Study title: A randomized parallel-group, placebo-controlled, double-blind, multi-center dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator BAY 1021189 over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF) - SOluble guanylate Cyclase stimulatoR in heArT failurE patientS with REDUCED EF (SOCRATES-REDUCED)

For this study, the protocol and subsequent protocol amendments were released as follows:

- **Original protocol,** Version 1.0, dated 16 JUL 2013
- **Amendment 01,** dated 16 SEP 2013
  (local amendment valid for Japan only)
- **Amendment 02,** (global amendment described in Section 13.1)
  (forming current integrated protocol Version 2.0, dated 06 JUL 2014)

This document integrates the original protocol and all global amendments.

Title page

Study title: A randomized parallel-group, placebo-controlled, double-blind, multi-center dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator BAY 1021189 over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF) - *SO*luble guanylate *C*yclase stimulato*R* in he*A*r*T* failur*E* patient*S* with *REDUCED* EF (SOCRATES-REDUCED)

Short title: Phase IIb safety and efficacy study of four dose regimens of BAY 1021189 in patients with worsening HF and reduced EF (SOCRATES-REDUCED)

Test drug:	BAY 1021189		
Study purpose:	Safety, efficacy, pharmacokinetics		
Clinical study phase:	IIb	Date:	06 JUL 2014
EudraCT no.:	2013-002287-11	Version no.:	2.0
Study no.:	BAY 1021189 / 15371		
Sponsor:	**Bayer HealthCare AG, D-51368 Leverkusen, Germany**		
Sponsor's medical expert:	Eliana Samano, MD Bayer S.A Av. Domingos Jorge, 1100 - São Paulo - Brazil Phone: +55-11-5694-4007		

The study will be conducted in compliance with the protocol, International Conference on Harmonization –Good Clinical Practice (ICH-GCP) and any applicable regulatory requirements.

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Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: Lothar Roessig, MD Role: Global Clinical Leader

Date: Jul 7, 2014 Signature:

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

Synopsis--amended

Title	A randomized parallel-group, placebo-controlled, double-blind, multi-center dose finding phase II trial exploring the pharmacodynamic effects, safety and tolerability, and pharmacokinetics of four dose regimens of the oral sGC stimulator BAY 1021189 over 12 weeks in patients with worsening heart failure and reduced ejection fraction (HFrEF)
Short title	Phase IIb safety and efficacy study of four dose regimens of BAY 1021189 in patients with HFrEF suffering from worsening chronic HF (SOCRATES-REDUCED)
Clinical study phase	IIb
Study objective(s)	To find the optimal dose of the oral soluble guanylate cyclase (sGC) stimulator BAY 1021189 for Phase III that can be given in addition to standard therapy for heart failure with reduced EF (HFrEF) by characterizing the safety, tolerability, pharmacodynamic effects, and pharmacokinetics, and detecting a significant dose-response relationship in the primary endpoint change in NT-ProBNP at 12 weeks in patients with worsening chronic heart failure with reduced ejection fraction (HFrEF).
Test drug(s)	BAY 1021189 immediate-release (IR) tablet
Name of active ingredient	BAY 1021189
Dose(s)	1.25 mg once daily 2.5 mg once daily 5 mg once daily 10 mg once daily
Route of administration	Oral
Duration of treatment	12 weeks
Reference drug(s)	Placebo
Name of active ingredient	N/A
Dose(s)	N/A
Route of administration	Oral coated tablet
Duration of treatment	12 weeks
Indication	Heart failure (HF) with reduced ejection fraction (HFrEF)
Main inclusion criterion	Worsening chronic heart failure (WCHF) requiring hospitalization (or intravenous [IV] diuretic treatment for HF without hospitalization) with initiation of study treatment after clinical stabilization

Diagnosis	1. History of chronic HF: NYHA class II-IV and standard HF therapy ≥30 days before hospitalization[1] 2. Worsening HF at hospitalization[1] a. N-terminal pro brain natriuretic peptide (NT-proBNP) ≥1000 or BNP ≥300 if in sinus rhythm, **or** NT-proBNP ≥1600 or BNP ≥500 pg/mL in atrial fibrillation in local routine labs, **and** b. Symptoms and signs of congestion (clinical **or** radiographic signs in routine chest x-ray demonstrating pleural effusion, pulmonary congestion, or cardiomegaly) 3. Clinical stabilization defined by a. no IV vasodilator for >24h and no IV diuretic for >12h before randomization **and** b. Systolic blood pressure (SBP) ≥110 and <160 mmHg and resting heart rate (HR) ≥50 and <100 beats per minute (bpm) at randomization 4. Left ventricular ejection fraction (LVEF) <45% by echocardiography at randomization [1] or IV diuretic treatment for HF without hospitalization
Key exclusion criteria	1. IV inotropes at any time ***between*** hospitalization ***and randomization***[1] 2. Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HFrEF 3. Cardiac comorbidity o Specific HF etiologies, incl. hypertrophic cardiomyopathy with left ventricular (LV) outflow tract obstruction; pericardial disease; infiltrative or inflammatory myocardial disease; valvular heart disease with severe aortic or ***primary***[2] mitral regurgitation, moderate or severe aortic stenosis, any mitral stenosis requiring surgical repair, or active endocarditis; **or** o Acute coronary syndrome (ACS), including unstable angina, Non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), or coronary artery bypass grafting (CABG) within 60 days prior to randomization; **or** o ***Current*** indication for percutaneous coronary intervention (PCI) or CABG ***(at the time of randomization)***[3]; **or** o Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since; **or**

[1] Clarified via Amendment 2
[2] Clarified via Amendment 2
[3] Clarified via Amendment 2

	○ Symptomatic carotid stenosis, or TIA or stroke within 30 days prior to randomization; **or** ○ New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization; **or** ○ Listing for heart transplantation and/or anticipated/implanted ventricular assist device; **or** ○ Complex congenital heart disease 4. Non-cardiac comorbidity at the time of randomization ○ Glomerular filtration rate <30 mL/min/1.73 m^2 calculated by MDRD; **or** ○ Hepatic insufficiency Child-Pugh B or C; **or** ○ Body mass index (BMI) >45[4] kg/m^2; **or** ○ Malignancy or other non-cardiac condition limiting life expectancy to <1 year; or ○ Severe pulmonary disease with either requirement of continuous home oxygen or bronchial artery embolization for massive hemoptysis ***5. Previous (within 30 days of randomization) or concomitant*** participation in another clinical study with investigational ***medicinal***[5] product***(s).*** 6. ***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).***[6] ***7. Previous assignment to treatment during this study.***[7]
Study design	Prospective, randomized, placebo-controlled, double-blind, 5 parallel arm global multi-center dose finding phase II trial

[4] BMI exclusion changed from 40 to 45kg/m^2 via Amendment 2
[5] Clarified via Amendment 2
[6] Added via Amendment 2
[7] Added via Amendment 2

Methodology	Subjects will be randomized to either 1. Placebo and sham titration 2. 1.25 mg and sham titration 3. 2.5 mg and sham titration 4. 2.5 mg, which will be up-titrated to 5 mg after 14 days 5. 2.5 mg, which will be up-titrated to 5 mg after 14 days and to 10 mg after 28 days Titration steps at 14 and 28 days include sham titrations in groups 1, 2, and 3, and in group 4 after 28 days. Titration in all groups will depend on systolic blood pressure (SBP) before intake of the dose: • Double dose: If SBP ≥100 mmHg • Maintain dose: If SBP between 90 and <100 mmHg • Half the dose: if SBP <90 mmHg without symptoms of hypotension Dose halving is possible at any time if the physician feels this is necessary for safety reasons.
Discontinuation rules	Temporary discontinuation: • Systolic blood pressure (SBP) <90 mmHg with symptoms of hypotension, or adverse event (AE) of acute renal failure • Restart with half of the previously given dose after 24 h if SBP above 90 mmHg and symptoms resolve within 24 h, and if the AE of acute renal failure has resolved within 10 days Permanent discontinuation: • if SBP <90 mmHg with symptoms of hypotension persists for >24 hours, or the AE of acute renal failure does not resolve within 10 days • if SBP <90 mmHg or AE of acute renal failure occur at the dose of 1.25 mg
Type of control	Placebo-controlled
Number of subjects	Approximately 513 subjects will be screened and approximately 410 randomized
Primary variables	Change from baseline to week 12 in log-transformed NT-proBNP

Plan for statistical analysis	**Primary analysis** The goal of the primary statistical analysis is to detect a positive dose-response for the oral sGC stimulator BAY 1021189. The three highest dose arms (2.5 mg, 5 mg, and 10 mg) will be pooled and compared to placebo with a two-sample t-test at the one-sided significance level α = 5%. The test problem is defined by: $H_0^{pool}: \mu_{pool} \geq \mu_p$ vs. $H_1^{pool}: \mu_{pool} < \mu_p$, The primary efficacy analysis will be performed in the per protocol analysis set. **Secondary analyses** The dose-response relationship will be analyzed by a linear regression model of the form: $y_i = \beta_0 + \beta_1 x_i + e_i$. A descriptive test will be performed to assess whether the slope of the regression line is negative: H_0: $\beta_1 \geq 0$. If the null hypothesis for the primary analysis has been rejected, the individual dose arms will be compared to placebo in a hierarchical order, starting with the 10 mg arm and going down to the 1.25 mg arm. Each hypothesis will be tested with a two-sample t-test at the one-sided significance level α = 5%, only if all previous hypotheses have been rejected.

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List of abbreviations

ACE	Angiotensin converting enzyme
ACS	Acute coronary syndrome
A. fib.	Atrial fibrillation
AE	Adverse event
ALT	Alanine aminotransferase (also known as GPT)
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase (also known as GOT)
ASWT	Anteroseptal wall thickness
ATC	Anatomical Therapeutic Chemical
ATP	Ant-tachycardic pacing
BPM	Beats per minute
BSA	Body surface area
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CEC	Clinical event committee
cGMP	Cyclic guanosine monophosphate
CI	Confidence index
CK	Creatine kinase
CO	Cardiac output
COPD	Chronic obstructive pulmonary disease
(e)CRF	(electronic) case report form
CRO	Contract research organization
CRT	Cardiac resynchronization therapy
CTX	Carboxyterminal cross-linking telopeptide
CV	Cardiovascular
DBP	Diastolic blood pressure
DMC	Data monitoring committee
E/A	Ratio of mitral peak velocity of early filling to mitral peak velocity of late filling
ECG	Electrocardiogram
Echo	Echocardiography
ED	Erectile dysfunction
E/E'	Ratio of mitral velocity of early filling to early diastolic velocity of the mitral annulus
EF	Ejection fraction
e.g.	Exempli gratia, for example
ESC	European Society of Cardiology
EU	European Union
EWDT	E-wave deceleration time
FAS	Full analysis set
GCP	Good clinical practice
GDF-15	Growth differentiation factor 15
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GMP	Good manufacturing practice

h	Hour / hours
HF	Heart failure
HR	Heart rate
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
IB	Investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.e.	*id est*, that is
IEC	Independent ethics committee
IMP	Investigational medicinal product
INN	International non-proprietary name
IRB	Institutional Review Board
IR	Immediate release
IV	Intravenous
IVSD	Intraventricular septum thickness
IxRS	Interactive voice/web response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	Left atrium, left atrial
LAV	LA volume
LAVI	LA volume index
LEPHT	Left ventricular systolic dysfunction associated with pulmonary hypertension riociguat trial
LLOQ	Lower limit of quantification
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVEDV	Left ventricular end-diastolic volume
LVESV	Left ventricular end-systolic volume
MAP	Mean arterial pressure
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mmHg	Millimeters of mercury
ms	Milliseconds
NO	Nitric oxide
NSTEMI	Non ST-elevation myocardial infarction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PIIINP	pro-collagen III N-terminal peptide
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PD	Pharmacodynamic(s)
PDE5	Phosphodiesterase type V
PH	Pulmonary hypertension
PH-sLVD	Pulmonary hypertension associated with left ventricular systolic dysfunction

PK	Pharmacokinetic(s)
PKS	Pharmacokinetics analysis set
PP	Pulse pressure
PPS	Per protocol set
prn	pro re nata, as needed
PVR	Pulmonary vascular resistance
PWT	Posterior wall thickness
QoL	Quality of life
RAVE	Electronic data capture system used by the sponsor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SBP	Systolic blood pressure
sGC	Soluble guanylate cyclase
SID	Subject identification number
STEMI	ST-elevation myocardial infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Systemic vascular resistance
TDI	Tissue Doppler imaging
TIA	Transitory ischemic attack
TIMP-4	Tissue inhibitor of matrix metalloproteinases 4
WCHF	Worsening chronic heart failure
WHO-DD	World Health Organization Drug Dictionary

1. Introduction

1.1 Background

Medical need: Heart failure (HF) is the leading cause of cardiovascular morbidity and mortality constituting the major public health problem worldwide. The European Society of Cardiology (ESC) represents countries with a population of >900 million, by and there are at least 15 million patients with HF in those 51 countries (1). An estimated 5.1 million patients have HF in the US with increasing prevalence, an incidence approaching 10 per 1000 population after 65 years of age, and a lifetime risk for developing HF is one in five for men and women (2). In developed countries 1–2% of the adult population has HF, with the prevalence rising to ≥10% among persons 70 years of age or older (3). HF is defined as a syndrome with typical symptoms and signs resulting from an abnormality of cardiac structure or function (4,5). It causes shortness of breath at rest or during exertion and/or fatigue and signs of fluid retention such as pulmonary congestion or ankle swelling.

HF with reduced ejection fraction: HF is associated with a wide spectrum of left ventricular (LV) functional abnormalities, ranging from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation and/or markedly reduced EF (4). Previously, LV EF has been widely used to define systolic function, assess prognosis, and select patients for therapeutic interventions (6). This concept resulted in the entity systolic HF, or more recently designated as HF with reduced EF (HFrEF). Major trials in patients with HFrEF mainly enrolled patients with an EF ≤35%, and it is only in these patients that effective therapies have been demonstrated to date. Other, more recent, trials enrolled patients with HF and EF >40-45%. These patients do not have a major reduction in systolic function, and many have an entirely normal EF (generally considered to be >50%), and the term HF with preserved EF (HFpEF) was created to describe this entity (5). It is important to differentiate those with HFrEF from those with HFpEF because these represent groups with different underlying pathophysiological, haemodynamic, and neurohormonal abnormalities and distinctly different clinical characteristics, varying risks for adverse outcomes, and dissimilar efficacy of existing therapies (7).

High event rates upon hospitalization for HF: Patients with worsening symptoms and/or signs of HF who require hospitalization represent an important subpopulation of patients with chronic HF. In these patients, the requirement of hospitalization for HF indicates more severe clinical presentation, and substantially worsened prognosis compared to outpatients not hospitalized for HF (8). While angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARB), beta-blockers, and mineralocorticoid-receptor antagonists (MRA) were shown to improve outcomes in chronic heart failure, the prognosis of patients who required hospitalization for HF remains unfavorable (9). The neurohumoral antagonists ACE inhibitors, ARB, beta-blockers, and MRA, as well as diuretics improve outcomes in patients with HFrEF as established by the results of numerous large-scale clinical trials in outpatients, and in selected populations also digoxin and other digitalis glycosides, hydralazine and isosorbide dinitrate and ivabradine. However, the number of annual hospitalizations for heart failure (HF) and the mortality rates among patients hospitalized for HF remains unacceptably high despite these treatments. Early mortality rates 60- to 90-day post-discharge in the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart

Failure (OPTIMIZE-HF) registry were 5% to 15% (10). In the CHARM trial, mortality increased from 4-fold to 16-fold after the first hospitalization for HF (11). In the EFFECT study, the long-term survival rate is 25% at 4.25 years post-discharge (12). Therefore, the search continues for safe and effective agents that improve outcomes when added to standard therapy in patients requiring hospitalization for HF.

Insufficient sGC signaling is a target in HF: The nitric oxide (NO)—soluble guanylate cyclase (sGC)—cyclic guanosine monophosphate (cGMP) pathway is a relevant mechanism in HF that is not targeted by neurohumoral antagonists. cGMP deficiency causes two important pathophysiologies in HF: Myocardial dysfunction and endothelial dysfunction, i.e. disturbed endothelium-dependent vasotone regulation due to impaired NO bioavailability, including the myocardial microcirculation (reviewed in Gheorghiade et al., Heart Failure Reviews 2012). Restoration of sufficient sGC–cGMP signaling appears to be an important pathophysiological target in HF. Previous attempts to increase cGMP remain limited. The long-term effects of nitrates and exogenous NO donors are limited by tolerance (13), and they cause endothelial dysfunction, oxidative stress, and release of endothelin-1 (14). Their venoselectivity may restrict the hemodynamic tolerability of these drugs (15). Underlying mechanism of the regional responses in different vascular beds is the dependency of nitrates and exogenous NO donors on biotransformation to the active, NO-containing compound (16). Direct small molecule stimulators of sGC overcome these limitations. Their regional vasoactivity and potential direct myocardial effects are independent of biotransformation and, therefore, might differ from nitrates. Therefore, these molecules could provide an advanced, tolerable option to restore cGMP signaling in HF (17).

