 and the definition of diabetic macula edema was specified.

The in- and exclusion criteria of the study were adjusted to better reflect the envisaged study population.

Streamlining of study conduct

Furthermore, some eligible patients refused participation in Part A1 of the clinical trial due to the high number and intensity of study visits. Therefore, the overall treatment duration was shortened to 48 weeks. In Part 1, the baseline profile Visit 1b was removed, the length of Visits 2 to 6 was shortened to up to 4 hours post dose and the number of assessments was reduced. These changes can safely be implemented based on the experience and data obtained from the CONCORD study and are expected to significantly reduce the burden on study participants.

Change in overall development Strategy

The clinical development of runcaciguat so far showed that the compound is well tolerated. However, pharmaceutical challenges may lead to inconvenient dosing regimens and a difficult to manage product supply chain. [redacted]

The Sponsor still plans to run the NEON-NPDR study with runcaciguat as a Proof of Concept (PoC) trial for sGC activators in NPDR, although runcaciguat will not be further developed. The Sponsor believes that this PoC trial will enable the optimal development of other sGC activators in NPDR and envisages to switch to such a compound in its portfolio.

Removal of Part B from the study

As of Amendment 3 and in line with the change in overall development strategy, Part B of the study is obsolete and has been removed from the protocol dossier. At the same instance, for ease of documentation and to enhance readability, a single protocol document was created integrating the relevant information from the Master- and Part A documents. This was done by moving all Sections applicable to the Study Part A document (Section 2 and all of its subsections, Sections 4.2 to 4.4, and Section 9 and all of its subsections) from the Master protocol into the Protocol Part A document without general highlighting as change. Only changes compared with the prior version of the Master protocol are listed in this Protocol document.

The Terms Part A and Part B were retired. Part 1 now refers to the PK/PD substudy and Part 2 refers to the main part of the PoC study.

Key changes in study design

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis / Rationale	Reference added to CONCORD study	Preliminary safety information can be derived from the CONCORD study that investigates runcaciguat in patients with chronic kidney disease.
Section 1.1 Synopsis / Rationale	Rationale expanded, by explaining the role of the clinical trial in the development of a subsequent sGC activator for treatment of NPDR	Late stage clinical development is not planned to be pursued with runcaciguat but with other sGC-activator(s).
Section 1.1 Synopsis Section 1.3 Schedule of Activities (SoA)	Deletion of baseline-visit 1b. The screening visit is called Visit 1 in both Parts 1 and 2.	Owing to the safety information that became available in the meantime from the CONCORD study, a baseline profile is no longer considered required for the assessment of cardiovascular and metabolic effects. Therefore, Visit 1b in Part 1 was eliminated; eliminating the need to differentiate the two pre-treatment visits.
Section 1.1 Synopsis Section 4.1 Overall design	Parts 1 and 2 will run in parallel. Therefore, Part 1 was relabeled as “PK/PD” sub-part, and description of study Parts 1 and 2 adapted accordingly.	With CONCORD safety data available, collection of safety data in a run-in is no longer needed prior to conducting Part 2 at ophthalmology sites. Part 1 is kept to investigate the PK/PD of runcaciguat in a subset of participants.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Table 1-1) Section 1.2 Schema Section 1.3 Schedule of activities (SoA) Section 3 Objectives and endpoints Section 7.2 Participant discontinuation Section 8 Study assessments	By shortening the treatment period to 48 weeks, the end-of-study visit was moved to Visit 16, and the descriptions of the visits were changed accordingly. Also, the timeframe for secondary and "other" efficacy endpoints has been adapted to the new treatment duration. The maximum amount of blood collected from each participant over the duration of the study was adapted to the shortened study duration.	48 weeks provide a sufficiently long treatment period to investigate the endpoint of 2-step improvement and may provide some preliminary information on the occurrence of vision-threatening complications.
Section 2 Introduction	The role of the NEON-NPDR in the context of sGC activator development was reworded. Information was added as to the exposure of patients with CKD to runcaciguat.	Clarification on the role of the NEON-NPDR study in the context of Sponsor's sGC program. New information available from clinical trial with runcaciguat in other indication became available.
Section 2.1 Study rationale	The role of the study in the context of the development of an sGC activator for treatment of NPDR was amended	Change in development strategy.
Section 4.1. Overall study design Section 9.4.3.1 Efficacy Section 9.4.4 Other Efficacy analyses	The treatment period was shortened to 48 weeks. Accordingly, the timeframe for secondary and "other" efficacy endpoints has been adapted to new treatment duration.	48 weeks provide a sufficiently long treatment period to investigate the endpoint of 2 step improvement and may provide some preliminary information on the occurrence of vision-threatening complications. The primary endpoint analysis at 24 weeks and the secondary evaluations at 48 week will allow sufficient data for the sponsor's decisions on the future development program of runcaciguat.
Section 4.1. Overall study design Section 4.1.1 Part 1 – PK/PD Section 9.5 Interim analysis	Parts 1 and 2 will be run parallel. Reference to „run-in" for Part 1 deleted, and description of study Parts 1 (PK/PD) and 2 (Proof of Concept) aligned to current situation.	With masked CONCORD safety data available on a large number of participants, Part 1, with planned 18 patients, is no longer needed as a run-in preceding Part 2. The titration scheme has been confirmed in the CONCORD study.
Section 4.1.2 Part 2 – Proof of concept	Interdependence of Part 2 with Part 1 deleted, interim snap-shot review deleted, treatment duration changed to 48 weeks.	With CONCORD safety data available, Part 1 is no longer needed as a run-in preceding Part 2.
Section 9.5 Interim analysis	Masked safety review at end of titration phase of Part 1 deleted.	Review no longer required, since safety of the titration regimen was confirmed in CKD patients in the CONCORD study.
Section 10.1.5.4 Safety assessment group	Masked safety review at end of titration phase of Part 1 deleted.	Review no longer required, since safety of the titration regimen was demonstrated in CKD patients in the CONCORD study.

