Observational Study Information

Acronym/Title	ROVER – Real World Outcomes of Patients Treated with Vericiguat in German Routine Care
Protocol version and date	v 1.0, 04 JUL 2024
IMPACT study number	22829
Study type / Study phase	Retrospective, non-interventional claims database study <☒ PASS> <Joint PASS: ☐ YES ☐ NO>
EU PAS register number	Study not yet registered

Active substance	Vericiguat (ATC Code C01DX22)
Medicinal product	Verquvo
Product reference	EU/1/21/1/1561/001-033
Procedure number	EMEA/H/C/005319/0000

Study Initiator and Funder	Bayer AG, 51368 Leverkusen
Research question and objectives	**Research question:** This study aims to describe clinical outcomes, demographic and clinical characteristics as well as real-world drug use patterns in patients initiating vericiguat in Germany. **The primary objective in this study is:** The primary objective of this study is to describe the occurrence of clinical effectiveness outcomes (Mortality, Hospitalization) of patients initiating vericiguat. **Secondary objective(s) in this study are:** • Description of sociodemographic (age, sex) and clinical characteristics (pre-defined comorbidities,

	medication of interest and hospitalization) of patients initiating vericiguat at baseline. • Description of drug use patterns such as persistence, adherence and titration in patients initiating vericiguat • Description of medication of interest in the 3 months before and after initiation of vericiguat. **Exploratory objective in this study is:** • Description of the occurrence of hypotension in patients initiating vericiguat.
Country of study	Germany
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD

The study will be conducted in compliance with the protocol
and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
CFR	Code of Federal Regulations
DMP	Data Management Plan
DSGVO	Datenschutzgrundverordnung (“General Data Protection Regulation”)
EBM	Einheitlicher Bewertungsmaßstab
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
HF	Heart failure
ICD	International Classification of Diseases
ICH	International Conference of Harmonization
INN	International Nonproprietary Name
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MPR	Medication Possession Ratio
N/A	Not Applicable
OS	Observational Study
OPS	Operation and Procedure key
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
QPPV	Qualified Person Responsible For Pharmacovigilance
SHI	Statutory Health Insurance
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

3.1. Main responsible parties

Contact details of the responsible parties at Bayer AG are available upon request.

3.2. Further responsible parties

Changes of responsible persons and/or the composition of the committees will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	ROVER – Real World Outcomes of Patients Treated with Vericiguat in German Routine Care
Protocol version and date	v 1.0, 04 JUL 2024
IMPACT study number	22829
Study type / Study phase	Observational / Phase IV
Author	PPD
Rationale and background	Vericiguat is an oral drug that helps patients with heart failure with reduced ejection fraction (HFrEF) by stimulating soluble guanylate cyclase (sGC) to dilate blood vessels and improve heart function. The VICTORIA trial showed it reduces cardiovascular deaths and hospitalizations. Side effects include low blood pressure and anaemia. Marketed as Verquvo®, it's available in Germany since September 2021. Starting at 2.5 mg daily, the dose can increase to 10 mg. Vericiguat is used alongside standard heart failure therapies. No evidence on the rate of outcomes under vericiguat therapy in routine care settings is available until now.
Research question and objectives	This study aims to describe clinical outcome, demographic and clinical characteristics as well as real-world drug use patterns in patients initiating vericiguat in Germany. **The primary objective in this study is:**

	• To describe the occurrence of clinical effectiveness outcomes (Mortality, Hospitalization) of patients initiating vericiguat. **Secondary objective(s) in this study are:** • Description of sociodemographic (age, sex) and clinical characteristics (pre-defined comorbidities, medication of interest and hospitalization) of patients initiating vericiguat at baseline. • Description of drug use patterns such as persistence, adherence and titration in patients initiating vericiguat • Description of medication of interest in the 3 months before and after initiation of vericiguat. **Exploratory objective in this study is:** • Description of the occurrence of hypotension in patients initiating vericiguat.
Study design	A retrospective single-arm cohort study including new users of vericiguat between SEP 2021 and SEP 2023 will be conducted.
Population	All patients with their first vericiguat prescription since market authorization in SEP 2021 who are aged 18 years or older will be included in the study.
Variables	Primary objective: All-cause hospitalizations, hospitalizations due to HF, death due to any cause Secondary objective: Comorbidities, comedication, measures to describe drug use patterns (e.g. medication possession ration, time until discontinuation) Exploratory objective: Diagnoses indicating the occurrence of hypotension
Data sources	The InGef database is an anonymized healthcare claims database with longitudinal data from approximately 10 million German insured members of one of more than 50 German statutory health insurance providers (SHIs) currently contributing data to the database (mainly company or guild health insurances).