Direct oral sGC stimulators: A novel class of sGC stimulators directly stimulates the NO receptor sGC with a dual mode of action. They sensitize sGC to endogenous NO by stabilizing the NO-sGC binding and also directly stimulate sGC via a different binding site, independently of NO. Single doses of another oral sGC stimulator BAY 60-4552 improved systemic and pulmonary hemodynamics in 42 subjects with systolic HF and elevated pulmonary capillary wedge pressure and mean pulmonary artery pressure (mPAP) at doses as low as 1 mg (significant decrease in mPAP, no control arm) (18). The 3 times daily administered oral sGC stimulator BAY 63-2521 (riociguat) has demonstrated safety and efficacy in PAH and CTEPH and was submitted for regulatory approval. In the Phase IIb Left ventricular systolic dysfunction associated with Pulmonary Hypertension riociguat Trial (LEPHT) study (IMP14308, NCT01065454) in patients with systolic HF and secondary pulmonary hypertension (PH), riociguat was well tolerated in these patients, and improved cardiac index, pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and quality of life in addition to standard HF treatment over 16 weeks without significantly changing systemic blood pressure or mPAP as primary endpoint (19). In these patients and in patients with PH, long-term extension studies are currently ongoing, further studying the safety of these compounds.

1.2 Previous experience in humans

A detailed description of the properties of BAY 1021189 and the results of the nonclinical and clinical pharmacology studies conducted so far are given in the Investigator's Brochure (IB). A brief overview of the results is provided in the following sections.

1.2.1 Dose selection

The starting dose as well as the dose range in this study is based on data from the following studies with BAY 60 4552, riociguat and BAY 1021189:

- single and multiple dose studies in healthy volunteers (including non-invasive characterization of hemodynamics, next to safety and pharmacokinetics) with BAY 1021189, and with related compounds riociguat, and BAY 60 4552
- multiple dose phase IIb LEPHT study: non-invasive and invasive hemodynamic, functional, and exploratory clinical effects of 16 weeks riociguat treatment in outpatients with advanced systolic HF and secondary PH on standard HF therapy in four dose titration arms (19).

In LEPHT, titration of the related compound riociguat was well tolerated, and improved cardiac index, pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), and quality of life, without significantly changing mPAP, systemic blood pressure, or heart rate in patients with advanced systolic HF on standard HF therapy (19). Therefore, the planned dose range of BAY 1021189 for phase IIb is based on data from LEPHT. Slopes of unbound plasma concentrations versus pharmacodynamic responses in single dose escalation studies in healthy volunteers indicate that BAY 1021189 has about one fifth of the potency of riociguat. Simulation of the plasma concentration time profile at steady state upon 2.5 mg once daily BAY 1021189 resulted in about 50% in exposures equipotent to the lowest riociguat quartile with a significant cardiac output increase in LEPHT. Therefore, 2.5 mg is expected to be the minimum effective dose, and 1.25 mg in the lowest dose arm is expected to have no effects. Since no blood pressure decrease was observed with 2.5 mg BAY1021189 in healthy volunteers, and the extrapolated equipotent dose of 0.5 mg Riociguat did not decrease blood pressure in patients with HF and secondary PH, a starting dose of 2.5 mg is considered safe in the upper three dose arms. 10 mg was the highest tolerated dose in healthy volunteers following single and multiple dosing, and is considered the maximum tolerated dose beyond which no further beneficial effect is anticipated in patients with HF.

1.3 Rationale of the study design

Parallel group design

A parallel group design was chosen to compare four different dose regimens and one placebo arm to find the optimal dose for ph III (Figure 1–1). Placebo control is used to control for observer and subject bias, and randomization to control for assignment bias.

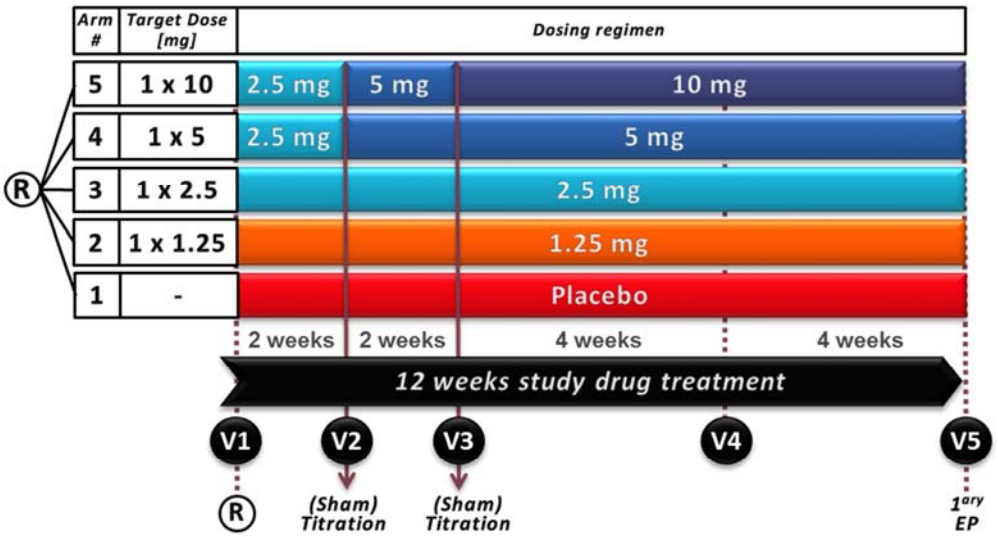

Figure 1–1: Study design.

Three arms will start with the dose of 2.5 mg which is half of the minimally effective dose in healthy volunteers. 2.5 mg is expected to be equipotent to 50% of the lowest exposure quartile of riociguat in LEPHT with already a significant effect on cardiac output in patients with HF. The 1.25 mg arm will characterize the dose-response relationship at the lower end of the range.

Based on the results from LEPHT, doses of BAY 1021189 with lower equipotency than the highest riociguat dose studied are expected to result in beneficial effects. This exposure equivalent of BAY 1021189 in the lowest two dose arms can be achieved without titration. Forced titration in the higher target dose arms will depend on blood pressure measurements and in addition on absence of intolerance and events of worsening renal function to prevent excess blood pressure responses. Dose doubling for titration of vasoactive HF medication is well established for ACE inhibitors, angiotensin receptor blocker (ARB) and beta-blockers (20). A similar dose doubling based on SBP was used in the closely related LEPHT population with advanced systolic HF receiving standard HF treatment and frequent coronary artery disease (CAD) to safely achieve effective target exposures. Despite the capacity to lower blood pressure in the highest exposure quartile cardiac output increased in the highest titration target dose arm at 16 weeks in the presence of standard HF treatment without decreases in the average SBP or increases in heart rate compared to placebo (19).

Duration of study drug treatment

The study has three phases: 1) screening is 0 - 28 days long, 2) study drug treatment is 12 weeks, 3) follow-up is within 30±5 days. This is - together with SOCRATES-PRESERVED - the first phase II study with BAY 1021189 in patients with HF. It follows the multiple dose escalation studies in healthy volunteers in phase I with 1 week maximum treatment duration, and a full development program of the predecessor oral t.i.d. sGC stimulator riociguat in PH. To study the dose ranges of once daily BAY 1021189 comparing a broad range from low to high exposure, titration to achieve higher exposures is used. Thus, it requires a 12 weeks total duration to allow for at least 8 weeks on the maximum target dose after two 2-week titration

intervals. Therefore, a shorter duration of 12 weeks would limit the interpretation of high target dose efficacy and safety.

Justification of secondary efficacy serum biomarkers

Besides assessment of clinical variables serum biomarkers bear the potential to better characterize HF patients at entry into a clinical trial and longitudinally upon treatment. Serum biomarkers quantify pathophysiological mechanisms such as pressure-volume overload, cardiomyocyte/ cardiac fibroblast stress, inflammation and remodeling. It was shown that the combination of biomarkers in panels provides incremental value for risk stratification of HF patients and adds prognostic value in the presence of clinical risk factors for predicting both short-term and one-year mortality (21,22). In the present study the most promising HF biomarkers were compiled based on information available in literature. Simultaneous assessment of a panel of biomarkers allows generating a molecular fingerprint of the investigated drug in both HFpEF and HFrEF. Exploration of a biomarker panel allows correlation of biomarkers with clinical variables and thereby enables validation of biomarkers with regard to their predictivity and prognostic properties. Individual rationale for the secondary biomarkers can be found in Section 7.6.1.1.

1.4 Benefit-risk assessment

Event rates remain unacceptably high in patients requiring hospitalization for HF. This indicates a need to develop additional therapies targeting mechanisms different from standard HF. The population with worsening chronic HFrEF will not only have a high prevalence of co-morbid atherosclerotic disease including CAD and cardiovascular disease , but also a frequent concomitant use of blood pressure lowering medication such as ACE inhibitors or ARB, ß blockers, and diuretics. The predecessor sGC stimulator riociguat has already been studied in such a population, i.e. advanced systolic HF, in combination with beta-blockers (>90% of patients), ACE inhibitors / ARB (>90% of patients), and mineralocorticoid receptor antagonists (>70% of patients) in the LEPHT study using titration based on the trough SBP. Despite the blood pressure lowering of higher doses of sGC stimulators, and despite significant improvements in cardiac index and quality of life in the presence of standard HF therapy, no significant blood pressure decrease after 16 weeks compared to placebo was observed up to the highest titration target dose arm at an even higher equipotency than the planned dose range in the BAY 1021189 program. Increases in high sensitivity troponin were not more frequent in the highest target dose arm compared to placebo, and the average glomerular filtration rate (GFR) increased non-significantly by 1 ml/min. Although the actual dose of 2 mg was only reached in 61% of patients randomized to the 2 mg arm, given the dose proportionality in LEPHT exposure analyses indicate that equally potent doses even above 1 mg riociguat (3rd exposure quartile) had no blood pressure lowering effects. Doses in the present study are not expected to have blood pressure lowering effects before the highest titration target is reached in the 10 mg arm.

Since the assumption of safety of any equivalence doses of BAY1021189 in this range depend thus far on extrapolations by pharmacokinetics/pharmacodynamics (PK/PD) modeling and simulation, an extra safety margin was built in. Starting doses in all arms are doses without hemodynamic effects in healthy volunteers, which are expected to be equipotent to half (2.5 mg starting dose arms) or less than half (in the 1.25 mg arm) of 0.5 mg riociguat, a blood

pressure-neutral starting dose in LEPHT. Although the two higher target dose arms are forced titration regimens, the two lower dose arms are fixed dose regimens with sham uptitration only.

2. Study objective

The objective of the study is to find the optimal dose of the oral sGC stimulator BAY 1021189 for Phase III that can be given in addition to standard therapy for heart failure with reduced EF (HFrEF) by characterizing the safety, tolerability, pharmacodynamic effects, and pharmacokinetics, and detecting a significant dose-response relationship in the primary endpoint change in NT-ProBNP at 12 weeks in patients with worsening chronic HFrEF.

3. Investigator[s] and other study personnel--amended

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature sheet before subject recruitment may start at the respective center. Likewise, all protocol amendments must be signed and dated by the principal investigator before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

The coordinating investigators for this study are:
Mihai Gheorghiade MD
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8036 Graz,

Austria

External data evaluation bodies (Study committees)

1. Independent data monitoring committee (DMC)

Ongoing safety monitoring during the conduct of the study will be performed by an external data monitoring committee (DMC).

Analysis periods and procedures will be defined in an operational charter (DMC charter) filed in the study file. Following data review, the DMC will provide written recommendations that will be transferred to Bayer. All other definitions will be provided in the DMC charter.

2. Steering committee

The conduct of this study will be overseen by the steering committee which is made up of a panel of experts in the field.

3. Central independent blinded echocardiography core lab

The echocardiography data will be collected centrally for independent blinded review and adjudication. Further procedural details will be documented in the core lab manual.

4. Central independent blinded clinical events committee *(CEC)*

Blinded adjudication of all hospitalizations and deaths will be performed by a central clinical events committee (CEC) as described in the CEC manual.[8] The committee will be provided with all relevant documentation related to the event. The procedures followed by the committee will be described in the ***CEC*** manual. Adjudication results will be the basis for the final analysis. Further details will be documented in the ***CEC*** manual.

4. Study design--amended

This is a prospective, randomized, placebo-controlled, double blind, 5 parallel arms, global multi-center dose finding phase II trial.

Screening

Screening may be initiated any time after admission of a subject to the hospital for HF (Figure 4–1). As an equivalent to hospitalization, use of IV diuretic treatment for HF without hospitalization is also accepted as indicator of worsening chronic HF.

Candidates for screening are required to have a history of chronic HF (New York Heart Association [NYHA] functional class II – IV) and treatment with standard HF therapy for ≥30 days prior to hospitalization or equivalent. Furthermore, suitable candidates need to fulfill the following criteria:

- history of LVEF <45%

[8] Revised via Amendment 2

- symptoms and signs of congestion [clinical **or** radiographic signs in routine chest x-ray demonstrating pleural effusion, pulmonary congestion (redistribution, interstitial or alveolar edema), or cardiomegaly] at hospitalization or equivalent
- NT-ProBNP or BNP above the cut-off given in the inclusion criteria at any time upon hospitalization or equivalent in local labs

These three screening criteria are collected from available clinical routine and do not represent study procedures.

Randomization

Subjects who meet the screening criteria are eligible for randomization upon clinical stabilization as defined in the inclusion criteria below. Randomization should occur when the LVEF <45% is confirmed in local baseline echocardiography by the investigator who will determine if the inclusion/exclusion criteria are met.

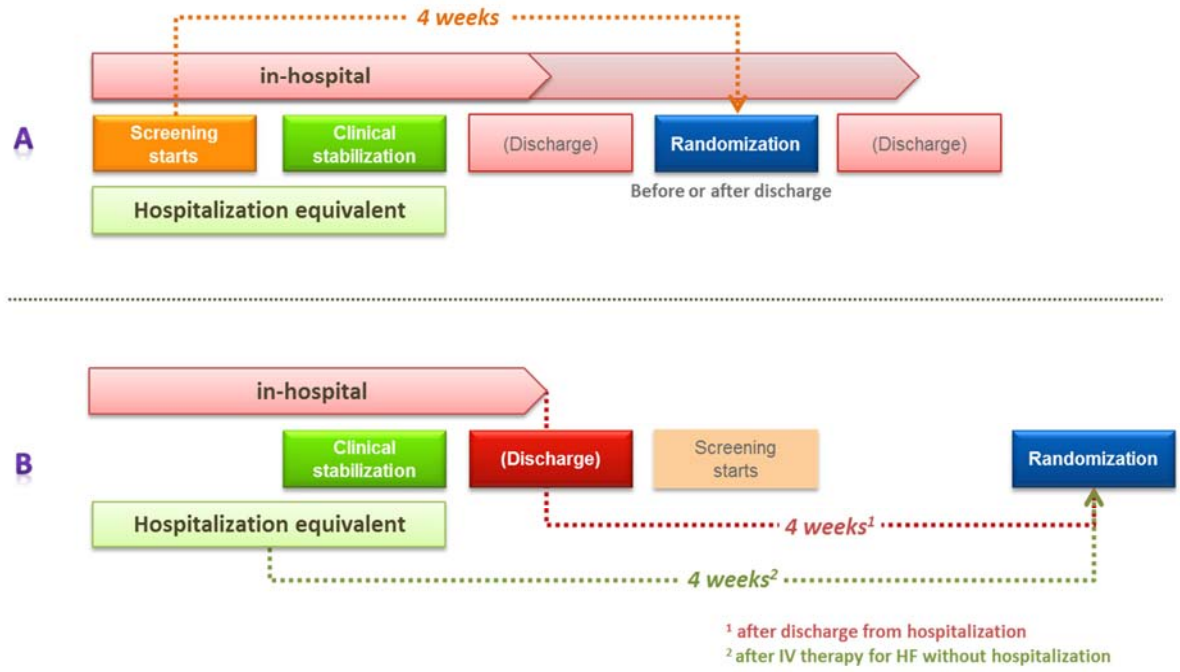

Figure 4–1: Time schedule of screening and randomization.