Other substantial changes

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SoA) (Table 1-3) Section 10.2 Appendix 2: Clinical laboratory tests Section 10.6 Appendix 6:Standardized meal (Part 1)	Glucose stix and standard meals were deleted.	With CONCORD safety data available, glucose measurements were limited to venous glucose from the central safety lab analysis. As a result, standardized meals are dispensable as well.
Section 1.3 Schedule of activities (SoA) (Tables 1-3, 1-4)	Deletion of “Anterior and posterior segment examination” as well as “DRSS 7-field fundus photography“ on Visit 6.	Reduction of burden for patients by reducing examinations with pupil dilation which are not expected to generate essential efficacy data.
Section 1.3 Schedule of activities (SoA)	Deletion of the 4-6 hour post-dose time point in Part 1. Activities scheduled for the 4-6 hour timepoint were moved to 2-4 hours post dose.	This change is intended to reduce patient burden. In healthy participant Phase 1 studies, the steep increase in plasma concentrations took place within 4 hours post-dose. Therefore, plasma concentrations at 4 hours post dose are considered a reasonable approximation of the effective concentration.
Section 1.3 Schedule of activities (SoA) Section 3 Objectives and endpoints Section 8.1.4 Visual function questionnaire (VFQ-25)	Deletion of visual function questionnaire (VFQ-25).	This change is intended to reduce patient burden. The study recruits patients without significant visual impairment. Also, no change in visual function could be seen in studies such as the Panorama Study or Protocol W over treatment periods of up to 2 years. Therefore, the VFQ-25 is not expected to be sensitive to assess efficacy in this clinical trial over a period of only 48 weeks.
Section 1.3 Schedule of activities (SoA) (Tables 1-3, 1-4)	Deletion of “Anterior and posterior segment examination” as well as “DRSS 7-field fundus photography“ on Visit 6.	Reduction of burden for patients by reducing examinations with pupil dilation which are not expected to generate essential efficacy data.
Section 1.3 Schedule of activities (SoA) (Table 1-3) Section 6.1.2 Medical devices Section 8.6.2 Ambulatory blood pressure monitoring (ABPM)	Ambulatory blood pressure monitoring was deleted.	This change is intended to reduce patient burden. Based on the experience from the CONCORD study, ambulatory blood pressure monitoring is no longer considered essential for the compound safety assessment in diabetic patients treated with runcaciguat.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of activities (SoA) Section 8.1.3 Albuminuria Section 8.6.1 Laboratory biomarkers Section 10.2 Appendix 2: Clinical laboratory tests	uACR assessment and consecutively also urine biomarker sample were deleted.	Similar data are expected to be generated in the CONCORD study. Therefore, the uACR assessments were deleted to reduce patient burden.
Section 1.3 Schedule of activities (SoA) (Table 1-3)	Phone contact 1 and 2 days post visit was deleted.	Active phone check-up no longer considered necessary, considering the experience from CKD patients treated with runcaciguat indicating good tolerability.
Section 1.3 Schedule of activities (SoA) Section 8.2.5 Pregnancy testing	Urine pregnancy test deleted from Visit 7 onwards.	Redundant with serum pregnancy test. Removed to reduce participant burden.
Section 2.3.1 Risk assessment Section 4.3 Justification for dose	Sections updated with exposure and safety information derived from unmasked assessment of safety data from the CONCORD study, along with DMC recommendations from the CONCORD study.	Updates required to justify reduction of safety assessments in Part 1 and the parallel conduct of Parts 1 and 2. Tolerability of the dosing regimen and titration scheme were confirmed in CONCORD study.
Section 2.3.1 Risk assessment Section 4.3 Justification for dose	The permissible eGFR limit has been lowered from 45 ml/min to 30 ml/min.	In the Phase 2 study of runcaciguat in chronic kidney disease (CONCORD), runcaciguat was well tolerated when participants with eGFR ≥ 25 mL/min were included. Since a similar tolerability is expected in patients with NPDR, it is considered appropriate to lower the eGFR exclusion threshold. This change is expected to facilitate recruitment and to improve the generalizability of the study data (safety and efficacy) across the general NPDR patient population.