	The WIG2 database is an anonymized and representative healthcare claims databases with longitudinal data from approximately 4 million (2014 – 2022) insured individuals.
Study size	Since no a priori hypotheses are specified and this study is only descriptive, sample size calculations are not applicable. Within the InGef Database it can be expected to include about 550 patients with at least one vericiguat prescription between 2021 and 2023. Within the WIG2 Database it can be expected to include about 190 patients with an initial vericiguat prescription. The number of patients may vary according to further inclusion criteria in this study (e.g. observation periods to be fulfilled).
Data analysis	The data analysis and statistical methods for the study will be exploratory, without testing pre-defined hypotheses. Hospitalization rates as well as mortality rates will be calculated as an incidence rate (cases per person years) as well as via the Kaplan Meier method. Adherence, titration, and persistence will be analyzed separately. Adherence will be assessed using the Medication Possession Ratio (MPR), titration patterns will be examined, and medication persistence will be evaluated using the Kaplan-Meier method. Socio-demographic and clinical characteristics, and comedications before and after vericiguat use will be described. Various statistical approaches will be employed to analyze these outcomes comprehensively, including sensitivity analyses to test the robustness of the findings. Factors associated with the outcomes will be explored with adequate regression models.
Milestones	The analysis for the study is scheduled to commence on July 1, 2024. Preliminary results are expected by July 14, 2024, followed by the final results on July 28, 2024. The study report will be completed by Dec 2024.

5. Amendments

Not applicable

6. Milestones

Table 2 presents planned milestones for the project. These milestones are based on a timely review and approval of the project. Administrative changes to milestones due to delays in study preparation and enrolment do not require amendments to the protocol. Revised study timelines and milestones which do not constitute a need for a formal protocol amendment are tracked in a stand-alone document (Annex 1).

Table 1: Milestones

Milestone	**Planned date**
Start of operational activities	05 JUL 2024
Preliminary results	14 JUL 2024
Final results	28 JUL 2024
End of operational activities	27 SEP 2024
Study report	31 DEC 2024

7. Rationale and background

Globally, approximately 64 million individuals grapple with heart failure (2). As per routine data analysis, the annual prevalence rate among adults stands at 4.7%, with men at 4.2% and women at 5.0%. Notably, nearly 90% of affected individuals are aged over 65 years, with an estimated annual incidence of 1.2% (3). In such cases, the heart muscle's inability to adequately pump blood and oxygen to meet the body's demand leads to symptoms like dyspnea, fatigue, and fluid retention, encompassing pulmonary congestion and peripheral edema.

Heart failure also correlates with diminished nitric oxide synthesis, a vasodilator. Vericiguat's action on stimulating the enzyme soluble guanylate cyclase (sGC) induces vasodilation of smooth muscle, thereby facilitating easier blood pumping by dilating blood vessels and, consequently, enhancing cardiovascular function (2,4).

The global Phase III trial, VICTORIA, assessed the drug's efficacy and safety in a population of worsening heart failure patients with ejection fraction (EF) < 45%, revealing a significant decrease in cardiovascular death or heart failure-related hospitalizations among vericiguat recipients compared to those on placebo.

Marketwise, vericiguat marketed as Verquvo®, is available in film-coated tablets of 2.5 mg, 5 mg, and 10 mg on the German market since September 15, 2021, solely on prescription and following medical consultation (6).

As per the Summary of Product Characteristics (SPC), initiation involves a daily 2.5 mg dose, with the target of 10 mg achieved by doubling the dose biweekly. This adjunctive treatment, when used alongside standard therapy, aims to reduce cardiovascular-related mortality and curtail heart failure-related hospitalizations (7). Adding vericiguat alongside initial treatments like ACEIs, ARNIs, beta-blockers, or MRA may be considered if conditions deteriorate during standard therapy. The therapy's advantage lies in minimal effects on blood pressure, distinct from other medications, with vericiguat not inducing electrolyte imbalances or exacerbating kidney function issues (2).