A: if screening starts upon admission to the hospital or equivalent, randomization must occur within 4 weeks, after the subject was clinically stabilized, and before or after discharge.
B: if screening started after discharge or after IV therapy for HF without hospitalization, then the randomization timeframe extends from discharge or after IV therapy for HF without hospitalization until up to 4 weeks after discharge.

Treatment

Subjects will be treated as given in Section 6.1 (Treatments and dosing regimen).

End-of-treatment
End of treatment is reached at visit 5 after 12 weeks of treatment, when echocardiography, laboratory, clinical, and safety read-outs are collected.

Follow-up
A safety follow-up visit is scheduled at 30±5 days after end of treatment or discontinuation of study drug. ***In addition, the vital status will be collected at 114±5 days after randomization for all subjects who prematurely discontinue study drug.***[9]

Primary variable
Change from baseline to week 12 in log-transformed NT-proBNP

End of study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last subject for all centers in the respective country has occurred.

The end of the study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

5. Study population

Subjects stabilized after hospitalization or IV diuretic treatment for worsening chronic HF with reduced EF who meet all inclusion and none of the exclusion criteria will be eligible for enrollment in the study.

5.1 Eligibility

5.1.1 Inclusion criteria

- Written informed consent signed before any study-specific procedure
- Worsening chronic heart failure (WCHF) requiring hospitalization (or IV diuretic treatment for HF without hospitalization) with initiation of study treatment after clinical stabilization

  Diagnostic methods:

  - History of chronic HF: NYHA class II-IV and treatment with standard HF therapy ≥30 days before hospitalization (or before IV diuretic treatment for HF without hospitalization)
  - Worsening HF at hospitalization (or at the time of IV diuretic treatment for HF without hospitalization)

[9] Added via Amendment 2

- NT-proBNP ≥1000 or BNP ≥300 if in sinus rhythm, **or** NT-proBNP ≥1600 or BNP ≥500 pg/mL in atrial fibrillation (A. fib.) in local routine labs, **and**
- Symptoms and signs of congestion [clinical **or** radiographic signs in routine chest x-ray demonstrating pleural effusion, pulmonary congestion (redistribution, interstitial or alveolar edema), or cardiomegaly]

o Clinical stabilization defined by

- no IV vasodilator for >24h and no IV diuretic for >12h before randomization **and**
- SBP ≥110 and <160 mmHg and resting HR ≥50 and <100 bpm at randomization (see Section 7.1.4)

o LVEF <45% by echocardiography at randomization

- Ability to understand and follow study-related instructions
- Men or confirmed postmenopausal women or women without childbearing potential based on surgical treatment such as bilateral tubal ligation, bilateral ovarectomy, or hysterectomy. Men enrolled in this study must agree to use adequate barrier birth control measures during the treatment period of the study.

5.1.2 Exclusion criteria--amended

- Legal lower age limitations for adults (country specific)
- IV inotropes at any time ***between*** hospitalization ***and randomization***[10]
- Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HF, including
  - subjects tolerant of and treated with isosorbide dinitrate for chronic HFrEF according to guideline recommendations
  - subjects requiring nitrates as anti-anginal therapy in addition or alternatively to beta-blockers
- Cardiac comorbidity (either of the following)
  - Specific HF etiologies, including
    - Hypertrophic cardiomyopathy with LV outflow tract obstruction; **or**
    - Pericardial disease, such as constrictive pericarditis; **or**
    - Infiltrative or inflammatory myocardial disease such as acute myocarditis, amyloidosis, sarcoidosis; **or**
    - Valvular heart disease ***with***

[10] Clarified via Amendment 2

- severe aortic or ***primary***[11] mitral regurgitation
- moderate or severe aortic stenosis
- any mitral stenosis requiring surgical repair
- active endocarditis

- Acute coronary syndrome, including unstable angina, NSTEMI or STEMI, or CABG within 60 days prior to randomization; or
- ***Current*** indication for PCI or CABG ***(at the time of randomization)***[12]
- Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since
- Symptomatic carotid stenosis, or transient ischemic attack (TIA) or stroke within 30 days prior to randomization
- New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization
- Listing for heart transplantation and/or anticipated/implanted ventricular assist device
- Complex congenital heart disease

- Non-cardiac comorbidity, indicated by either of the following at the time of randomization
  - Glomerular filtration rate <30 ml/min/1.73 m^2 calculated by Modification of Diet in Renal Disease [MDRD] formula (23)
  - Hepatic insufficiency classified as Child-Pugh B or C
  - Morbid obesity with a BMI >4***5***[13] kg/m^2
  - Malignancy or other non-cardiac condition limiting life expectancy to <1 year, per physician judgment
  - Severe pulmonary disease with either requirement of continuous home oxygen or bronchial artery embolization (BAE) for massive hemoptysis
  - Subjects with allergies, intolerance or hypersensitivity to investigational drug or any of the excipients
  - Medical condition or history thereof that in the opinion of the investigator would impair the ability to complete the planned study procedures

- Concomitant Treatment with a phosphodiesterase type V (PDE5) inhibitor or sGC stimulator

[11] Clarified via Amendment 2
[12] Clarified via Amendment 2
[13] BMI exclusion changed from 40 to 45 kg/m ^{2} via Amendment 2

- ***Previous (within 30 days of randomization) or concomitant*** participation in another clinical study with investigational ***medicinal*** product(s).[14]

- ***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).***[15]

- ***Previous assignment to treatment during this study.***[16]

Note: Re-screening is only permitted on one occasion if the subject's previous screening visit was >30 days before the date of re-screening, and re-screening examinations will only be performed after having received a second written informed consent from the subject.

5.2 Withdrawal of subjects from study drug and replacement

5.2.1 Withdrawal--amended

Subjects *must* be withdrawn from study drug for the following reasons:

- At their own request or at the request of their legally acceptable representative at any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of the study drug would be harmful to the subject's well-being.
- If any adverse event occurred, the investigator believes that for safety reasons (i.e., adverse event) it is in the best interest of the subject to stop study drug. Investigators must reassess the subject's individual risk-benefit ratio on a continuous basis.
- If SBP <90 mmHg with symptoms of hypotension persists >24 hours, or an AE of acute renal failure does not resolve within 10 days, or in case of repeated occurrence of an AE of acute renal failure upon resumption of study drug, or if the subject does not tolerate the lowest dose of 1.25 mg, or if more than one dose reduction is required (see Section 6.1).
- In case of pregnancy or breastfeeding.
- If any investigational drug other than the study drug is used.
- If subject interrupts intake of study drug lasts for more than 10 consecutive days, or for more than a total of 14 days during the treatment period (see Section 6.1.2).
- If the subject develops clear indication for nitrates, such as angina which cannot be managed with alternative antianginals (***see Section 6.8***).[17]

[14] BMI exclusion changed from 40 to 45 kg/m 2 via Amendment 2
[15] Added via Amendment 2
[16] Added via Amendment 2
[17] Editorial change via Amendment 2

Subjects *may* be withdrawn from study drug for the following reasons:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- If any exclusion criterion applies during treatment.
- If a significant violation of the protocol occurs, as defined by the sponsor and the coordinating investigator.
- If the randomization code is broken via Interactive Voice / Web Response System (IxRS).

A “drop-out” is defined as a subject who permanently discontinues study drug any time after randomization for any reason

A “screening failure” is defined as a subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study prior to randomization.

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the subject's medical records.

If a subject prematurely discontinues study drug and if any study drug has been taken, the subject must be advised to return to the study center for the premature discontinuation visit as soon as possible. All attempts should be made to collect echocardiography, laboratory, clinical, and safety read-outs as soon as possible upon discontinuation of study drug. The visit should take place as soon as possible after study drug was discontinued, and replaces all other scheduled visits before the safety follow-up visit. This safety follow-up visit will take place at 30±5 days after last intake as for all other subjects who have taken study drug. ***In addition, the vital status will be collected after premature discontinuation for all subjects at 114±5 days after randomization. This serves to standardize the collection of vital status information at the timepoint of 12 weeks + safety follow-up period of 30±5 days, for all randomized subjects irrespective of duration of study drug treatment.***[18]

5.2.2 Replacement

Randomized subjects who withdraw prematurely will not be replaced

5.3 Subject identification

Upon signing the informed consent form, each subject will be assigned a unique 9-digit subject identification (SID) number for unambiguous identification throughout the study; it is constructed as follows:

[18] Added via Amendment 2

Digits 1 - 2: Unique country number

Digits 3 - 5: Study center number, unique within any country

Digits 6 - 9: Subject number, unique within any study center of a given country. Sequential number reflecting the order in which the subjects signed the informed consent form at the center

6. Treatment[s]

6.1 Treatments and dosing regimen

BAY 1021189 IR tablets are pink coated tablets, containing 1.25 mg, or 5 mg BAY 1021189. BAY1021189 matching placebo tablets will also be supplied.

Subjects will take BAY 1021189 and placebo once daily in the morning with food. The starting dose will be 1.25 mg or 2.5 mg of BAY 1021189 or matching placebo.

Subjects will be randomized to either

1. Placebo and sham titration
2. 1.25 mg and sham titration
3. 2.5 mg and sham titration
4. 2.5 mg, which will be up-titrated to 5 mg after 14 days
5. 2.5 mg, which will be up-titrated to 5 mg after 14 days and to 10 mg after 28 days

Titration steps at 14 and 28 days include sham titrations in groups 1, 2, and 3, and after 28 days in group 4. The maximal dose of BAY1021189 is 10 mg o.d. in the 10 mg treatment group, 5 mg o.d. in the 5 mg treatment group, 2.5 mg o.d. in the 2.5 mg group, and 1.25 mg o.d. in the 1.25 mg group.

Titration in all groups will depend on systolic blood pressure (SBP) before intake of the dose:

- Double dose: If SBP ≥100 mmHg
- Maintain dose: If SBP between 90 and <100 mmHg
- Halve the dose: if SBP <90 mmHg without symptoms of hypotension

Dose halving is possible at any time if the investigator feels this is justified for safety reasons. If a second dose halving is required this will result in discontinuation of study drug treatment, and down-titration attempts from a dose of 1.25 mg will result in discontinuation (see discontinuation rules).

6.1.1 Temporary discontinuation from study drug

- Temporary discontinuation for hypotension or renal failure:
    - Reasons:
        - SBP <90 mmHg with symptoms of hypotension, **or**

- Adverse event (AE) of acute renal failure (report as AESI, see Section 7.1.6)

- Restart with half dose
  - after 24 hours if SBP recovers ≥ 90 mmHg and symptoms resolved
  - within 10 days once the AE of acute renal failure has resolved
- If temporary discontinuation was necessary before visit 3, then uptitration will be possible in line with titration rules; after visit 3, no subsequent uptitration will be allowed

- Temporary discontinuation for any other reason
  - Discontinuation up to 3 days
    - Resume study drug intake as planned with unchanged dose unless otherwise required
  - Discontinuation for 3 to 10 days
    - Restart with half the dose the subject took at the time the study drug was discontinued
    - If discontinuation occurred before visit 3, then uptitration will be possible in line with titration rules; if discontinuation occurred after visit 3, no subsequent uptitration will be allowed

6.1.2 Permanent discontinuation from study drug

- if SBP <90 mmHg with symptoms of hypotension persists >24 hours, or the AE of acute renal failure does not resolve within 10 days
- if SBP <90 mmHg or AE of acute renal failure occur at the dose of 1.25 mg
- in case of the repeated occurrence of an AE of acute renal failure upon resumption of study drug
- if study drug was discontinued for more than 10 consecutive days or for a total of 14 days before visit 5 (see Section 5.2.1)

For follow-up of subjects after discontinuation see Section 5.2.1.

6.2 Identity of study treatment

Table 6–1: Identity of test drug / BAY 1021189 tablets and matching placebo

Sponsor's substance code	BAY 1021189
Generic name / brand name	Not applicable
Sponsor's material name and number	BAY 1021189 TABL 1.25 MG 109 COAT Material no: 80627793 BAY 1021189 TABL 5.0 MG 108 COAT Material no: 80627807 BAY 1021189 PLAC TABL 110 COAT Material no: 80627785
Formulation	Coated tablet
Tablet strength	1.25 mg, 5 mg or placebo
Composition	Active ingredient: BAY 1021189 micronized Other ingredients: Cellulose microcrystalline, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, sodium laurilsulfate, talc, titanium dioxide, ferric oxide Placebo: Cellulose microcrystalline, hypromellose, lactose monohydrate, magnesium stearate, talc, titanium dioxide, ferric oxide
Type of primary packaging	Blister: Film 300 µm primary packaging colorless transparent, Foil 20 µm Al sealable to primary packaging
Marketing Authorization Holder if applicable	Not applicable

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk ware of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance (QA) group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor study file.

Study drugs need to be stored according to the label text.

6.3 Treatment assignment

Following a screening visit, eligible subjects stabilized after an episode of worsening chronic HF will be randomly allocated 1:1:1:1:1 via block randomization to one of the 5 equally sized groups (4 BAY1021189 groups, 1 placebo group) using an Interactive Voice/Web Response System (IxRS) and will receive treatment with study drug or placebo for 12 weeks. The study site investigator or designee will assign kit numbers at drug dispensing visits via IxRS. Subjects are to take 2 tablets once daily in the morning throughout study drug treatment. In case subjects are randomized in the afternoon first tablets can be taken then and should be continued the next day in the morning.

6.4 Blinding--amended

Tablets containing 1.25 mg and 5 mg BAY 1021189 and placebo tablets will be identical in appearance (size, shape, color). The packaging and labeling are designed to maintain the blinding of the investigator's team and to the subjects. The study data will remain blinded for each treatment group, until database lock and authorization of data release.

In the event of suspected unexpected serious adverse reactions (SUSARs; see Section 7.5.1.5), the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment.

In this study, the following events are outcome events and/or consistent with the underlying condition and will be considered as disease related in the defined study population:

- ***Acute heart failure***
- ***Chronic heart failure***
- ***Worsening chronic heart failure***
- ***Arrhythmia / cardiac arrest***
- ***Myocardial Infarction***
- ***Transient Ischemic attack or stroke***
- ***CV death***

For the purposes of this trial, these events will not be subject to systematic unblinding and expedited reporting process, if reported as serious adverse drug reactions. They will be captured in the Global Pharmacovigilance database, in the eCRF and undergo regular central adjudication and unblinded DMC review.[19]

Emergency unblinding by the investigator

In case of emergency or any finding that requires unblinding, the investigator will be able to break the blind for an individual subject via IxRS according to the unblinding procedure

[19] Outcome events consistent with underlying condition not subject to unblinding as SAEs added via Amendment 2.

implemented. This will allow breaking the blind for an individual subject without impairing the study as a whole unless safety findings required unblinding.

The code can be broken by the investigator, or other responsible person, when knowledge of the subject's treatment is required for the clinical management of the subject. Whenever possible, the sponsor is to be contacted to discuss the case before the code is broken. If it becomes necessary to know the individual treatment during the study and thus to break the code for that subject, the date, time, and reason are to be recorded in the subject's medical notes and relevant eCRF page. The investigator is required to promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to a serious adverse event) of the study treatment.

Unblinding for ongoing safety monitoring

To allow ongoing safety monitoring during the conduct of the study by an external DMC, members of the Committee will receive unblinded safety data. The involvement of an external Statistical Analysis Center in this process will ensure that unblinded information is not available for third parties. Details of the process are described in the DMC charter.

6.5 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization (CRO)), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug via IxRS and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

6.6 Treatment compliance

To monitor compliance, the investigator will be required to complete a drug dispensing log for each subject. Overall compliance with study drug intake should be between 80% and 120% of the scheduled drug intake at the end of study drug treatment. The date of dispensing the study drug to the subject will be documented.

Study drug will be dispensed at Visit 1, Visit 2, Visit 3, and at Visit 4. Subjects should return all remaining unused study drug at each visit.

Accountability has to be determined for all tablets at each visit. To facilitate this, subjects must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

6.7 Post-study therapy

The investigator must provide follow-up medical care for all subjects who complete the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care as required.

6.8 Prior and concomitant therapy--amended

Permitted standard background treatment

- Standard HF treatment following guideline recommendations (4,5)
- Any dose adaptations, addition, changed or added route of administration, omission or cessation of concomitant standard therapy including diuretics, ACE inhibitors, ARB, aldosterone antagonists, ß-blockers and digoxin are possible whenever deemed necessary by the investigator such as uptitrations in line with guideline-recommended dosing irrespective of blinded titration of the study drug .
- All changes in background therapy will be recorded and analyzed including changes in doses.