Section 2.3.2 Benefit assessment	An individual clinical benefit from participation in the study over 48 weeks of treatment is unlikely.	Discussion of potential benefits modified according to shortened treatment period
Section 5.2 Exclusion criteria	Exclusion criteria 1 and 18 changed to allow enrolment of patients with HbA1c up to 11% and eGFR as low as 30 mL/min.	Alignment with selection criteria of the Phase 2 CONCORD study. In the CONCORD study, inclusion of participants with HbA1c up to 11% and eGFR ≥25 mL/min was well tolerated. The change is expected to facilitate recruitment and to improve the generalizability of the study data (safety and efficacy) across the general NPDR patient population.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria	Definition of diabetic macular edema in exclusion criterion 6 changed to allow recruitment of patients with increased retinal thickness not needing treatment intervention, as per Investigator judgement, and below OCT-determined thickness thresholds.	Exclusion criterion changed not to exclude patients with minor, not clinically significant DME unlikely to interfere with the planned study interventions and assessments. The exclusion criterion is similar to the equivalent exclusion criterion in Protocol W.
Section 5.4 Screen failures	Rescreening allowed for participants screen-failed under prior protocol versions.	Considering the changes in I/E criteria and the time passed since prior screening, re-screening of participants screen-failed under protocol versions up to 3.0 is deemed appropriate.
7.1.1 Permanent discontinuation 7.1.2.Temporary discontinuation	Permanent discontinuation after repeated relevant hypotension and any other repeated discontinuation is no longer mandatory but at the discretion of the investigator. An upper duration limit was defined for temporary discontinuations.	Based on the experience from the CONCORD study, a strict rule for permanent discontinuation does not seem to be warranted in case of repeat discontinuations. Instead an upper limit of days 14 continuous or 21 days overall off treatment was defined as resulting in permanent discontinuation
Section 7.1.2 Temporary discontinuation	eGFR criterion for temporary discontinuation aligned with CONCORD study protocol.	Change necessary due to change in exclusion criterion 18 relative to eGFR.
Section 8.2.1 Physical examination	Assessment of Neuropathy Disability score deleted from physical examination.	Non-core assessment deleted to reduce patient burden. Furthermore, ophthalmologists often lack equipment and expertise to perform the assessment.
Section 8.2.3 Electrocardiograms	Transfer of ECGs to Central reading center for QT-assessment to be decided later	Considering the change in overall development strategy, standardized QT assessment may not be performed. No risk for QT prolongation was identified for runcaciguat.
Section 9.2 Sample size determination	A clarification was added that the primary-endpoint assessment will include all patients from Part 1 and Part 2. A combined total of approximately 98 patients are planned to be randomized in both parts. The relative contribution of Part 1 and Part 2 to the combined total may vary.	The number of participants in Part 1 could deviate from the planned target of 18. As the statistical analysis will be done on the combined total of participants in Part 1 and 2, sample size calculations were not done separately for either subpart.
Section 9.4.6 Other Analysis	Change in urinary albumin/creatinine ratio (UACR) was deleted from the protocol.	UACR assessment, from the group of “other” endpoints, was deleted to reduce patient burden as it was considered as non-essential for the objective of this study in NPDR patients.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Interim analysis	Interim analysis will be after 24 weeks of treatment with top-line efficacy and safety results over both parts.	Since the duration of the study has been shortened to 48 weeks, the Week 48 analysis will be the final analysis, rather than the previously planned interim analysis.