No evidence on the rate of outcomes under vericiguat therapy in routine care settings is available until now.

8. Research questions and objectives

This study aims to describe occurrence of outcomes, demographic and clinical characteristics as well as real-world drug use patterns in patients initiating vericiguat in Germany.

8.1. Primary objective

The primary objective in this study is:

- Description of all-cause mortality rates after initiation of vericiguat.
- Description of all-cause and heart failure related hospitalization rates after initiation of vericiguat.

8.2. Secondary objective(s)

The secondary objective(s) in this study are:

- Description of adherence, titration and persistence of vericiguat drug use
- Description of sociodemographic (age, sex) and clinical characteristics (e.g. pre-defined comorbidities, medication of interest) of patients initiating vericiguat at baseline.
- Description of medication of interest in the 3 months before and after initiation of vericiguat.

8.3. Exploratory objective(s)

The exploratory objective(s) in this study are:

- Description of the occurrence of hypotension in patients initiating vericiguat

9. Research methods

9.1. Study design

This study is a non-interventional, retrospective, single-arm cohort study of patients initiating Verquvo (Vericiguat) in Germany. The study is based on anonymized patient data from two longitudinal claim databases.

All adult patients (aged 18 years or older) who received an initial vericiguat prescription (index date) between the 15th of Sep 2021 and 30st of Sep 2023 (InGef - Index identification period) will be included in the overall study population.

In the WIG2 database, inclusion occurs based on data availability between 15th of Sep 2021 and 31st of Dec 2022 (WIG2 – Index identification period).

Adherence, titration, persistence as well as mortality, hospitalization, other clinical and patient characteristics will be described at index or within the pre-defined patient individual baseline

and follow-up periods. Therefore, different pre-defined study cohorts will build according to different observation periods and further conditions.

A schematic presentation of the study time frame of each cohort is shown in section 9.2.2.

9.2. Setting

The study uses longitudinal, cross-sector claims data from German health insurance funds, including outpatient and inpatient data as well as outpatient drug prescriptions.

The Ingef Database includes the data years between 2014 and 2024 of about 10 Mio. persons. Due to the time delay, especially for outpatient claims data (approx. 6 - 9 months), it can be assumed that the database will be complete up to and including 30st Sep 2023, in accordance with the internal quality controls for data completeness.

The WIG2 Database includes the data years between 2014 and 2022 of about 4 Mio. persons.

9.2.1. Study population and selection criteria

9.2.1.1. Inclusion criteria Study Cohort 1

Study cohort 1: This population will be used for the analysis of persistence of Vericiguat, mortality rates and hospitalization rates. In addition, a "*sub cohort 1a"* will be extracted with a second prescription of vericiguat to investigate the adherence and titration patterns. For all persons from the *InGef / WIG2 database*, the following inclusion criteria apply:

- Patients with an initial prescription of vericiguat (index date) according to ATC Code C01DX22.
- At least 18 years or older on the initial prescription of vericiguat.
- Patients with continuous insurance (with an allowed one-month insurance gap, according to *§19 SGB V*) within the 365 days prior to the respective index date (one year pre-observation time).
- Patients with continuous insurance (with an allowed one-month insurance gap, according to *§19 SGB V*) between the index date and the last day of the respective insurance period, until their death or on 30st Sep 2023 (InGef) respectively on 31st Dec 2022 (WIG2) at the latest, whichever comes first.

Subcohort 1a: Patients with at least one additional vericiguat prescription within the respective follow-up period, which was not issued on the same day as the initial prescription.

9.2.1.2. Exclusion criteria Study Cohort 1

No exclusion criteria for any population will be applied.

9.2.1.3. Inclusion criteria Study Cohort 2

Study cohort 2: This cohort will be used to describe the medication use before and after the initial vericiguat prescription. For all persons from ***Study cohort 1***, the following inclusion criteria apply:

- Patients who fulfill all inclusion criteria from *"Study Cohort 1"*.
- Continuous insurance (with an allowed one-month insurance gap, according to *§19 SGB V*) within 3 months before (pre-observation time) and 3 months after (follow-up) the initial prescription of vericiguat (index date).