Prohibited prior and concomitant medications:

- Nitrates or NO donors: any routes are not allowed during study drug treatment; IV therapy with nitrates or NO donors is only allowed until 24 h before randomization. ***It is recommended that nitrates should not be administered to any subject previously on study drug earlier than 3 days after the last dose of study drug. Should there be an urgent need for nitrate administration, they should be administered in a monitored inpatient setting.***[20]
- Other IV vasodilators: only allowed until 24 h before randomization
- PDE5 inhibitors: only allowed until 24 h before randomization
- sGC stimulators other than the study drug are not allowed during study drug treatment

7. Procedures and variables

7.1 Schedule of procedures--amended

Time deviations from the given visit schedule will be documented as protocol deviations, if applicable. Respective time windows are specified in the sections below. For a tabulated overview, see study flow chart below.

[20] Editorial change; moved from Section 5.2.1 via Amendment 2.

Table 7–1: Study Flow Chart--amended

Study period	Screening[1]	Baseline	Titration / Sham titration		Treatment	End of treatment	Safety Follow-Up[11]
Visit		**1**	**2**	**3**	**4**	**5[3]**	
Day / Window	**-28 - 0[1]**	**0**	**14±2[2]**	**28±2[2]**	**56±2[2]**	**84±2[2]**	**+30±5**
▪ Signed written informed consent available ▪ Demographic data ▪ Medical and surgical history ▪ Local lab for eligibility	●						
Concomitant medication	●		Record any new or ongoing medication or changes in dosage				
Smoking & alcohol history	●					●[4]	
Check in- / exclusion criteria	●	●					
Randomization (IxRS)		●					
Quality of life (KCCQ, EQ-5D-3L)		●		●	●	●	
NYHA class	●	●	●	●	●	●	
Blood pressure, heart rate[5]	●	●[5,6]	●[5]	●[5]	●[5]	●[5,6]	●
Echocardiography		●[6]				●[6]	
Central lab blood sample[7]		●	●	●	●	●	●
Central lab PK sampling[8] Prior to study drug intake 1-3 hours post study drug 4-6 hours post study drug		 ● ●	● ●	● ● ●	● ●	●[12]	
Central lab exploratory biomarkers		●				●	
Physical exam, weight, height[9]	●	●	●	●	●	●	●
12-lead ECG[10]	●	●	●	●	●	●	●
Adverse events	●	●	●	●	●	●	●
Drug accountability, collect unused study drug			●	●	●	●	
Dispense study drug		●	●	●	●		
Titration / sham titration			●	●			

1 Can start from hospitalization (or equivalent) up to 4 weeks after discharge (or after clinical stabilization upon hospitalization equivalent) and no more than 4 weeks before randomization
2 Allows for timeframes of 5 days, e.g. visit 2 can take place on day 12 to 16
3 Completion or premature discontinuation visit (in case of premature stop of study drug, the same measurements and procedures should be performed as at visit 5)
4 Only smoking at visit 5
5 3 measurements, 2 min apart; measurements are taken prior to and at 2 h ***± 15 min*** post study-drug dosing[21]
6 Additional ***HR*** and blood pressure ***measurement*** during echocardiography[22]
7 NT-ProBNP, clinical chemistry, hematology, coagulation
8 Samples are taken ***at baseline / trough at Visits 2 – 4 (prior to study drug dosing) and at Visit 5; at Visit 1 and Visit 3, 1-3 h and 4-6 h post study-drug dosing; and at Visit 2 and Visit 4, 1-3 h post study-drug dosing***[23]
Optional additional pre-dose sample on Day 1 (trough ***20-***24 hours after first study drug) for hospitalized subjects.
9 Height will be only measured once at the screening visit. Automatic calculation of body mass index (BMI) in the electronic case report form (eCRF) will use this result
10 In supine position, after resting for at least 10 min

[21] Clarified via Amendment 2
[22] Revised via Amendment 2
[23] Revised via Amendment 2

11 In case of premature discontinuation of study treatment, vital status will be collected 114±5 days after randomization by any method (telephone call, visit etc).[24]
12 At trough (no study drug intake at Visit 5)[25]
Abbreviations: IxRS, Interactive voice/web response system; KCCQ, Kansas City Cardiomyopathy Questionnaire; EQ-5D-3L, EuroQol Group 5-dimension, 3-level questionnaire; NYHA, New York Heart Association; ECG, electrocardiogram

7.1.1 Timing of assessment

All visits from Visit 1 to the last visit under treatment, i.e. Visit 5 must be started in the morning. Subjects will be instructed to take their daily dose at the study site (not taken at home) at visits 2, 3, and 4 as indicated in the study procedures.

Procedures for the screening visit can be performed on several days. Alternatively, screening visit and Visit 1 including randomization of subjects can take place on the same day.

If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of a study site investigator.

7.1.2 Informed consent

Before any screening examination takes place, potentially eligible subjects will be given a full explanation as to what the study would involve. This will be done both verbally and in writing in the form of a written subject information leaflet. Subjects will be given sufficient time to consider their participation in the study and to ask any questions. Subjects who are willing to take part in the study will then be asked to sign a subject information / informed consent form. This signature must be collected prior to the screening visit.

Screening examinations will only be performed after having received the subject's written informed consent.

7.1.3 Screening visit - Day -28 to 0

Screening can start upon any time after admission to the hospital for HF (see Section 4, study procedures: time schedule). As an equivalent to hospitalization, IV diuretic treatment for HF without hospitalization is also acceptable for screening as an indicator of worsening chronic HF.

The following procedures will be performed within 4 weeks before randomization of the subject:

- Confirm signed informed consent is available
- Allocation of unique SID number (see Section 5.3)
- Demographic data and other population characteristics including sex, race, ethnic group, year of birth, age, smoking history, and alcohol consumption (see Section 7.2.1)

[24] Added via Amendment 2
[25] Clarified via Amendment 2

- Medical history, incl. NYHA class (see Section 7.2.2)
- Prior and concomitant medication (see Section 6.8)
- Physical examination including height and weight [body mass index (BMI) will be calculated automatically in the eCRF] (see section 7.2.3)
- 12-lead electrocardiogram (ECG) in supine position, after resting for at least 10 min
- Vital signs in sitting position [blood pressure (BP) and heart rate (HR) after resting for at least 10 min], 3 measurements, 2 min apart; means will be calculated in the eCRF
- Continuous assessment of AEs will start immediately after signing the informed consent until the follow-up visit (if applicable)
- Assess inclusion and exclusion criteria (see Section 5.1), including those based on results from routine clinical procedures
    - local laboratory results for entry in the eCRF:
        - NT-proBNP or BNP or both if available (the value closest after hospitalization for HF or equivalent should be entered)
        - Serum creatinine (to calculate eGFR; the most recent value after IV diuretic therapy and within 1 week before randomization should be entered)
    - LVEF in previous history (to assist screening in particular if LVEF in previous history was between 40 and 45%, an additional non-mandatory routine echo may be considered if available; only the LVEF at randomization at investigator's discretion is essential for eligibility)
    - Symptoms and signs of congestion [clinical **or** radiographic signs in routine chest x-ray demonstrating pleural effusion, pulmonary congestion (redistribution, interstitial or alveolar edema), or cardiomegaly] upon hospitalization for HF or equivalent
- Schedule Visit 1 (Baseline) within 4 weeks after screening

7.1.4 Visit 1 (Baseline and randomization) - Day 0--amended

Randomization should occur latest until within 4 weeks after informed consent:

- Before randomization:
    - Assess subject eligibility (see Section 5.1; echo criteria see below)
    - The Kansas City Cardiomyopathy Questionnaire (KCCQ) and The EuroQol Group 5-dimension, 3-level Questionnaire (EQ-5D-3L) (see Section 7.3.2.4)
    - Assessment of NYHA class
    - Concomitant medications (see Section 6.8)
    - Adverse events (see Section 7.5)
    - Physical examination incl. weight

- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
- 12-lead ECG in supine position, after resting for at least 10 min
- Echocardiography (see echo manual)
  - LVEF will be assessed for eligibility at the discretion of the investigator
  - All echo exams according to the manual will be processed for independent central blinded adjudication in the echo core lab, and analysis of change from baseline will be based on these central results
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, exploratory biomarkers (central lab, see Section 7.6.1)

- Randomization to BAY 1021189 once daily or placebo (see Section 6.1)
- Dispense study drug for the first 2 week interval until Visit 2 and instruct the subject on how to take the study drug
- Subject to take first dose of study drug (exact time of intake must be documented)
- 2 h ***± 15 min***[26] after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart (exact collection time must be documented; peak drug concentration expected within 2 h after intake)
- Blood samples for PK after drug intake (exact collection times must be documented):
  - 1-3 h
  - 4-6 h
  - optional timepoint 20-24 h, i.e. before intake of the second dose of study drug (only in subjects who are not discharged the day after randomization)
- Schedule Visit 2 for Day 14±2

Screening visit and Visit 1 (Day 1) including randomization of subjects can take place on the same day. In this case, procedures listed for both visits need to be performed only once.

7.1.5 Visit 2 - Day 14±2--amended

Subjects need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled).

- Before titration / sham titration
  - Assessment of NYHA class
  - Concomitant medications (see Section 6.8)
  - Adverse events (see Section 7.5)
  - Physical examination incl. weight

[26] Clarified via Amendment 2

- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
- 12-lead ECG in supine position, after resting for at least 10 min
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, pharmacokinetics prior to drug intake (exact collection time to be documented; central lab, see Section 7.6.1)
- Drug accountability, incl. exact time of last dose intake the day before, and collect unused drug

- Titration/sham titration in accordance with dosing regimen in Section 6.1 and dispense study drug accordingly
- Subject to take first dose of titrated / sham titrated study drug (exact time of intake must be documented)
- 2 h ***± 15 min***[27] after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood samples for PK after drug intake (exact collection time must be documented):
  - 1-3 h
- Schedule Visit 3 for Day 28±2

7.1.6 Visit 3 - Day 28±2--amended

Subjects need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled).

- Before titration / sham titration
  - KCCQ and EQ-5D-3L (see Section 7.3.2.4)
  - Assessment of NYHA class
  - Concomitant medications (see Section 6.8)
  - Adverse events (see Section 7.5)
  - Physical examination incl. weight
  - Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
  - 12-lead ECG in supine position, after resting for at least 10 min
  - Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, pharmacokinetics prior to drug intake (exact collection time to be documented; central lab, see Section 7.6.1)

[27] Clarified via Amendment 2

- Drug accountability, incl. exact time of last dose intake the day before, and collect unused drug

- Titration/sham titration in accordance with dosing regimen in Section 6.1 and dispense study drug accordingly
- Subject to take first dose of titrated / sham titrated study drug (exact time of intake must be documented)
- 2 h ***± 15 min***[28] after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood sample for PK after drug intake (exact collection times must be documented):
  - 1-3 h
  - 4-6 h
- Schedule Visit 4 for Day 56±2

7.1.7 Visit 4 - Day 56±2--amended

Subjects need to come for this visit without taking the morning dose of the study drug (this applies only for the study drug. All others medications shall be taken as scheduled).

- Before daily drug intake
  - KCCQ and EQ-5D-3L (see Section 7.3.2.4)
  - Assessment of NYHA class
  - Concomitant medications (see Section 6.8)
  - Adverse events (see Section 7.5)
  - Physical examination incl. weight
  - Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
  - 12-lead ECG in supine position, after resting for at least 10 min
  - Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, pharmacokinetics prior to drug intake (exact collection time to be documented; central lab, see Section 7.6.1)
  - Drug accountability, incl. exact time of last dose intake the day before, and collect unused drug
- Dispense study drug accordingly in accordance with dosing regimen in Section 6.1
- Subject to take daily dose of study drug (exact time of intake must be documented)

[28] Clarified via Amendment 2

- 2 h ***± 15 min***[29] after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood sample for PK after drug intake (exact collection time must be documented):
  - 1-3 h
- Schedule Visit 5 for Day 84±2

7.1.8 Visit 5 (End of Treatment) - Day 84±2--amended

Subjects need to come to site after having taken the last dose of the study drug the morning before (this applies only for the study drug. All others medications shall be taken as scheduled).

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)
- Assessment of NYHA class
- ***Smoking history***[30]
- Concomitant medications (see Section 6.8)
- Adverse events (see Section 7.5)
- Physical examination incl. weight
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
- 12-lead ECG in supine position, after resting for at least 10 min
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, exploratory biomarkers, pharmacokinetics (exact collection time to be documented; central lab, see Section 7.6.1)
- Echocardiography (see section 7.3.2.1, all echo exams according to the manual will be processed for independent central blinded adjudication in the echo core lab)
- Drug accountability, incl. exact time of last dose intake the day before, and collect unused drug
- Schedule Follow-Up visit 30±5 days after Visit 5

7.1.9 Premature Discontinuation visit--amended

This visit will take place as soon as possible after premature discontinuation of study treatment due to any reason except death or lost to follow-up. The investigator should make every possible effort to ensure the visit take place.

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)

[29] Clarified via Amendment 2
[30] Added via Amendment 2

- Assessment of NYHA class
- ***Smoking history***[31]
- Concomitant medications (see Section 6.8)
- Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If a serious adverse event (SAE) has occurred, this should be followed up until the subject's condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable]
- Physical examination incl. weight
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; mean will be calculated in the eCRF
- 12-lead ECG in supine position, after resting for at least 10 min
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, exploratory biomarkers, pharmacokinetics (central lab, see Section 7.6.1)
- Echocardiography (all echo exams according to the manual will be processed for independent central blinded adjudication in the echo core lab)
- Drug accountability, incl. exact time of last dose intake, and collect unused drug
- Schedule Follow-Up visit 30±5 days after last intake of study drug

7.1.10 Follow-up visit (30±5 days after last intake of study drug) --amended

All randomized subjects should attend the follow-up visit.

- Concomitant medications
- Adverse events (see Section 7.5) [In case a (serious) adverse event has occurred, the event must be adequately followed-up. If an SAE has occurred, this should be followed up until the subject's condition has resolved or stabilized. Additional local legal requirements for follow-up procedures of AEs and SAEs have to be fulfilled if applicable.]
- Physical examination including weight
- 12-lead ECG in supine position, after resting for at least 10 min
- Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart; means will be calculated in the eCRF
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation (central lab, see Section 7.6.1)

[31] Added via Amendment 2

- ***If any subject fails to attend the follow-up visit and is deemed lost to follow-up after reasonable efforts to be contacted, every attempt should be made to obtain the vital status at a minimum (see Section 7.1.11).***[32]

7.1.11 Additional follow-up after premature discontinuation (Day 114±5 after randomization)

All randomized subjects who prematurely discontinue study drug treatment should be followed-up for vital status 114±5 days after randomization, regardless of the timepoint of premature study drug discontinuation. Vital status information can be collected by any method (telephone call, visit etc). [33]

7.2 Population characteristics

7.2.1 Demographic

The following demographic data will be collected in the eCRF:

- Year of birth and age at the screening visit
- Ethnic group
- Race (according to local law)
- Sex

7.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases, or surgeries) meeting all criteria listed below will be collected:

- Starting prior to signing the informed consent
- Pertaining to the study indication (e.g. orthopedic surgery which are not related to the development of heart failure do not need to be entered)
- Considered relevant to the study (e.g. smoking and alcohol history, CV diseases, incl. erectile dysfunction [ED])
- NYHA class
- Latest assessed LVEF value
- Comorbidities: chronic A. fib, arterial hypertension, hyperlipidemia, CAD, diabetes mellitu, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), sleep apnoea, anemia, erectile dysfunction
- Ischemic vs. non-ischemic cardiomyopathy
- Last HF hospitalization before the current HF worsening

[32] Added via Amendment 2
[33] Added via Amendment 2

- Medical history related to concomitant medication
- Device therapy [ICD incl. previous appropriate interventions such as shocks or ant-tachycardic pacing (ATP); cardiac resynchronization therapy (CRT); Pacemaker]

Detailed instructions on the differentiation between medical history and AEs can be found in Section 7.5.1.1.

7.2.3 Physical examination

All diagnoses, symptoms, signs, or findings during physical examination at screening that have a start date before signing of the informed consent and will be recorded in the medical history, all others (with a start date after signing the informed consent) will be recorded as AEs (see Section 7.5.1.1).