Organizational changes, corrections, and clarifications

Section # and Name	Description of Change	Brief Rationale
Throughout	Description of the protocol package has been deleted, together with mentions to referring to Study Part B, Part B Study protocol, and Master protocol.	As of this amendment, Part B of the study has been removed. Late stage clinical development is not planned to be pursued with runcaciguat but with other sGC-activator(s). Former Part A now corresponds to the study as a whole. Therefore, for ease of readability, all applicable sections of Master protocol have been transferred to the current protocol. All mentions of Part B and Master protocol have been removed throughout the document.
Terminology throughout the document	Part A.1 renamed Part 1, Part A.2 renamed Part 2.	With the deletion of Part B from the protocol, the term “Part A” was eliminated.
Section 1.3 Schedule of activities (SoA)	Dispensation of urine pregnancy test at Visits 13 and 14 was added.	Added as separate activity after deletion of on-site pregnancy test.
Section 4.1.1 Part 1 – PK/PD	Text changed to reflect the changes to the Schedule of Activities.	Alignment with changes to schedule of activities. For details see changes to Section 1.3, above.
Section 4.2 Scientific rationale for study design	Mention of CONCORD data in addition to previously performed Phase 1 studies	Available masked CONCORD data support the planned use of runcaciguat in the NEON-NPDR study
Section 4.3 Justification for dose	Reference to masked CONCORD data added and discussed in the context of dose-justification and titration regimen	The titration scheme in the NEON-NPDR is the same as in the CONCORD study. This titration scheme was well tolerated.
Section 5 Study population	A clarification was added that participants should show typical fundus alterations as described in the DRSS criteria for moderately severe and severe NPDR without DME in need of treatment and no previous experience of anti-VEGF treatment.	To depict better the study population.
Section 5.6 Selection of the study eye	Preference for choosing the eye without any sign of DME as study eye added.	To minimize risk of intermittent requirement of DME treatment.

Section # and Name	Description of Change	Brief Rationale
Section 6.3 Measures to reduce bias	Re-dispensing of unopened and undamaged bottles to the same participant allowed. Sentence moved to section 6.4.	To avoid wasting of clinical trial supplies. Section 6.4 more appropriate.
Section 6.8 Concomitant Therapy	sGC stimulator vericiguat added to list of prohibited medications.	Vericiguat obtained marketing approval.
Section 8.1.1 Ophthalmology assessments	Further clarification on archiving ophthalmology data on the site was provided.	Clarification
Section 8.1.1.3 Fluorescein angiography	All FA images will be archived. The method of archiving was deleted.	Method of archiving left to the discretion of the investigational site.
Section 8.1.1.4 OCT	A reference was added to specify the use of CRT measured by central reading Centre in the context of the amended EC6.	Change necessary in the context of the amendment of EC 6.
Section 8.2.1 Physical examination	Clarification that height is measured only at screening was added.	Clarification
Section 8.2.3 Electrocardiograms	The resting time before ECG recordings was reduced from 10 to 5 minutes.	The resting time was aligned throughout the protocol and with vital sign assessments. The 5-minute resting period is deemed sufficient for the purpose of ECG-assessments in this study.
Section 8.2.4 Clinical safety laboratory assessments Section 10.2. Appendix 2: Clinical laboratory tests	eGFR calculation to be done by the central laboratory. Paragraph on eGFR calculation deleted from Section 10.2 as unnecessary.	eGFR to be determined by central laboratory to allow real-time reporting of results which are used as a stopping criterion.
Section 8.4 Pharmacokinetics	Duration of PK sampling only until Visit 12. Snap-shot interim analysis deleted. PK data will first be assessed at the 24-week interim analysis.	Aligned with reduced treatment duration. Aligned with new plans for interim analyses.
Section 8.4 Pharmacokinetics	Sentence “Non-compartmental PK parameters will not be evaluated in this study“ was deleted.	The sentence was deleted to allow greater flexibility and the possibility of exploratory analyses.
Section 9.5 Interim analysis	Interim analysis will be after 24 weeks of treatment with top-line efficacy and safety results over both parts. Interim analysis for Part 1 restricted to week 24 only.	Since the duration of the study has been shortened to 48 weeks, the Week 48 analysis will be the final analysis, rather than the previously planned interim analysis.
Section 10.2 Appendix 2: Clinical laboratory tests	Two paragraphs explaining the possibility to perform additional laboratory tests were deleted as they were redundant with a third paragraph that remains.	Deletion to avoid redundant text. Redundant with paragraph in protocol Section 8.2.4

In addition, minor editorial and formatting revisions, including clarifications of existing text, have been made throughout the document.