9.2.1.4. Exclusion criteria Study Cohort 2

No exclusion criteria for any population will be applied.

9.2.2. Study time frame

A schematic overview of the study design illustrating the above-described study time periods is shown in **Figure 1** as example for the InGef Database.

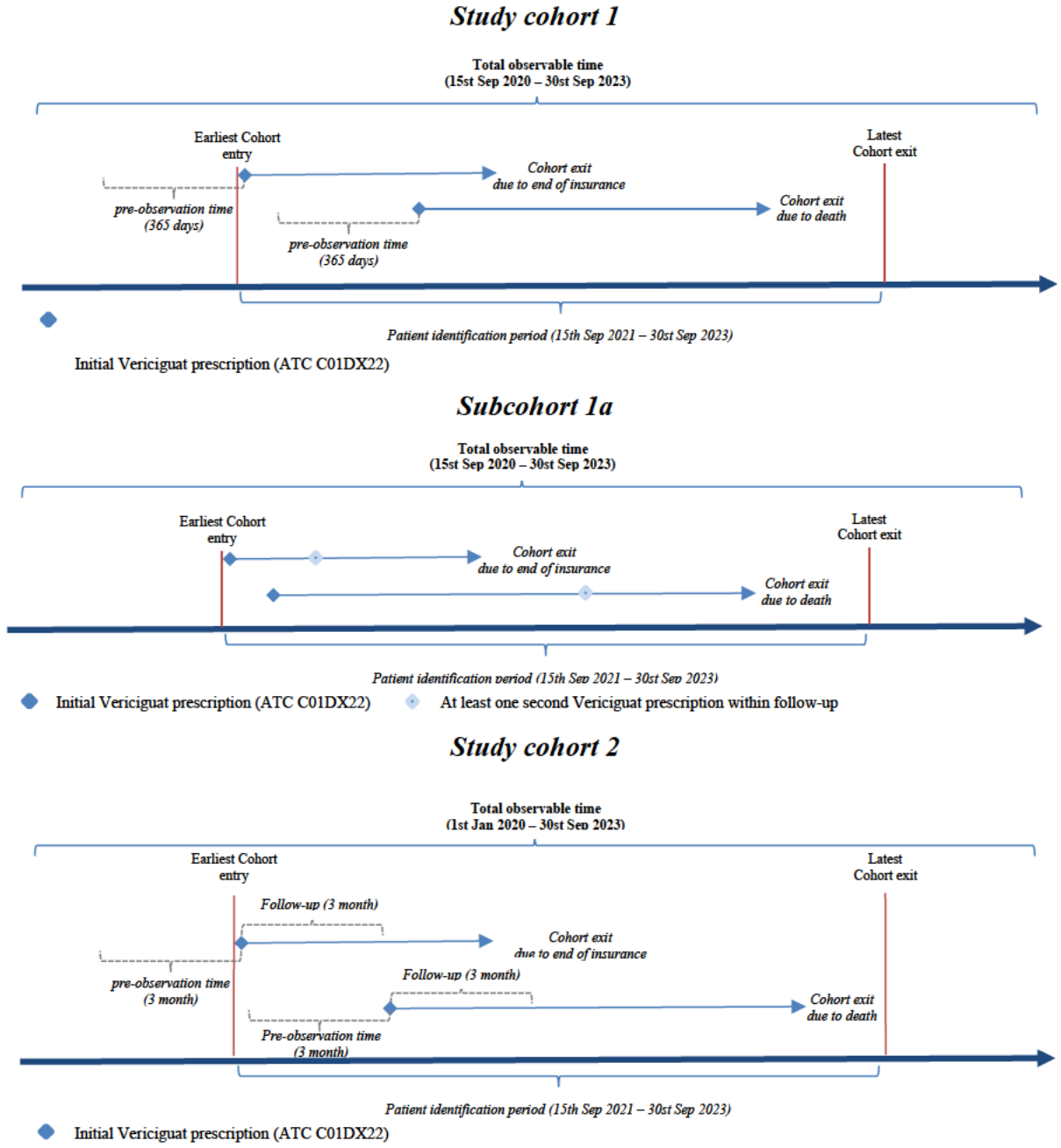

Figure 1: Schematic overview of the Cohort selection

Observation periods

Cohort entry: Each patient joins the cohort at the time of the first prescription of vericiguat. The earliest possible cohort entry date is on 15th Sep 2021, and the latest possible cohort entry date is on 30st Sep 2023 (Latest cohort entry InGef) respectively on 31th Dec 2022 (Latest cohort entry WIG2).