Physical examination includes the following signs & symptoms of HF:

- Dyspnea
- Orthopnea
- Fatigue
- Jugular venous distension
- Rales
- Edema

7.3 Efficacy

The following parameters will be used to assess the efficacy of the study drug treatments:

7.3.1 Primary Efficacy Variable

Choice of NT-ProBNP as primary efficacy variable

NT-ProBNP was significantly reduced by riociguat in the advanced systolic HF population of LEPHT. This effect is in line with the meaningful hemodynamic improvement with riociguat treatment, including decreased systemic and peripheral resistance and increased stroke volume without increases in pulmonary capillary wedge pressure, heart rate, and high sensitivity troponin t or serum creatinine. In order to explore this capacity in a population with less refractory stages of HF and in an additional lower equipotency range of the novel once daily sGC stimulator, the change in NT-ProBNP is considered a quantitative measure dose-response measure of this beneficial hemodynamic profile for dose selection to study clinical outcomes in a subsequent pivotal phase III.

Reductions in natriuretic peptide levels, whether achieved spontaneously or through application of appropriate medical therapy, appear to be associated with improvement in clinical outcomes (38). Therefore, selection of the BAY 1021189 dose by virtue of its quantitative NT-ProBNP-reducing capacities in phase II for studying clinical outcomes in phase III is promising.

The primary endpoint is:

Change from baseline to week 12 in log-transformed NT-proBNP.

7.3.2 Exploratory Efficacy Variables

7.3.2.1 Echocardiography--amended

Echocardiography exams, collected data, and processes for central blinded adjudication in the echo core lab are given in the echo manual. SBP, DBP, ***and HR***[34] will be measured during echocardiography in addition to acquisition of echo data. Echocardiography variables for exploratory analyses include

- LV ejection fraction (LVEF, %)
- LV end-diastolic volume (LVEDV), LVED volume index (LVEDVI, calculated as LVEDV/BSA)
- LV end-systolic volume (LVESV), LVES volume index (LVESVI, calculated as LVESV/BSA)
- Left atrial (LA) size (LA diameter, area, volume [LAV], volume index [LAVI, calculated as LAV/BSA])
- Lateral and septal e' (early diastolic mitral annular relaxation velocity at the lateral and septal mitral annulus, respectively, incl. calculation of average e')
- Pulmonary artery systolic pressure (PASP), estimated by tricuspid regurgitation velocity and inferior vena caval diameter, its change with respiration and hepatic vein flow in patients with tricuspid regurgitation
- Mitral regurgitation
- LV mass, LV mass index (calculated as LV mass/BSA)
- Wall thicknesses, incl. intra-ventricular septum diameter (IVSD), posterior wall thickness (PWT), anteroseptal wall thickness (ASWT)
- E, A (if in sinus rhythm), calculation of E/A and E/e' (using lateral, septal, average e') ratios
- E-wave deceleration time (EWDT)
- Stroke volume (SV, calculated by LVEDV - LVESV) and derived parameters, including SV index (SVI, calculated as SV/BSA), cardiac output (CO, calculated as SV*HR, CO), cardiac index (CI, calculated as CO/BSA), total arterial compliance (SAC, calculated as SV/PP), total peripheral resistance (TPR, calculated as MAP/CO*80)
- Effective arterial elastance (Ea), estimated as end-systolic pressure [end-systolic pressure (Pes) calculated as SBP times 0.9 (24)] divided by SV (SBP*0.9/SV)
- Ea index [EaI, calculated as Pes/(SV index)]

[34] Clarified and added via Amendment 2

- Left ventricular end-systolic elastance (Ees, calculated by a modified single-beat [sb] method employing systolic [Ps] and diastolic [Pd]) arm-cuff pressures, i.e. SBP and DBP measured during echocardiography, respectively; echo-Doppler SV, echo-derived EF and an estimated [est] normalized ventricular elastance at arterial end-diastole [ENd]: Ees(sb)=[Pd-(ENd(est)•Ps•0.9)]/(ENd(est) •SV), with ENd estimated from a group-averaged value adjusted for individual contractile/loading effects as described by Chen et al. (25)
- Ratio of Ea/Ees
- Stroke work, calculated as end-systolic pressure (Pes) × SV
- Stroke work/end-diastolic volume
- Strain and strain rate by speckle tracking imaging

7.3.2.2 Further efficacy biomarkers

For collection of biomarkers see Section 7.6.1.1 (Central labs). Biomarkers include

- Natriuretic peptides: BNP will be analyzed alongside NT-proBNP
- Galectin-3, growth differentiation factor 15 (GDF-15), osteopontin, pro-collagen III peptide (PIIINP), ST2, tissue metallopeptidase inhibitor 4 (TIMP-4), cGMP

7.3.2.3 Blood pressure and heart rate

For collection of blood pressure and heart rate see Section 7.6.3 (Vital signs)

- Systolic blood pressure (SBP)
- Diastolic blood pressure (DBP)
- Heart rate (HR)

The following calculated parameters are derived from measured SBP and DBP. Calculation will be performed centrally by data management.

- Mean arterial pressure (MAP)
- Pulse pressure (PP)

7.3.2.4 Health-related quality of life by KCCQ and EQ-5D-3L

EQ-5D and KCCQ are health assessment questionnaires that evaluate the subjects' health status and quality of life. The subject will be instructed to fill in the questionnaires themselves before any other procedure of each visit. Subsequently, a member of the site investigator's team will enter the responses into the eCRF.

The EuroQol Group 5-dimension, 3-level questionnaire (**EQ-5D-3L**) was introduced in 1990. The EQ-5D-3L essentially consists of 2 pages - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The

respondent is asked to indicate his / her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'best imaginable health state' and 'worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. It should be noted that the numerals 1 - 3 have no arithmetic properties and should not be used as a cardinal score.

The KCCQ is the leading health-related quality-of-life measure for patients with CHF. It was developed in the late 1990s to early 2000s by Dr. John Spertus at the Mid-America Heart Institute, Kansas City, MO, USA. It is a 23-item questionnaire that independently measures the impact of patients' HF, or its treatment, on 6 distinct domains:

1) Symptoms / signs – the KCCQ Symptom scale quantifies the frequency and severity of clinical symptoms in HF, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea, and edema / swelling.

2) Functional status – the KCCQ Physical Limitation scale measures the limitations patients experience, due to their HF, in performing routine activities.

3) Health perceptions – the KCCQ Quality of Life scale is designed to reflect patients' assessment of their quality of life, given the current status of their HF.

4) Social limitations – the KCCQ Social Limitation scale quantifies the extent to which HF symptoms impair patients' abilities to interact in social roles.

5) Self-efficacy and knowledge – numerous studies have underscored the importance of patients being engaged in the management of their disease. The KCCQ Self-efficacy scale quantifies patients' perception of how to prevent HF exacerbations and manage complications when they arise.

6) Change in symptoms – unlike the other 5 domains that provide cross-sectional quantification of patients' current status, the KCCQ Symptom Stability domain measures recent changes in patients' symptoms. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of the study and thereafter.

In addition, there are 2 summary scales, a Clinical Summary scale that combines the total symptom and physical function scores to replicate the NYHA Classification; and an Overall Summary Score that includes the total symptom, physical function, social limitations, and quality of life scores.

7.3.2.5 Clinical efficacy variables--amended

The following endpoints will be analyzed to explore the efficacy of study drug treatments on clinical outcomes:

- Composite endpoint of death from any cause, CV hospitalization, or emergency presentation for WCHF until Visit 5 (Day 84±2)
- Composite endpoint of CV death, CV hospitalization, or emergency presentation for WCHF until Visit 5 (Day 84±2)

- Change in health-related quality of life from baseline to Visit 5 (Day 84±2) assessed by the KCCQ and EQ-5D-3L
- Major adverse cardiovascular events (MACE): CV death, non-fatal acute myocardial infarction, non-fatal cerebrovascular accident (transient ischemic attack or stroke)

Hospitalizations [i.e. any unplanned admission to hospital, i.e. completion of hospital admission procedures and 1 overnight (i.e. date change) stay or until death of subject occurs] or deaths will be classified in 2 primary categories: CV and non-CV. The pre-specified secondary categories for CV hospitalizations are as follows:

- Worsening heart failure
- Acute myocardial infarction
- Arrhythmia
- Transient ischemic attack and stroke
- Other CV hospitalizations

In addition, every other hospitalization classified as CV hospitalization by the central clinical event committee will be considered as such. Non-CV hospitalizations will be classified in 5 secondary categories: accidental / trauma, infection, malignancy, renal failure, and other non-CV hospitalizations (to be specified). The pre-specified secondary categories for CV deaths are as follows:

- Death due to heart failure or cardiogenic shock
- Death due to acute myocardial infarction
- Sudden cardiac death
- Death due to stroke
- Death due to other CV causes

In addition, every other death classified as CV death by the central committee will be considered as such. Non-CV death will be classified in 2 secondary categories: nonmalignant causes and malignant causes.

Detailed definitions will be provided in the ***manual*** of the ***CEC***[35].

Emergency presentation for WCHF will be defined as newly developing signs and symptoms of WCHF after start of treatment with study drug requiring unscheduled non-hospitalization healthcare resource utilization (emergency room and non-routine clinic visits) and IV treatment with diuretics, ***vasodilators***,[36] and / or positive inotropic agents.

Blinded adjudication of all hospitalizations and deaths will be performed by a central ***CEC*** as described in the ***CEC manual***. Non-CV hospitalizations will not be considered for the composite endpoint. All emergency presentations for WCHF reported by the investigators as

[35] Clarified via Amendment 2
[36] Clarified and added via Amendment 2

adverse event of special interest will also be considered for the composite endpoint as well as all deaths reported until Visit 5 (Day 84±2) of each subject.

7.3.2.6 Further clinical efficacy variables

- Change in NYHA functional class
- ICD / CRT-D interventions such as appropriate shocks and anti-tachycardic pacing when diagnostic of sustained ventricular tachycardias (VT) in pre-defined rapid zone
- A. fib. (new / recurrent onset; A.fib. associated adverse events)
- Changes in concomitant standard HF therapy, including ACE inhibitors, ARBs, ß-blockers, diuretics etc.: dose adaptations, addition or omission of concomitant medication
- Composite Congestion Score (26):

Score	0	1	2	3
Signs/Symptoms				
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
Jugular venous distension (cmH_2O)	≤6	6–9	10–15	≥15
Rales	None	Bases	To <50%	To >50%
Edema	Absent / trace	Slight	Moderate	Marked

The complete list of variables to be analyzed for this study will be provided in the statistical analysis plan.

7.4 Pharmacokinetics / pharmacodynamics--amended

For the investigation of systemic exposure to BAY 1021189 and its relationship with treatment effects, the plasma concentrations of BAY 1021189 will be determined at different time points using a sparse sampling approach in all participating subjects.

Blood samples will be collected at the following timepoints:

- Visit 1: 1-3 h and 4-6 h after drug intake (exact collection time must be documented).
- For subjects hospitalized at Visit 1: optional blood sampling 20-24 h after first drug intake (before intake of second dose of study drug).
- ***Visit 2: baseline / trough (prior to drug intake); 1-3 h after drug intake (exact collection time must be documented).***[37]
- ***Visit 3: baseline / trough (prior to drug intake); 1-3 h and 4-6 h after drug intake (exact collection time must be documented)***

[37] 4-6 hr post study drug intake PK sample removed from Visit 2 and Visit 4 via Amendment 2.

- Visit 4: baseline / trough (prior to drug intake); 1-3 h after drug intake (exact collection time must be documented).
- Visit 5: baseline / trough.

The PK analysis will be performed under the responsibility of Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, GDD-GED-DMPK Bioanalytics, 42096 Wuppertal, Germany.

7.5 Safety

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject 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

A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE
  (e.g. social hospitalization for purposes of respite care, or if they are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of “no” would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of “yes” indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject’s response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a “reasonable causal relationship” to protocol-required procedure(s).

Possible answers are “yes” or “no”

7.5.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

7.5.1.3 Assessments and documentation of adverse events

Attention is to be paid to the occurrence of AEs at all stages of the examination. Thus, the subject should be closely observed by the investigator.

Adverse events (AEs) observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the subject will be documented. The observation period for AEs will start with signing the informed consent, and will end with the last visit of follow-up. In case of ongoing study-related adverse events and medically relevant adverse events at the end of the study, the investigator is urged to monitor the subject and document the outcome on the subject's source document.

The investigator is responsible for the grading of each category mentioned. An assessment of the **seriousness** of the event will be made by the investigator, who is to complete a special form provided by the sponsor in the case of a SAE. However, SAEs will also be recorded on the AE page of the eCRF.

The sponsor has to carry out a separate assessment for expectedness, seriousness, and causal relationship to study drug.

Emerging AEs will be allocated to the period in which they have started, e.g. a symptom starting in the treatment period and continuing in the follow-up period without deterioration will only be documented in the treatment period.

When assigning the cause of death, "death" should not be recorded as an AE on the AE page.

Instead, "death" is the outcome of underlying AE(s).

7.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.5.1.1.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

The following non-serious AEs need to be reported in 24 hours:

1) Events of special interest; 2) Pregnancy and its outcome; 3) Re-challenge of AEs.

Notification of the independent ethics committees (IECs)/ institutional review boards (IRBs)

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

7.5.1.5 Expected adverse events--amended

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics for BAY 1021189.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

See also Section 6.4, disease-related events consistent with the underlying condition.[38]

7.5.1.6 Adverse events of special safety interest--amended

For this trial, the following safety related event of special interest has been defined:

- Acute renal failure (such as serum creatinine x2 or GFR decreased >50% or to <15 mL/min/1.73m^2)
- Newly developing signs and symptoms of WCHF requiring IV treatment with diuretics, ***vasodilators,***[39] and / or positive inotropic agents (see Section 7.3.2.5)

Any of these events have to be reported as an "important medial event" (see Section 7.5.1.1) and therefore as a SAE to the sponsor within 24 hours of becoming aware of the event as described in Section 7.5.1.4.

In any case, adverse events of special interest fulfilling any seriousness criterion should be reported as SAE (see also Section 7.5.1.1).

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study subject during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported.

Bayer usually does not gather information of drug exposure via the father, however, if those cases are reported, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

7.5.3 Safety biomarkers

The following safety biomarkers will be determined in addition to efficacy biomarkers and safety labs: Carboxyterminal cross-linking telopeptide (CTX); bone-specific alkaline phosphatase (bAP)

[38] Added via Amendment 2
[39] Added via Amendment 2

7.6 Other procedures and variables

The following safety variables will be assessed during the study:

- Blood sample for laboratory parameter measurements (see Section 7.6.1.1)
- 12-lead ECG
- Vital signs (blood pressure and heart rate): see Section 7.3.2.3
- Data regarding adverse events will be collected at all visits after signing of the informed consent

7.6.1 Laboratory assessments

7.6.1.1 Central laboratory

Only centrally analyzed blood samples will be considered for analysis.

The name and address for the central lab service provider can be found in the documentation supplied by the vendor. The following laboratory tests will be performed centrally:

NT-proBNP (primary endpoint)

Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelets; red blood cell distribution width (RDW)

Clinical Chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), creatine kinase (CK), lipase, creatinine, MDRD-calculated eGFR, urea, uric acid, bilirubin (total, conjugated, unconjugated), total protein, serum albumin, sodium, potassium, magnesium, calcium, phosphorus, glucose, cholesterol (total, LDL, HDL), triglycerides, high-sensitivity c-reactive protein (hsCRP), high-sensitivity troponin t.

Coagulation: partial thromboplastin time (PTT), international normalized ratio (INR)

Exploratory biomarkers: cGMP, BNP, galectin-3, PIIINP, GDF-15, osteopontin, ST2, TIMP-4, CTX, bAP

Biomarker	Mechanism	Rationale for use in HFrEF	Reference
Galectin-3 (Gal-3)	(Cardiac) fibroblast / cardiomyo-cyte stress	Gal-3 is barely detectable in cardiomyocytes but cardiac fibroblasts express high levels of this protein	29
		Serum Gal-3 predicts short-, mid- and long-term mortality and HF-associated hospitalization in early & late stage HFpEF and HFrEF	
GDF-15	Cardiomyo-cyte stress	GDF-15 is hardly detectable in the healthy myocardium but becomes induced upon cardiac diseases	30,31
		In early HF GDF-15 correlates strongly with indices of myocardial remodeling (LVMI, LVEDD, LVEF, LA diameter). In chronic HF GDF-15 predicted mortality	
ST2	Myocardial stress	In HF ST2 mRNA and protein are upregulated and protein becomes detectable in serum.	32
		In severe chronic HF change in serum ST2 independently predicts mortality or transplant.	
TIMP-4	CV tissue remodeling	TIMP-4 is expressed predominantly in the heart and vascular wall	33
		Serum TIMP-4 decreased upon VAD implantation	
PIIINP	Tissue remodeling / collagen synthesis	PIIINP is produced and secreted into the circulation upon collagen synthesis	34,35,36
		Increased baseline PIIINP levels are associated with increased risk of death in CHF patients and decreased in response to spironolactone or eplerenone	
Osteopontin (OPN)	Inflammation / tissue remodeling	OPN mRNA and protein are hardly detectable in healthy myocardium, but become detectable upon cardiomyocyte and fibroblast injury	37
		Plasma OPN decreased in CRT responders vs. increased in non-responders; changes in LVESV and plasma OPN correlated significantly	

7.6.1.2 Local laboratory

At the screening visit, local laboratory results from routine clinical examinations will be assessed to check the eligibility of the subject.