10.8.3 Amendment 2

Amendment 2 (13 JAN 2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment:

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.

A description of changes applicable to protocol part A and a brief rationale is outlined in the table below.

Section # and Name	Description of Change	Brief Rationale
Table 1-5 Section 8.2.3 Electrocardiograms	Triplicate ECGs only recorded up to study Visit 6 (inclusive) of Part A.1	Triplicate ECG recordings to be done throughout the titration period only to support analyses of QT-time relative to exposure on visit days with extended duration.
Section 6.4 Study intervention compliance	Use of the smartphone app for supporting and tracking participant adherence to study drug intake was changed to be optional.	Competent Authority and Ethics Committee request
Section 8.1.1.1 Color fundus photography (CFP)	Additional exploratory efficacy endpoints based on color fundus photographs were added.	Potential additional explorative assessments to be disclosed.
Section 8.1.1.5 Optical coherence tomography angiography (OCT-A)	The experimental nature of the software used to assess cross -sectional macular full depth line scans was indicated.	It was deemed appropriate to highlight the experimental nature of this OCT-A based image acquisition.

In addition, minor editorial and formatting revisions have been made throughout the document.

10.8.4 Amendment 1

Amendment 1 (23 NOV 2020)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall rationale for the amendment:

This amendment was implemented to follow requests from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) and central Independent Ethics Committee (IEC).
A description of changes applicable to protocol Part A and a brief rationale is outlined in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 4.1.1 Part A1 – Run in Section 10.1.5.4 Safety assessment group	Decisions made by safety assessment group will be reviewed by DMC.	Health authority request
Section 5.2 Exclusion criteria	Exclusion criterion 27 has been modified to include time period for prohibited medication	Health authority request
Section 5.2 Exclusion criteria	Exclusion criteria 28 and 29 have been modified to prohibit the use of nitrates, NO donors, PDE5 inhibitors, non-specific PDE inhibitors and sGC stimulators within 1 week or less than 5 half-lives (whichever is longer) before first study drug administration	Health authority request
Section 6.5.1 Intra-individual dose-titration decisions	Investigator should reduce the dose instead of maintaining it in cases of serious or severe AEs related to runcaciguat, or in cases of relevant hypotension (e.g. symptoms of hypotension in combination with either SBP < 90 mmHg or SBP decrease by >30 mmHg or both)	Health authority request
Section 6.5.2 Stopping rules (study level)	Safety findings observed by DMC which ~~preclude~~ indicate unacceptable pharmacological effects, reasonably attributable to runcaciguat [result in an immediate stop of dosing and will result in a temporary halt of the study]	Correction of obvious mistake
Section 7.1.1 Permanent discontinuation	Modification of discontinuation criteria: participants must be withdrawn from study intervention on all cases of repeated incidents of relevant hypotension or tachycardia, and in cases of safety concerns for a participant by the investigator or the sponsor	Health authority request
Section 8.1.2 Vision threatening complications	Treatment of the vision threatening complication should follow local standards and guidelines.	Health authority scientific advice recommendation
Section 8.2.5 Pregnancy testing	Urine pregnancy testing was corrected to be done locally, serum pregnancy test is done centrally.	Non-substantial correction

Section # and Name	Description of Change	Brief Rationale
Section 8.5 Genetics Section 8.6 Biomarkers	More detailed description of the genetic testing was included	Ethics Committee request
Section 10.1.5.4 Safety assessment group	Addition that the decision by the safety assessment group will be reviewed by the DMC based on an unmasked safety review.	Health authority request
Section 10.1.5.1 Central reading centers	The digital retinal images OCT scans, fluorescence angiographies, and ECG print-outs will be assessed by independent central reading centers	Correction of obvious mistake in protocol as to examinations to be provided to central reading centers, in accordance with existing language in protocol Sections 8.1.1.1, 8.1.1.3, 8.1.1.4, 8.1.1.5.
Section 10.2 Appendix 2: Clinical laboratory tests	Missing serum pregnancy test was added	Non-substantial correction

In addition, minor editorial and formatting revisions have been made throughout the document.

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