Cohort exit: Patients leave the cohort either at the time the insurance ends, at the time of their death or on 30st Sep 2023 (Latest cohort exit InGef) respectively on 31th Dec 2022 (Latest cohort entry WIG2) at the latest, whichever comes first.

Study Cohort 1:

Baseline period: For the description of e.g. predefined diseases and concomitant medications, an observation period of 12 months prior to the respective index date is defined.

Follow-up: For the description of persistence, hospitalization rates and mortality rates, the follow-up period is defined as the time between the patient individual "cohort entry" and the "cohort exit".

Subcohort 1a:

Follow-up: For the description of adherence, the follow-up period is defined as the time between the patient individual *"cohort entry"* and the *"cohort exit"*.

Study Cohot 2:

Pre-observation time: For the description of concomitant medications, an observation period of 3 months prior (Index - 3 months) to the respective index date is defined.

Follow-up: For the description of concomitant medications, an observation period of 3 months after (Index + 3 months) the respective index date is defined.

9.2.3. Representativeness

InGef Database

Using the total available data from the InGef research database, whose insured persons are predominantly from company and guild health insurances, no direct representativeness of the calculated outcomes in relation to the German population or the SHI population can be assumed. However, it has been shown that patients included in the InGef research database seem to be comparable regarding main characteristics (sociodemographics, comorbidity, comedication, mortality, etc. (13)

WIG2 Database

Data will be extracted from the WIG2 database. Representativeness of the database has been demonstrated for the whole SHI population regarding age, gender and morbidity (Ständer et al. 2020) (14)

9.3. Variables

The variables required for this study are listed in this section separately for the analysis of each individual outcome. The description of the individual variables follows the general structure of the analysis data set to be created, from which the outcomes (see also *section 9.3.2*) are analyzed. This ensures that the calculation of the individual outcomes by *WIG2* and *InGef* is based on uniform variable definitions and that identical analysis datasets are created.

9.3.1. Variables obtained from data sources

Sociodemographic characteristics

- Patient ID (PID)
- Sex: Each patient (i) can be assigned to one of the genders (m/f) at different points in time.
- Birth date: Each patient (i) is associated with a birth date.

Mortality

- Death date: Last transmitted death date of each patient, assuming the possibility of correction deliveries.
- Reason for end of insurance period: Reason for end of an insurance period which can be amont others death

Pre-defined comorbidities

- ICD-10 GM Codes (ambulant/hospital): All ICD Codes of each patient from the ambulant and hospital sector.
- ICD-Setting: Contains the information if an ICD Code comes from the *"ambulant"* or *"hospital"* sector.
- Diagnosis Type: Each hospital case is associated with different diagnosis types (*"admission", "main", "secondary"*). Each ambulant case is also associated with different types (*"exclusion"*, *"suspicion of"*, *"confirmed"*, *"condition after"*)

Pre-defined medications

- Prescription ID:
- ATC-Code: Includes all ATC-Codes from all prescriptions of each patient.
- Prescription Date: Each prescription is associated with a prescription date (s_{ij}).

Hospitalizations

- Hospital Case ID: Includes all full hospitalized cases that immediately follow each other or overlapping are counted as one hospital case.
- Admission Type: Each hospital case is associated with different admission types (ambulant, part- and full hospitalized).
- Diagnosis Type: Each hospital case is associated with different diagnosis types (admission, main, secondary).