At least the following parameters must be measured at the screening visit and entered in the eCRF to check the subject's eligibility for the study:

- NT-ProBNP or BNP (cut-off: see inclusion criteria)
- Serum creatinine (eGFR will be calculated automatically in the eCRF using the MDRD formula)

7.6.2 12-lead ECG

ECGs in supine position will be assessed locally as safety measures: standard electrocardiograms (12-lead ECG) according to Goldberger / Einthoven and Wilson will be recorded after resting for at least 10 min at the screening visit, Visit 1 to Visit 5 or at the premature discontinuation visit as well as at the follow-up visit. All ECG print-outs will be identified with the SID as well as date and time of recording and will be attached to the subject's file.

ECG printouts will be examined by the investigator on the day of recording for safety and quality. Any new clinically relevant abnormality will be documented as an AE.

ECGs will be transferred and assessed centrally. The reading will be done in a standard way. Only the results of the central evaluation will be used for statistical evaluation of ECG data. The following ECG parameters will be analyzed: heart rate (HR), PR interval (PR), QRS duration (QRSD), QT interval (QT), and QT interval corrected for HR (QTc).

7.6.3 Vital signs--amended

After the subject having rested for at least 10 min, 3 measurements of vital signs, i.e. BP (SBP and DBP) and HR, will be performed at 2 min intervals at the screening visit, Visit 1 to 5 or at the premature discontinuation visit as well as at the follow-up visit in a sitting position.

Timepoints at visits (see flowchart):

- At the screening visit, visit 5, premature discontinuation visit and at follow-up visit: upon presentation after physical examination
- At visit 1 to 4: in addition 2 hours ***±15 minutes***[40] after drug intake

7.7 Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.

8. Statistical methods and determination of sample size

8.1 General considerations

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics (mean, standard deviation, minimum, median, quartiles, and maximum).

Medical history findings and AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes and medication by Anatomical Therapeutic Chemical (ATC) codes according to World Health Organization Drug Dictionary (WHO-DD).

[40] Clarified via Amendment 2.

Statistical analyses will be performed using statistical analysis system (SAS); the version used will be specified in the statistical analysis plan (SAP). Within this protocol the principle analyses for this study are described. Further details on the statistical analyses will be provided in the SAP that will be approved before database release.

The primary analysis will be performed on subjects with complete data in the primary endpoint. Handling of missing data for secondary endpoints and/or secondary analyses will be detailed in the SAP.

8.2 Analysis sets

Full analysis set (FAS): includes all subjects randomized to treatment. The FAS will be used to display baseline characteristics and to display efficacy analyses.

Safety analysis set (SAF): includes all FAS subjects that have at least one dose of study drug administered. The SAF will be used to display safety analyses.

Per protocol set (PPS): includes all subjects randomized to treatment that have a valid measurement of NT-proBNP at baseline and at week 12 and showed no major protocol deviations. The PPS will be the primary analysis set for the primary efficacy analysis.

Pharmacokinetics analysis set (PKS): includes all subjects randomized to treatment that have at least one valid set of PK/PD measurements.

Final decisions regarding validity for the individual analysis sets will be made during the Validity Review Meeting and documented in the Validity Review Report.

8.3 Variables

8.3.1 Primary variable

Change from baseline (visit 1) to week 12 (visit 5) in log-transformed NT-proBNP:
y = log-transformed NT-proBNP at week 12 – log-transformed baseline NT-proBNP

The goal of the primary statistical analysis is to detect a significant dose-response relationship.

8.3.2 Secondary variables

A detailed description of further variables can be found in Section 7.3.

8.3.3 Safety and tolerability variables

Safety and tolerability variables are described in Section 7.5

8.4 Statistical and analytical plans

8.4.1 Demographic and other baseline characteristics

Demographic variables and baseline characteristics will be summarized overall and by treatment group in FAS, SAF and PPS.

Specific baseline characteristics include

- Heart rhythm: sinus rhythm vs. A. fib.
- Diabetes vs. no diabetes
- Ischemic vs. non-ischemic cardiomyopathy

Disposition of subjects will be summarized overall and by treatment group. The number of subjects who withdrew from the study or from study treatment will be summarized along with the reason for discontinuation.

8.4.2 Efficacy--amended

Primary analysis

The goal of the primary statistical analysis is to detect a positive relationship between the oral sGC stimulator BAY 1021189 dose and the change in log-transformed NT-ProBNP from baseline to week 12. It is expected that log-transformed NT-proBNP will (on average) decrease from baseline to week 12 in subjects treated with BAY 1021189.

The primary endpoint will be analyzed in the per protocol analysis set. The analysis will be performed as randomized, thereby the analysis will assess the dose-response for the actual regimens used in this study. It is anticipated that most subjects will be uptitrated to the highest possible dose in each arm. Number of subjects with (sham) down-titrations from or incomplete (sham) up-titrations to the highest possible dose per arm are anticipated to be low but possible in every dose arm. Especially, also within the placebo arm, no complete mock up-titration is anticipated for a few subjects. In contrast to per-actual-dose or per-exposure approaches, the as randomized approach assures no bias is introduced by omitting subjects from especially the higher dose arms not up-titrated to or down-titrated from the respective highest possible dose.

For the primary analysis, the three highest dose arms (2.5 mg, 5 mg, and 10 mg) will be pooled and compared to placebo with a two-sample t-test at the one-sided significance level $\alpha = 5\%$. The 1.25 mg dose arm is assumed to have no or at most a very minimal effect and is hence not included in the pool of assumed effective dose arms. The test problem is defined by:

$$H_0^{pool}: \quad \mu_{pool} \geq \mu_p \quad \text{vs.} \quad H_1^{pool}: \quad \mu_{pool} < \mu_p,$$

where μ_{pool} is the mean change from baseline to week 12 in the pooled dose arms 2.5 mg, 5 mg, and 10 mg, respectively. μ_p is the mean change from baseline to week 12 in the placebo arm.

Analysis results will be back-transformed to the original scale for display of the results.

Secondary analyses

To obtain further insight on the responses in the primary endpoint, especially in the case when no significant result is obtained in the primary analysis, the dose-response relationship is analyzed by a linear regression model of the following form: $y_i = \beta_0 + \beta_1 x_i + e_i$, where

y_i	change from baseline in primary endpoint for subject i
β_0	Intercept (effect of null dose)

β_1 Slope parameter (dose-response relationship)
x_i assigned dose of subject *i*
e_i random error for subject i (assumed to be iid ~$N(0,\sigma^2_e)$)

The linear regression model will ensure the model can be fit even when no strict monoton dose-response relationship is observed (i.e. inconsistent point estimates). However, as part of the secondary analyses additional non-linear models will be fit to estimate the actual (non-linear) dose-response curve (see below).

The test problem is defined by

null hypothesis: H_0: $\beta_1 \geq 0$ vs.

alternative hypothesis: H_1: $\beta_1 < 0$.

If the null hypothesis of the primary analysis is rejected, the individual dose arms will each be compared to placebo with a two-sample t-test at the one-sided significance level $\alpha = 5\%$ in a sequential order (i.e., if all the previous null hypotheses have been rejected, the next null hypothesis will be tested):

- The 10 mg dose vs. Placebo: $H_0^{10}: \mu_{10} \geq \mu_p$ vs. $H_1^{10}: \mu_{10} < \mu_p$
- The 5 mg dose vs. Placebo: $H_0^{5}: \mu_{5} \geq \mu_p$ vs. $H_1^{5}: \mu_{5} < \mu_p$
- The 2.5 mg dose vs. Placebo: $H_0^{2.5}: \mu_{2.5} \geq \mu_p$ vs. $H_1^{2.5}: \mu_{2.5} < \mu_p$
- The 1.25 mg dose vs. Placebo: $H_0^{1.25}: \mu_{1.25} \geq \mu_p$ vs. $H_1^{1.25}: \mu_{1.25} < \mu_p$

where μ_{10}, μ_5, $\mu_{2.5}$, $\mu_{1.25}$, and μ_p are the mean changes from baseline to week 12 in the individual dose arms 10 mg, 5 mg, 2.5 mg, 1.25 mg, and placebo, respectively.

In case the primary analysis has not been successful, the comparisons of individual dose arms to placebo will be performed descriptively only.

The primary analysis will be repeated as a per actual dose analysis and a per exposure analysis. This analysis will give further insight into the response of the primary variable of subjects that have not been up-titrated onto the highest possible dose.

An exploratory analysis to estimate the (non-linear) shape of the true dose-response curve will be performed for the primary endpoint ***(some text deleted as of Amd 2[41])*** to aid in deciding which is the optimal dose. Further details on the functional dose-response models to be used and their statistical implementation will be specified in the SAP.

Analyses of exploratory efficacy variables

[41] The original protocol stated “each of the two primary endpoints”. This was an editorial change to “for the primary endpoint.” via Amendment 2. The original protocol included only one primary endpoint (see Section 8.3.1).

All echocardiography variables, as well as all efficacy biomarkers (including NT-proBNP), composite congestion score, and NYHA class and their changes from baseline will be summarized descriptively, including descriptive p-values.

Incidences of the composite clinical efficacy endpoints

- death from any cause, CV hospitalization, or emergency presentation for WCHF
- CV death, CV hospitalization, or emergency presentation for WCHF
- Major adverse cardiovascular events (MACE)

as well as their components will be given by treatment group. Frequency, durations, and recurrence metrics of hospitalizations, e.g. time to hospitalization or death, days out of hospital vs. in hospital etc.) will be analyzed.

Values and changes from baseline of KCCQ and EQ-5D-3L as well as their corresponding subscores/individual dimensions will be analyzed descriptively by visit and treatment group.

Sensitivity analyses

A comparison of the pooled two highest dose arms (5 mg and 10 mg) vs. placebo will be performed.

In order to adjust for (discrepant) baseline characteristics across treatment groups, sensitivity analyses will be performed including the respective baseline characteristic as covariate in the primary analysis model.

A meta-analysis of this study (15371) and of the study 15829 in subjects with HFpEF, which is conducted at the same time, will be specified in a separate SAP.

8.4.3 Safety

Adverse events

The adverse events analysis will be performed as treated in the SAF. All tabulations will be descriptive only.

The incidence of treatment-emergent AEs will be tabulated by treatment group. AEs are considered to be treatment-emergent if they have started or worsened after first application of study drug up to 5 days after end of treatment with study drug. Further tables will be produced for serious and/or drug-related treatment-emergent AEs. The incidence of AEs during follow-up (i.e. AEs occurring more than 5 days after end of treatment with study drug) will be tabulated separately.

Further safety parameters

Mortality in the 12 week period of the study will be summarized descriptively. Any deaths in the study period will be listed, with day of death relative to start and stop of study drug and cause of death.

The safety evaluation of laboratory data will include:

- Descriptive analysis of continuous laboratory parameters, and their changes from baseline by visit and treatment group.

- Incidence rates of treatment-emergent laboratory values outside of normal range by treatment group.
- Listings of laboratory data out of normal range.

Vital signs and their changes from baseline will be analyzed descriptively by visit and by treatment group.

The incidence rates of treatment-emergent ECG abnormalities will be tabulated by treatment group. A descriptive analysis of continuous ECG parameters and their changes from baseline by visit and treatment group will also be presented.

8.4.4 Pharmacokinetics/Pharmacodynamics

BAY 1021189 peak and trough plasma concentrations will be summarized per visit, separated according to actual dose. The following statistics will be calculated for each of the sampling points: arithmetic mean, standard deviation and coefficient of variation, geometric mean, geometric standard deviation and coefficient of variation, minimum, median, and maximum value and the number of measurements.

Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value a data point below LLOQ will be substituted by one half of this limit.

In addition, PK and, if applicable, PK/PD modeling using population approaches (e.g. NONMEM (39) to describe BAY 1021189 pharmacokinetics including potential influence of relevant subject covariables (e.g. age, gender, body weight, etc.) or potentially to relate parameters of clinical safety and efficacy response with BAY 1021189 plasma concentrations will be investigated under a separate detailed PK/PD evaluation plan.

8.5 Determination of sample size

Five dose regimens are compared in this study: 0.0 mg (Placebo), 1.25 mg (minimal effect dose), 2.5 mg, 5.0 mg, and 10.0 mg dose arm. The assumed treatment effects on log-transformed NT-ProBNP for these five dose levels are 0.000, -0.036, -0.135, -0.206, and -0.220 log(pg/mL), respectively.

Given this assumed dose-response relationship, the assumed mean treatment effect in the pooled 2.5 mg, 5 mg, and 10 mg arms is -0.187 log(pg/mL). Assuming a standard deviation of 0.52 log(pg/mL) for the primary efficacy endpoint, 65 valid subjects per treatment group will be required to achieve 80% power for the primary analysis (i.e., to conclude a significant difference between the pooled three highest dose treatment arms vs. placebo arm) with one-sided $\alpha = 5\%$. The total sample size therefore amounts to 325 valid subjects.

Assuming a 20% drop-out and invalidity rate, i.e. subjects not being valid for the per protocol analysis set, 410 subjects will need to be randomized to treatment. Assuming in addition a 20% screen-failure rate, approximately 513 subjects will need to be screened for this study.

9. Data handling and quality assurance

9.1 Data recording

Specific data (race and ethnic group) may be entered directly into the eCRF, for all other data source documentation must be available at the site. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (e.g. TOSCA; SAS). Clinical data management will be performed in accordance with applicable sponsor's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IxRS, laboratory, ECG, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

10. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by GCP guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to the Sponsor. The responsible unit (e.g. EC/IRB, head of the study center/medical institution) must supply to the Sponsor, upon request, a list of the EC/IRB members involved in the vote and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consenter (if the subject is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject / legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the subject's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

If the subject is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

11.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

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13. Protocol amendments

13.1 Amendment 2 (06 JUL 2014)

Description of the Amendment

Amendment 2 is the first global amendment to the original protocol, dated 16 JUL 2013. Amendment 1 (16 SEP 2013) is a local amendment for Japan only and is not included in the global integrated protocol.

The purpose of Amendment 2 is to implement clarifications (primarily in exclusion criteria and study procedures) and to correct minor errors or omissions.

13.1.1 Overview of changes to the study

13.1.1.1 Modification 1 – Clarifications and minor revisions

Exclusion criteria were clarified**.** The rationale for these revisions is to facilitate enrollment of appropriate subjects, to prevent overinterpretation and exclusion of eligible subjects, and to minimize protocol deviations.

- The exclusion criterion "IV inotropes at any time **after** hospitalization" was revised to "IV inotropes at any time between hospitalization and randomization" to clarify that there is no prohibition of inotropes after randomization (if HF rehospitalization occurs).
- The exclusion criterion "…valvular heart disease with severe aortic or mitral regurgitation…"was revised to "…valvular heart disease with severe aortic or **primary** mitral regurgitation…" to clarify that secondary (functional) mitral regurgitation is not excluded.
- The exclusion criterion " ..or coronary artery bypass grafting (CABG) within 60 days prior to randomization; or indication for PCI or CABG" was revised to "…or coronary artery bypass grafting (CABG) within 60 days prior to randomization. Current indication for PCI or CABG (at time of randomization)" to clarify that no 60 days lag time is required after elective PCI.
- Excluded BMI was changed from **>40 kg/m^2** to **>45 kg/m^2** to to adapt the upper range of eligible BMI to the observed clinical characteristics at participating sites,in order to recruit a population that is representative, including those with high BMI. The additional mandatory criterion of NT-ProBNP/BNP will ensure the presence of HF in those subjects with very high BMI.

Sections affected include:

- Synopsis
- Section 5.1.2, Exclusion criteria

Study procedures were clarified: The rationale for these revisions is to minimize protocol deviations.

- Measurements post study drug were revised from 2h post study drug to 2h ±15 min post study-drug dosing.
- 4 – 6 h PK samples: "(towards the end of the visit)" was deleted, as this is irrelevant; the defined timepoint is 4 – 6 hours post dose.
- Proper use of nitrates was moved from Section 5.2.1 (Withdrawal) to Section 6.8 (Prior and Concomitant Therapy) for clarity and correctness.
- Smoking history was inadvertently omitted from Visit 5 (End of Treatment) and the Premature Discontinuation Visit, and was included in these visits.