- ICD-Codes: Contains all available ICD-10 GM Codes of each *Hospital Case ID*.
- Admission date (*ADH*): Date of admission to the hospital (*DDHi*). In case of overlapping hospital stays the date of the first admission (*min(ADH$_i$)*).
- Discharge date (*DDH*): Date of discharge from the hospital. In case of overlapping hospital stays the date of the latest discharge (*max(DDH$_i$)*).
- Length of hospital stay (*LOS* in days): The Length of stay (*LOS*) is calculated as follows:

$$LOS_i = \begin{cases} DDH_i - ADH_i & if\ no\ overlapping\ admission\ and\ discharges \\ max(DDH_i) - min(ADH_i) & where\ DDH_{i1} \leq ADH_{i2} \end{cases}$$

  Where:

  - LOS_i = Time in days for case *i*
  - DDH_i = Discharge date for case *i*
  - ADH_i = Admission date for case *i*
  - max(DDH_i) = Latest discharge date among overlapping cases
  - min(ADH_i) = Earliest admission date among overlapping cases

Persistence measures (Time until discontinuation):

For each patient $i(i = 1, \dots, n)$ and each prescription j $(j = 1, \dots, m)$, the following variables are needed to measure persistence of vericiguat treatment:

- Prescription Date and Tablet Count: Each patient (i) is associated with a prescription date (s_{ij}) and the number of tablets prescribed (a_{ij}) for vericiguat. Overlapping days of supply of different packages are assumed to be additive and therefore, will be shifted forwards (stockpiling assumption).
- Derived End Date: The end date (e_{ij}) of each prescription is derived by adding the number of tablets prescribed to the prescription date: $(e_{ij} = s_{ij} + a_{ij})$. It's assumed that one tablet is consumed per day.
- Total length of all hospital stays: For each patient, we calculate the total length of all hospital stays (*SUM_LOS$_i$*) that occur before or at the time of the 90-day gap $SUM\_LOS = \sum_{\text{all hospital stays } i}(LOS_i)$ for all hospital stays i where $ADH_i \leq (e_{ij} + gap)$.

Adherence measures

For each patient $i(i = 1, \dots, n)$ and each prescription j $(j = 1, \dots, m)$, the following variables are needed to measure adherence of vericiguat treatment with patients MPR (Medication Possession Ratio) within a certain treatment period:

- Prescription Date and Tablet Count: Each patient (i) is associated with a prescription date (s_{ij}) and the number of tablets prescribed (a_{ij}) for vericiguat.
- Days of supply with vericiguat treatment: sum of days with supply based on all prescriptions except the last one within the follow-up period. This is done by

determining the expected duration based on the pack size (14, 28, 98 tablets) and the number of prescribed packs. It will be assumed that patients use one tablet per day.

- Vericiguat treatment period in which adherence will be described: Days between the prescription date of the first prescription and the prescription date of the last prescription of vericiguat.

Titration

For each patient $i(i = 1, \dots, n)$ and each prescription j $(j = 1, \dots, m)$, the following variables are needed to measure titration patterns of vericiguat treatment:

- Prescription Date and Tablet Count: Each patient (i) is associated with a prescription date (s_{ij}) and the number of tablets prescribed (a_{ij}) for vericiguat.
- Starting Dose of vericiguat (mg): First received vericiguat dose (Index prescription) in mg: 2.5mg, 5mg, 10mg.

Hypotension

- ICD-10 GM Codes (ambulant/hospital): All ICD Codes of each patient from the ambulant and hospital sector.
- ICD-Setting: Contains the information if an ICD Code comes from the *"ambulant"* or *"hospital"* sector.
- Diagnosis Type: Each hospital case is associated with different diagnosis types (*"admission", "main", "secondary"*). Each ambulant case is also associated with different types (*"exclusion"*, *"suspicion of"*, *"confirmed"*, *"condition after"*)

9.3.2. Outcome definitions

Relevant endpoints to this study are defined separately for each study objective. The study endpoints are determined using the predefined variables described above. The statistical methods used to analyze the individual endpoints are described in *section 9.7*. Table shells with exemplary representation of each outcome are listed in a stand-alone document.

9.3.2.1. Outcomes for the primary objective

Mortality

All-cause mortality will be analyzed within the "*Study Cohort 1"* after the vericiguat index. For closer information's about the statistical methods used to analyze the mortality also see *section 9.7*.

- Number of died patients (n Died): Number of patients who died between the *"vericiguat index date"* and *"cohort exit"* according to their death date.

Hospitalization measurements

Hospitalization will be analyzed within the "*Study Cohort 1"* after the vericiguat index irrespective of discontinuation of therapy (intention to treat). For closer information's about the statistical methods used to analyze the hospitalization also see *section 9.7*.

All-cause hospitalization:

- Hospitalized patients: Number of patients with at least one *"full hospitalization case"* between the *"Vericiguat index date"* and *"cohort exit"*.
- Hospitalization cases: Sum of all fully hospitalized cases of all patients between the *"vericiguat index date"* and *"cohort exit"*. Hospital cases that immediately follow each other or overlapping are counted as one hospital case *(see section 9.3.1)*.

HF-specific Hospitalization:

- HF-caused hospitalized patients: Number of patients with at least one *"full hospitalization case"* with a main or secondary inpatient diagnosis according to ICD-10 GM Code I50.x or I11.0 or I13.0 or I13.2 between the *"vericiguat index date"* and *"cohort exit"*.
- HF-caused hospitalization cases: Sum of all fully hospitalized cases with a main or secondary inpatient diagnosis according to ICD-10 GM Code I50.x or I11.0 between the *"vericiguat index date"* and *"cohort exit"*. Hospital cases that immediately follow each other or overlapping are counted as one hospital case *(see section 9.3.1)*.

A composite outcome based on all-cause mortality and HF hospitalization will be additionally defined. The earliest date on which one of the two individual outcomes has been reached will be considered as the date of the composite outcome.

9.3.2.2. Outcomes for the secondary objectives

While persistence will be calculated within *"Study Cohort 1"*, adherence and titration patterns will be analyzed within *"Sub cohort 1a"*. This will be done using the following outcome measures:

Adherence measurements

- MPR: The treatment duration and the days of supply of the last prescription will not be included in the treatment duration and definition of the Medication Possession Ratio (MPR) since this last prescription would be included as adherence of 100% per definition and would thus lead to overestimation of the MPR. The Patient MPR is defined as follow:

$$MPR_i = \frac{days\ of\ supply}{treatment\ duration} = \frac{\sum_j^{m-1}(a_{ij})}{s_{im} - s_{i1}}$$

Where:

- MPR_i is the MPR for patient *i.*
- m is the number of prescriptions for patient i.
- s_{ij} is the date of the j-th prescription of patient *i.*
- s_{i1} is the date of the patient's first prescription.
- s_{im} is the date of the patient's last prescription.

a_{ij} is the number of tablets of the j-th prescription of patient i.

- MPR categories: The patients MPR will be divided into the following categories:
  - MPR $\geq$ 80%: Patients MPR $\geq$ 0.8

Titration

- Titration pattern: Titration will be calculated as logical variable for each patient according to the following titration pattern. If more than one strength of vericiguat is prescribed on the same day, the prescriptions are ordered in increasing strength and the patient counts as up titrated. Continuous treatment will not be required in the context of the titration analysis.
  - Up-titration (yes/no, time until patient is up-titrated for the first time): First vericiguat prescription with a higher dose compared to the previous vericiguat prescription. The date of this subsequent prescription will be defined as the date of first up titration.
  - Up-titration to 5mg (yes/no, time until 5 mg is reached): If a patient was up-titrated during the follow up period and 5mg is the dose reached. The prescription date of the first up-titration to 5 mg will be defined as the date up-titration to 5 mg.
  - Up-titration to 10mg (yes/no, time until 10 mg reached): If a patient was up-titrated during the follow up period and 10 mg is the dose reached. The prescription date of the first up-titration to 10 mg will be defined as the date up-titration to 10 mg.
  - Down-titration (yes/no): First vericiguat prescription with a lower dose compared to the previous vericiguat prescription. The date of this subsequent prescription will be defined as the date of first down-titration. Information on the dose, to which the patient was down titrated will be obtained as well.
  - Down-titration to 5mg (yes/no): If a patient was down-titrated during the follow up period to 5mg.
  - Down-titration to 2.5mg (yes/no): If a patient was down-titrated during the follow up period to 2.5mg.
  - Maximum dose reached: Highest dose reached during the observation period irrespective of up titration and down titration.