Sections affected include:

- Synopsis
- Section 5.2.1, Withdrawal
- Section 6.8, Prior and Concomitant Therapy
- Section 7.1, Schedule of procedures, including Table 7-1 and subsections 7.1.3 to 7.1.11
- Section 7.4, Pharmacokinetics / pharmacodynamics
- Section 7.6.3, Vital signs

Safety definition of worsening CHF

IV vasodilators were included as indicative of WCHF. The rationale for this change is to be consistent with CEC manual.

Sections affected include:

- Section 7.5.1.6, Adverse events of special safety interest
- Section 7.3.2.5, Clinical efficacy variables

Adjudication of hospitalization and death events

The protocol was clarified in that there is only one committee, the Clinical Events Committee (CEC), and only one manual, the CEC manual, to adjudicate events.

Sections affected include:

- Section 3, Investigator[s] and other study personnel
- Section 7.3.2.5, Clinical efficacy variables

Echocardiography

The protocol was clarified in that HR is also measured during echocardiography.

Sections affected include:

- Section 7.3.2.1, Echocardiography

13.1.1.2 Modification 2 - Corrections

"Suspected clinical events of CV" and "due to CV events" were removed from the independent blinded central assessment. The rationale for this change is that all deaths and hospitalizations will be processed for independent blinded central assessment by the CEC, not only the suspected CV events.

Sections affected include:

- Section 3, Investigator[s] and other study personnel

The exploratory efficacy analysis to estimate the (non-linear) shape of the true dose-response curve incorrectly indicated that there are 2 primary endpoints, but there is only one primary endpoint. This was corrected.

Sections affected include:

- Section 8.4.2, Efficacy

13.1.1.3 Modification 3 - Additions

Addition of **vital status** at approximately 114 days for discontinued subjects.

Collection of vital status was added at 114±5 days after randomization for all subjects who prematurely discontinue study drug. The rationale for this change is to obtain vital status upon full duration of study follow-up also in those subjects who prematurely discontinued, and to standardize the collection of vital status information at the timepoint of 12 weeks + safety follow-up period of 30±5 days for exploratory analysis in the ITT population.

Sections affected include:

- Section 4, Study design
- Section 5.2.1, Withdrawal
- Table 7-1
- Section 7.1.10, Follow-up visit (30 ±5 days after last intake of study drug)
- Section 7.1.11, Additional follow-up visit after premature discontinuation (Day 114±5 after randomization)

Addition of **disease-related events**

The rationale for this change is to avoid systematic unblinding of events undergoing adjudication as possible clinical outcome events, and to reduce bias of exploratory analysis of

differences in these clinical outcomes, by specifying disease related events that will not be subject to systematic unblinding and expedited reporting if SAEs.

Sections affected include:

- Section 6.4, Blinding
- Section 7.5.1.5, Expected adverse events

Addition of **exclusion criteria**

The rationale for this change is to be consistent with the current protocol SOP (09 APR 2014), the following exclusion criteria were added:

- 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).
- Previous assignment to treatment during this study.

Sections affected include:

- Synopsis
- Section 5.1.2, Exclusion criteria

13.1.1.4 Modification 4 - Revision of PK data collection

The 4 – 6 hr post-dose PK sample at Visits 2 and 4 was removed (will still be collected at Visits 1 and 3).

Rationale: The PK information for a thorough characterization of study drug plasma concentrations (1 to 3 hours post study drug and 4 to 6 hours post study drug at all treatment visits) can be obtained from the initial subset of patients prior to Amendment 2. The removal of the 4-6 hour PK sample at Visits 2 and 4 decreases the burden of study procedures and visit durations for the subsequent subset of subjects after implementation of Amendment 2.

Sections affected include:

- Section 7.1, Schedule of procedures, including Table 7-1 and subsections 7.1.4 to 7.1.8
- Section 7.4, Pharmacokinetics / pharmacodynamics

13.1.2 Changes to the protocol text:

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. In the display of modifications, the “old text” refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the “old text”. Additions are <u>underlined</u> in the “new text”. Corrections of typing errors, editorial changes, or omissions are not highlighted in this amendment.

Synopsis: Modification 1; Modification 3

Original protocol

Key exclusion criteria	1. IV inotropes at any time ~~after~~ hospitalization 2. Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HFrEF 3. Cardiac comorbidity o Specific HF etiologies, incl. hypertrophic cardiomyopathy with left ventricular (LV) outflow tract obstruction; pericardial disease; infiltrative or inflammatory myocardial disease; valvular heart disease with severe aortic or mitral regurgitation, moderate or severe aortic stenosis, any mitral stenosis requiring surgical repair, or active endocarditis; **or** o Acute coronary syndrome (ACS), including unstable angina, Non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), or coronary artery bypass grafting (CABG) within 60 days prior to randomization, or indication for percutaneous coronary intervention (PCI) or CABG; **or** o Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since; **or** o Symptomatic carotid stenosis, or TIA or stroke within 30 days prior to randomization; **or** o New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization; **or** o Listing for heart transplantation and/or anticipated/implanted ventricular assist device; **or** o Complex congenital heart disease 4. Non-cardiac comorbidity at the time of randomization o Glomerular filtration rate <30 mL/min/1.73 m^2 calculated by MDRD; **or** o Hepatic insufficiency Child-Pugh B or C; **or** o Body mass index (BMI) >~~40~~ kg/m^2; **or** o Malignancy or other non-cardiac condition limiting life expectancy to <1 year; or o Severe pulmonary disease with either requirement of continuous home oxygen or recent bronchial artery embolization for massive hemoptysis ~~5.~~ Participation in another clinical study ~~or treatment~~ with ~~another~~ investigational product ~~≤30 days prior to randomization~~

Amended to

Key exclusion criteria	1. IV inotropes at any time between hospitalization and randomization 2. Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HFrEF 3. Cardiac comorbidity o Specific HF etiologies, incl. hypertrophic cardiomyopathy with left ventricular (LV) outflow tract obstruction; pericardial disease; infiltrative or inflammatory myocardial disease; valvular heart disease with severe aortic or primary mitral regurgitation, moderate or severe aortic stenosis, any mitral stenosis requiring surgical repair, or active endocarditis; or o Acute coronary syndrome (ACS), including unstable angina, Non-ST elevation myocardial infarction (NSTEMI) or ST elevation myocardial infarction (STEMI), or coronary artery bypass grafting (CABG) within 60 days prior to randomization; or o Current indication for percutaneous coronary intervention (PCI) or CABG (at the time of randomization); or o Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since; or o Symptomatic carotid stenosis, or TIA or stroke within 30 days prior to randomization; or o New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization; or o Listing for heart transplantation and/or anticipated/implanted ventricular assist device; or o Complex congenital heart disease 4. Non-cardiac comorbidity at the time of randomization o Glomerular filtration rate <30 mL/min/1.73 m2 calculated by MDRD; or o Hepatic insufficiency Child-Pugh B or C; or o Body mass index (BMI) >45 kg/m²; or o Malignancy or other non-cardiac condition limiting life expectancy to <1 year; or o Severe pulmonary disease with either requirement of continuous home oxygen or bronchial artery embolization for massive hemoptysis 5. Previous (within 30 days of randomization) or concomitant participation in another clinical study with investigational medicinal product(s). 6. 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). 7. Previous assignment to treatment during this study.

Section 3, Investigator[s] and other study personnel: Modification 2

Original protocol

4 Central independent blinded clinical events committee

~~All suspected clinical events of cardiovascular (CV) deaths and hospitalizations due to CV events including recurrent hospitalizations for HF will be processed for independent blinded central assessment.~~ The committee will be provided with all relevant documentation related to the event. The procedures followed by the committee will be described in the ~~events committee~~ manual. Adjudication results will be the basis for the final analysis. Further details will be documented in the ~~events committee~~ manual.

Amended to

4 Central independent blinded clinical events committee (CEC)

Blinded adjudication of all hospitalizations and deaths will be performed by a central clinical events committee (CEC) as described in the CEC manual. The committee will be provided with all relevant documentation related to the event. The procedures followed by the committee will be described in the CEC manual. Adjudication results will be the basis for the final analysis. Further details will be documented in the CEC manual.

Section 4, Study design: Modification 3

Original Protocol

Follow-up
A safety follow-up visit is scheduled at 30±5 days after end of treatment or discontinuation of study drug.

Amended to

Follow-up
A safety follow-up visit is scheduled at 30±5 days after end of treatment or discontinuation of study drug. In addition, the vital status will be collected at 114±5 days after randomization for all subjects who prematurely discontinue study drug.

Section 5.1.2, Exclusion criteria: Modification 1; Modification 3

Original protocol

- Legal lower age limitations for adults (country specific)
- IV inotropes at any time ~~after~~ hospitalization
- Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HF, including
    - subjects tolerant of and treated with isosorbide dinitrate~~/hydralazine~~ therapy for chronic HFrEF according to guideline recommendations
    - subjects requiring nitrates as anti-anginal therapy in addition or alternatively to beta-blockers
- Cardiac comorbidity (either of the following)
    - Specific HF etiologies, including
        - Hypertrophic cardiomyopathy with LV outflow tract obstruction; **or**
        - Pericardial disease, such as constrictive pericarditis; **or**
        - Infiltrative or inflammatory myocardial disease such as acute myocarditis, amyloidosis, sarcoidosis; **or**
        - Valvular heart disease
            - severe aortic or mitral regurgitation
            - moderate or severe aortic stenosis
            - any mitral stenosis requiring surgical repair
            - active endocarditis
    - Acute coronary syndrome, including unstable angina, NSTEMI or STEMI, or CABG within 60 days prior to randomization, or indication for PCI or CABG
    - Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since
    - Symptomatic carotid stenosis, or transient ischemic attack (TIA) or stroke within 30 days prior to randomization
    - New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization
    - Listing for heart transplantation and/or anticipated/implanted ventricular assist device
    - Complex congenital heart disease
- Non-cardiac comorbidity, indicated by either of the following at the time of randomization

- Glomerular filtration rate <30 ml/min/1.73 m^2 calculated by Modification of Diet in Renal Disease [MDRD] formula (23)
- Hepatic insufficiency classified as Child-Pugh B or C
- Morbid obesity with a BMI >~~40~~ kg/m^2
- Malignancy or other non-cardiac condition limiting life expectancy to <1 year, per physician judgment
- Severe pulmonary disease with either requirement of continuous home oxygen or ~~recent~~ bronchial artery embolization (BAE) for massive hemoptysis
- Subjects with allergies, intolerance or hypersensitivity to investigational drug or any of the excipients
- Medical condition or history thereof that in the opinion of the investigator would impair the ability to complete the planned study procedures

- Concomitant Treatment with a phosphodiesterase type V (PDE5) inhibitor or sGC stimulator

- Participation in another clinical study ~~or treatment~~ with ~~another~~ investigational product ~~≤30 days prior to randomization~~

Amended to

- Legal lower age limitations for adults (country specific)

- IV inotropes at any time <u>between</u> hospitalization <u>and randomization</u>

- Concurrent or anticipated nitrate use (all routes, incl. prn) for the treatment of ischemic heart disease or HF, including
  - subjects tolerant of and treated with isosorbide dinitrate therapy for chronic HFrEF according to guideline recommendations
  - subjects requiring nitrates as anti-anginal therapy in addition or alternatively to beta-blockers

- Cardiac comorbidity (either of the following)
  - Specific HF etiologies, including
    - Hypertrophic cardiomyopathy with LV outflow tract obstruction; **or**
    - Pericardial disease, such as constrictive pericarditis; **or**
    - Infiltrative or inflammatory myocardial disease such as acute myocarditis, amyloidosis, sarcoidosis; **or**
    - Valvular heart disease <u>with</u>
      - severe aortic or <u>primary</u> mitral regurgitation

- moderate or severe aortic stenosis
- any mitral stenosis requiring surgical repair
- active endocarditis

- Acute coronary syndrome, including unstable angina, NSTEMI or STEMI, or CABG within 60 days prior to randomization; or
- Current indication for PCI or CABG (at the time of randomization)
- Significant cardiac ischemia in a stress test within a year of enrollment without revascularization since
- Symptomatic carotid stenosis, or transient ischemic attack (TIA) or stroke within 30 days prior to randomization
- New initiation of cardiac resynchronization therapy (CRT) within 60 days prior to randomization
- Listing for heart transplantation and/or anticipated/implanted ventricular assist device
- Complex congenital heart disease

- Non-cardiac comorbidity, indicated by either of the following at the time of randomization
  - Glomerular filtration rate <30 ml/min/1.73 m^2 calculated by Modification of Diet in Renal Disease [MDRD] formula (23)
  - Hepatic insufficiency classified as Child-Pugh B or C
  - Morbid obesity with a BMI >45 kg/m^2
  - Malignancy or other non-cardiac condition limiting life expectancy to <1 year, per physician judgment
  - Severe pulmonary disease with either requirement of continuous home oxygen or bronchial artery embolization (BAE) for massive hemoptysis
  - Subjects with allergies, intolerance or hypersensitivity to investigational drug or any of the excipients
  - Medical condition or history thereof that in the opinion of the investigator would impair the ability to complete the planned study procedures

- Concomitant Treatment with a phosphodiesterase type V (PDE5) inhibitor or sGC stimulator

- Previous (within 30 days of randomization) or concomitant participation in another clinical study with investigational medicinal product(s).

- 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).
- Previous assignment to treatment during this study.

-

Section 5.2.1, Withdrawal: Modification 1, Modification 3

Original protocol

Subjects *must* be withdrawn from study drug for the following reasons:

…

- If ~~patient~~ interrupts intake of study drug lasts for more than 10 consecutive days, or for more than a total of 14 days during the treatment period (see Section 6.1.2).
- If the ~~patient~~ develops clear indication for nitrates, such as angina which cannot be managed with alternative antianginals.
  ~~It is recommended that nitrates should not be administered to any patient previously on study drug earlier than 3 days after the last dose of study drug. Should there be an urgent need for nitrate administration, they should be administered in a monitored inpatient setting.~~

Subjects *may* be withdrawn from study drug for the following reasons:

…

If a subject prematurely discontinues study drug and if any study drug has been taken, the subject must be advised to return to the study center for the premature discontinuation visit as soon as possible. All attempts should be made to collect echocardiography, laboratory, clinical, and safety read-outs as soon as possible upon discontinuation of study drug. The visit should take place as soon as possible after study drug was discontinued, and replaces all other scheduled visits before the safety follow-up visit. This safety follow-up visit will take place at 30±5 days after last intake as for all other subjects who have taken study drug.

Amended to

Subjects *must* be withdrawn from study drug for the following reasons:

…

- If <u>subject</u> interrupts intake of study drug lasts for more than 10 consecutive days, or for more than a total of 14 days during the treatment period (see Section 6.1.2).
- If the <u>subject</u> develops clear indication for nitrates, such as angina which cannot be managed with alternative antianginals. (<u>See Section 6.8</u>)

Subjects *may* be withdrawn from study drug for the following reasons:

…

If a subject prematurely discontinues study drug and if any study drug has been taken, the subject must be advised to return to the study center for the premature discontinuation visit as soon as possible. All attempts should be made to collect echocardiography, laboratory,

clinical, and safety read-outs as soon as possible upon discontinuation of study drug. The visit should take place as soon as possible after study drug was discontinued, and replaces all other scheduled visits before the safety follow-up visit. This safety follow-up visit will take place at 30±5 days after last intake as for all other subjects who have taken study drug. In addition, the vital status will be collected after premature discontinuation for all subjects at 114±5 days after randomization. This serves to standardize the collection of vital status information at the timepoint of 12 weeks + safety follow-up period of 30±5 days, for all randomized subjects irrespective of duration of study drug treatment.

Section 6.4, Blinding: Modification 3

Original protocol

In the event of suspected unexpected serious adverse reactions (SUSARs; see Section 7.5.1.5), the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment.

Amended to

In the event of suspected unexpected serious adverse reactions (SUSARs; see Section 7.5.1.5), the subject's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment.

In this study, the following events are outcome events and/or consistent with the underlying condition and will be considered as disease related in the defined study population:

- Acute heart failure
- Chronic heart failure
- Worsening chronic heart failure
- Arrhythmia / cardiac arrest
- Myocardial Infarction
- Transient Ischemic attack or stroke
- CV death

For the purposes of this trial, these events will not be subject to systematic unblinding and expedited reporting process, if reported as serious adverse drug reactions. They will be captured in the Global Pharmacovigilance database, in the eCRF and undergo regular central adjudication and unblinded DMC review.

Section 6.8, Prior and concomitant medication: Modification 1

Original protocol

Prohibited prior and concomitant medications:

- Nitrates or NO donors: any routes are not allowed during study drug treatment; IV therapy with nitrates or NO donors is only allowed until 24 h before randomization.

Amended to

- Nitrates or NO donors: any routes are not allowed during study drug treatment; IV therapy with nitrates or NO donors is only allowed until 24 h before randomization. It is recommended that nitrates should not be administered to any subject previously on study drug earlier than 3 days after the last dose of study drug. Should there be an urgent need for nitrate administration, they should be administered in a monitored inpatient setting.

Section 7.1, Schedule of procedures: Modification 1; Modification 3; Modification 4

Original protocol

Table 7-1: Study Flow Chart

Study period	Screening[1]	Baseline	Titration / Sham titration		Treatment	End of treatment	Safety
Visit		1	2	3	4	5[3]	
Day / Window	-28 - 0[1]	0	14±2[2]	28±2[2]	56±2[2]	84±2[2]	+30±5
▪ Signed written informed consent available ▪ Demographic data ▪ Medical and surgical history ▪ Local lab for eligibility	●						
Concomitant medication	●		Record any new or ongoing medication or changes in dosage				
Smoking & alcohol history	●					●[4]	
Check in- / exclusion criteria	●	●					
Randomization (IxRS)		●					
Quality of life (KCCQ, EQ-5D-3L)		●		●	●	●	
NYHA class	●	●	●	●	●	●	
Blood pressure, heart rate[5]	●	●[5,6]	●[5]	●[5]	●[5]	●[5,6]	●
Echocardiography		●[6]				●[6]	
Central lab blood sample[7]		●	●	●	●	●	●
Central lab PK sampling[8]		●	●	●	●	●	
Central lab exploratory biomarkers		●				●	
Physical exam, weight, height[9]	●	●	●	●	●	●	●
12-lead ECG[10]	●	●	●	●	●	●	●
Adverse events	●	●	●	●	●	●	●
Drug accountability, collect unused study drug			●	●	●	●	
Dispense study drug		●	●	●	●		
Titration / sham titration			●	●			

[1] Can start from hospitalization (or equivalent) up to 4 weeks after discharge (or after clinical stabilization upon hospitalization equivalent) and no more than 4 weeks before randomization

[2] Allows for timeframes of 5 days, e.g. visit 2 can take place on day 12 to 16

[3] Completion or premature discontinuation visit (in case of premature stop of study drug, the same measurements and procedures should be performed as at visit 5)

[4] Only smoking at visit 5

[5] 3 measurements, 2 min apart; measurements are taken prior to and at 2h post study-drug dosing

[6] Additional and blood pressure during echocardiography

[7] NT-ProBNP, clinical chemistry, hematology, coagulation

[8] Samples are taken ~~prior to (not required at Visit 1) and at 1-3 h and 4-6 h post study-drug dosing~~; optional additional pre-dose sample on Day 1 (trough 24 hours after first study drug) for hospitalized ~~patient~~s

[9] Height will be only measured once at the screening visit. Automatic calculation of body mass index (BMI) in the electronic case report form (eCRF) will use this result

[10] In supine position, after resting for at least 10 min

Abbreviations:

IxRS, Interactive voice/web response system; KCCQ, Kansas City Cardiomyopathy Questionnaire; EQ-5D-3L,

EuroQol Group 5-dimension, 3-level questionnaire; NYHA, New York Heart Association; ECG, electrocardiogram

Amended to

Table 7-1: Study Flow Chart--amended

Study period	Screening[1]	Baseline	Titration / Sham titration		Treatment	End of treatment	Safety Follow-Up[11]
Visit		1	2	3	4	5[3]	
Day / Window	-28 - 0[1]	0	14±2[2]	28±2[2]	56±2[2]	84±2[2]	+30±5
▪ Signed written informed consent available ▪ Demographic data ▪ Medical and surgical history ▪ Local lab for eligibility	●						
Concomitant medication	●		Record any new or ongoing medication or changes in dosage				
Smoking & alcohol history	●					●[4]	
Check in- / exclusion criteria	●	●					
Randomization (IxRS)		●					
Quality of life (KCCQ, EQ-5D-3L)		●		●	●	●	
NYHA class	●	●	●	●	●	●	
Blood pressure, heart rate[5]	●	●[5,6]	●[5]	●[5]	●[5]	●[5,6]	●
Echocardiography		●[6]				●[6]	
Central lab blood sample[7]		●	●	●	●	●	●
Central lab PK sampling[8] Prior to study drug intake 1-3 hours post study drug 4-6 hours post study drug		 ● ●	 ● ●	 ● ●	 ● ●	●[12]	
Central lab exploratory biomarkers		●				●	
Physical exam, weight, height[9]	●	●	●	●	●	●	●
12-lead ECG[10]	●	●	●	●	●	●	●
Adverse events	●	●	●	●	●	●	●
Drug accountability, collect unused study drug			●	●	●	●	
Dispense study drug		●	●	●	●		
Titration / sham titration			●	●			

1 Can start from hospitalization (or equivalent) up to 4 weeks after discharge (or after clinical stabilization upon hospitalization equivalent) and no more than 4 weeks before randomization
2 Allows for timeframes of 5 days, e.g. visit 2 can take place on day 12 to 16
3 Completion or premature discontinuation visit (in case of premature stop of study drug, the same measurements and procedures should be performed as at visit 5)
4 Only smoking at visit 5
5 3 measurements, 2 min apart; measurements are taken prior to and at 2 h ± 15 min post study-drug dosing
6 Additional HR and blood pressure measurement during echocardiography
7 NT-ProBNP, clinical chemistry, hematology, coagulation
8 Samples are taken at baseline / trough at Visits 2 – 4 (prior to study drug dosing) and at Visit 5; at Visit 1 and Visit 3, 1-3 h and 4-6 h post study-drug dosing; and at Visit 2 and Visit 4, 1-3 h post study-drug dosing
Optional additional pre-dose sample on Day 1 (trough 20-24 hours after first study drug) for hospitalized subjects.
9 Height will be only measured once at the screening visit. Automatic calculation of body mass index (BMI) in the electronic case report form (eCRF) will use this result
10 In supine position, after resting for at least 10 min
11 In case of premature discontinuation of study treatment, vital status will be collected 114±5 days after randomization by any method (telephone call, visit etc).
12 At trough (no study drug intake at Visit 5)
Abbreviations: IxRS, Interactive voice/web response system; KCCQ, Kansas City Cardiomyopathy Questionnaire; EQ-5D-3L, EuroQol Group 5-dimension, 3-level questionnaire; NYHA, New York Heart Association; ECG, electrocardiogram

Section 7.1.4, Visit 1 (Baseline and randomization) – Day 0: Modification 1

Original protocol

- …
- 2 h after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart (exact collection time must be documented; peak drug concentration expected within 2 h after intake)
- Blood samples for PK after drug intake (exact collection times must be documented):
    - 1-3 h
    - 4-6 h ~~(towards the end of the visit)~~
    - optional timepoint 20-24 h, i.e. before intake of the second dose of study drug (only in ~~patients~~ who are not discharged before the day after randomization)

Amended to

- …
- 2 h <u>±15 min</u> after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart (exact collection time must be documented; peak drug concentration expected within 2 h after intake)
- Blood samples for PK after drug intake (exact collection times must be documented):
    - 1-3 h
    - 4-6 h
    - optional timepoint 20-24 h, i.e. before intake of the second dose of study drug (only in <u>subjects</u> who are not discharged the day after randomization)

Section 7.1.5, Visit 2 – Day 14±2: Modification 1

Original protocol

- …
- 2 h after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood samples for PK after drug intake (<u>exact collection times</u> must be documented):
    - 1-3 h
    - ~~4-6 h (towards the end of the visit)~~

Amended to

- …
- 2 h ±15 min after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood samples for PK after drug intake (exact collection time must be documented):
    - 1-3 h

Section 7.1.6, Visit 3 – Day 28±2: Modification 1; Modification 4

Original protocol

- …
- 2 h after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood ~~s~~amples for PK after drug intake (exact collection times must be documented):
    - 1-3 h
    - 4-6 h ~~(towards the end of the visit)~~

Amended to

- …
- 2 h ±15 min after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood sample for PK after drug intake (exact collection times must be documented):
    - 1-3 h
    - 4-6 h

Section 7.1.7, Visit 4 – Day 56±2: Modification 1; Modification 4

Original protocol

- …
- 2 h after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood ~~s~~amples for PK after drug intake (exact collection time~~s~~ must be documented):
    - 1-3 h
    - ~~4-6 h (towards the end of the visit)~~

Amended to

- …
- 2 h ±15 min after drug intake: Vital signs in sitting position (BP and HR after resting for at least 10 min), 3 measurements, 2 min apart
- Blood sample for PK after drug intake (exact collection time must be documented):
    - 1-3 h

Section 7.1.8, Visit 5 (End of Treatment)– Day 84±2: Modification 1; Modification 4

Original protocol

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)
- Assessment of NYHA class
- Concomitant medications (see Section 6.8)
- …
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, exploratory biomarkers, pharmacokinetics ~~prior to drug intake~~ (exact collection time to be documented; central lab, see Section 7.6.1)
- …
- ~~1 -3 h and 4-6 h after drug intake (towards the end of the visit; exact collection time to be documented): blood sample for pharmacokinetics~~
- Schedule Follow-Up visit 30±5 days after Visit 5

Amended to

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)
- Assessment of NYHA class
- Smoking history
- Concomitant medications (see Section 6.8)
- …
- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation, exploratory biomarkers, pharmacokinetics (exact collection time to be documented; central lab, see Section 7.6.1)
- …

- Schedule Follow-Up visit 30±5 days after Visit 5

Section 7.1.9, Premature Discontinuation visit: Modification 1

Original protocol

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)
- Assessment of NYHA class
- Concomitant medications (see Section 6.8)

Amended to

- KCCQ and EQ-5D-3L (see Section 7.3.2.4)
- Assessment of NYHA class
- Smoking history
- Concomitant medications (see Section 6.8)

Section 7.1.10, Follow-up visit (30±5 days after last intake of study drug): Modification 3

Original protocol

- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation (central lab, see Section 7.6.1)

Amended to

- Blood sample for NT-ProBNP, hematology, clinical chemistry, coagulation (central lab, see Section 7.6.1)
- If any subject fails to attend the follow-up visit and is deemed lost to follow-up after reasonable efforts to be contacted, every attempt should be made to obtain the vital status at a minimum. (see Section 7.1.11)

Section 7.1.11 – Modification 3

7.1.11 Additional follow-up after premature discontinuation (Day 114±5 after randomization)

- All randomized subjects who prematurely discontinue study drug treatment should be followed-up for vital status 114±5 days after randomization, regardless of the timepoint of premature study drug discontinuation. Vital status information can be collected by any method (telephone call, visit etc).

Section 7.3.2.1, Echocardiography—Modification 1

Original protocol

Echocardiography exams, collected data, and processes for central blinded adjudication in the echo core lab are given in the echo manual. SBP ~~and~~ DBP will be measured during echocardiography in addition to acquisition of echo data. Echocardiography variables for exploratory analyses include

Amended to

Echocardiography exams, collected data, and processes for central blinded adjudication in the echo core lab are given in the echo manual. SBP, DBP, and HR will be measured during echocardiography in addition to acquisition of echo data. Echocardiography variables for exploratory analyses include

Section 7.3.2.5, Clinical efficacy variables—Modification 1

Original protocol

Detailed definitions will be provided in the ~~charter~~ of the ~~central committee~~.

Emergency presentation for WCHF will be defined as newly developing signs and symptoms of WCHF after start of treatment with study drug requiring unscheduled non-hospitalization healthcare resource utilization (emergency room and non-routine clinic visits) and IV treatment with diuretics, and / or positive inotropic agents.

Blinded adjudication of all hospitalizations and deaths will be performed by a central clinical event committee as described in the ~~Adjudication Committee charter~~. Non-CV hospitalizations will not be considered for the composite endpoint. All emergency presentations for WCHF reported by the investigators as adverse event of special interest will also be considered for the composite endpoint as well as all deaths reported until Visit 5 (Day 84±2) of each subject.

Amended to

Detailed definitions will be provided in the manual of the CEC.

Emergency presentation for WCHF will be defined as newly developing signs and symptoms of WCHF after start of treatment with study drug requiring unscheduled non-hospitalization healthcare resource utilization (emergency room and non-routine clinic visits) and IV treatment with diuretics, vasodilators and / or positive inotropic agents.

Blinded adjudication of all hospitalizations and deaths will be performed by a central CEC as described in the CEC manual. Non-CV hospitalizations will not be considered for the composite endpoint. All emergency presentations for WCHF reported by the investigators as adverse event of special interest will also be considered for the composite endpoint as well as all deaths reported until Visit 5 (Day 84±2) of each subject.

Section 7.4, Pharmacokinetics / pharmacodynamics—Modification 4

Original protocol

Blood samples will be collected at the following timepoints:

- Visit 1: 1-3 h and 4-6 h ~~(towards the end of the visit)~~ after drug intake (exact collection time must be documented).
- For subjects hospitalized at Visit 1: optional blood sampling 20-24 h after first drug intake (before intake of second dose of study drug).
- Visits ~~2 to~~ 4: baseline / trough (prior to drug intake); 1-3 h ~~and 4-6 h~~ ~~(towards the end of the visit)~~ after drug intake (exact collection time must be documented).
- Visit 5: baseline / trough.

The PK analysis will be performed under the responsibility of Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, GDD-GED-DMPK Bioanalytics, 42096 Wuppertal, Germany.

Amended to

Blood samples will be collected at the following timepoints:

- Visit 1: 1-3 h and 4-6 h after drug intake (exact collection time must be documented).
- For subjects hospitalized at Visit 1: optional blood sampling 20-24 h after first drug intake (before intake of second dose of study drug).
- <u>Visit 2: baseline / trough (prior to drug intake); 1-3 h after drug intake (exact collection time must be documented).</u>
- <u>Visit 3: baseline / trough (prior to drug intake); 1-3 h and 4-6 h after drug intake (exact collection time must be documented)</u>
- Visit 4: baseline / trough (prior to drug intake); 1-3 h after drug intake (exact collection time must be documented).
- Visit 5: baseline / trough.

The PK analysis will be performed under the responsibility of Bayer HealthCare Bioanalytics Laboratory, Bayer Pharma AG, GDD-GED-DMPK Bioanalytics, 42096 Wuppertal, Germany.

Section 7.5.1.5, Expected adverse events—Modification 3

Original protocol

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

Amended to

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations**.**

See also Section 6.4, disease-related events consistent with the underlying condition**.**

Section 7.5.1.6, Adverse events of special safety interest—Modification 1

Original protocol

For this trial, the following safety related event of special interest has been defined:

- Acute renal failure (such as serum creatinine x2 or GFR decreased >50% or to <15 mL/min/1.73m^2)
- Newly developing signs and symptoms of WCHF requiring IV treatment with diuretics, and / or positive inotropic agents (see Section 7.3.2.5)

Amended to

For this trial, the following safety related event of special interest has been defined:

- Acute renal failure (such as serum creatinine x2 or GFR decreased >50% or to <15 mL/min/1.73m^2)
- Newly developing signs and symptoms of WCHF requiring IV treatment with diuretics, vasodilators and / or positive inotropic agents (see Section 7.3.2.5)

Section 7.6.3, Vital signs—Modification 1

Original protocol

Timepoints at visits (see flowchart):

- At the screening visit, visit 5, ~~PD~~ visit and at follow-up visit: upon presentation after physical examination
- At visit 1 to 4: in addition 2 hours after drug intake

Amended to

Timepoints at visits (see flowchart):

- At the screening visit, visit 5, premature discontinuation visit and at follow-up visit: upon presentation after physical examination
- At visit 1 to 4: in addition 2 hours ±15 minutes after drug intake

Section 8.4.2, Efficacy—Modification 2

Original protocol

An exploratory analysis to estimate the (non-linear) shape of the true dose-response curve will be performed for ~~each of~~ the ~~two~~ primary endpoint~~s~~ to aid in deciding which is the optimal dose. Further details on the functional dose-response models to be used and their statistical implementation will be specified in the SAP.

Amended to

An exploratory analysis to estimate the (non-linear) shape of the true dose-response curve will be performed for the primary endpoint (some text deleted as of Amd 2) to aid in deciding which is the optimal dose. Further details on the functional dose-response models to be used and their statistical implementation will be specified in the SAP.

14. Appendices

Not applicable