Persistence measurements

- Patient persistence: Persistence will be calculated as a binominal variable 1 | 0 for each patient according to the following criteria:

- A patient is considered **'discontinued = 1'** at the end date of the $(j)th$ prescription (e_{ij}) if at least one prescription has an end date plus the 90-day *gap* plus *SUM_LOS* less than the start date of the next prescription $(s_{i(j+1)})$, or if the end date of the last prescription plus the 90-day *gap* plus *SUM_LOS* is less than the date of lost-to-follow-up at cohort exit (t_i).
- A patient is considered **'not discontinued = 0'** if, for all prescriptions (j), the end date of the current prescription plus a gap of 90 days plus the sum of length of all hospital stays $(e_{ij} + gap + SUM\_LOS)$ is ≥ to the start date of the next prescription $(s_{i(j+1)})$. Days in hospital are assumed to be additive and therefore, the days of supply with vericiguat will be shifted forwards (stockpiling assumption).
- A patient is censored at (t_i) if the end date of the *last prescription* + *gap* + *SUM_LOS* is ≥ (t_i).

Socio-demographic characteristics:

- Sex: For all patients initiating vericiguat, sex (m/f) is defined at the vericiguat Index date.
- Age: Time in years between the patients *"birth date"* and the patients *"index date"*.
- Age Groups: Age is categorized into the following age groups: 18-50, 51-60, 61-70, 71-80, 81-90, >90 at the vericiguat Index.
- Age Tertiles: Age is categorized into age tertiles at the vericiguat index date.

Clinical characteristics:

- Pre-defined comorbidities: All vericiguat new user with at least one ICD-10 GM Code according to *Table 3 (see appendix)* as *confirmed outpatient* or *inpatient main or secondary* diagnosis, within the respective pre-observation period of 12 months before the vericiguat index date.
- Pre-defined comedications: All vericiguat new user with at least one prescription according to *Table 4 (see appendix)* within the respective pre-observation period of 3 months before the vericiguat index date.
- All-cause hospitalization: Number of patients with at least one *"full hospitalization case"* within the respective pre-observation period of 12 months before the vericiguat index date.
- Worsening HF event: Number of patients with a HF hospitalization or use of intravenous diuretics.
  - HF hospitalization: *"full hospitalization case"* with a main or secondary inpatient diagnosis according to ICD-10 GM Code I50.x or I11.0 within the

respective pre-observation period of 12 months before the vericiguat index date.

- i.v. diuretics. Prescription on i.v. diuretics within the respective pre-observation period of 12 months before the vericiguat index date.
- The time from the last worsening HF event during the baseline period until index date will be counted and categorized into 1-30 days, 31-60 days, 61-90 days, 91-180 days, 181-365 days. The same time-related categories will be calculated for HF hospitalization and i.v. diuretics.

Medications of interest before and after the Vericiguat index

- Pre-defined medications: All vericiguat new user with at least one prescription according to *Table 4 (see appendix)* within the respective pre- and post-observation period of 3 months before and after the vericiguat index date.
- Received dose (mg): Received dose of each pre-defined medication.

9.3.2.3. Variables to define the exploratory objective

Hypotension

All vericiguat new user with at least one ICD-10 GM Code I95.x as *confirmed outpatient* or *inpatient main or secondary* diagnosis during the first 90 days after index.

9.4. Data sources

9.4.1. InGef Database

The InGef database is an anonymized healthcare claims database with longitudinal data from approximately *10 million* German insured members of one of more than *50* German statutory health insurance providers (SHIs) currently contributing data to the database (mainly company or guild health insurances). Data are available on the patient level and individuals can be followed over a longitudinal period of up to *10 years* and across different healthcare sectors. It should be noted that the number of insured members for which data is available in the InGef database may change over time, e.g. when individual SHIs withdraw consent to use the data or data from new SHIs is included.

General information on the InGef research database is displayed in Table 1.

Table 1 Information in the InGef research database

Demographics	Date of birth Sex Date of death Insurance status (e.g. retired, family insurance) Period of insurance coverage

Outpatient Care	Diagnosis (ICD-10-GM) and quarter in which the diagnosis was documented Procedures performed (EBM and OPS code) and date of performance
Pharmacy	Drugs dispensed (ATC and PZN code) Quantity dispensed Day of prescription Day of dispensing Type of physician prescribing (e.g. cardiologist, general practitioner) Costs of drugs dispensed from SHI perspective
Hospital care	Additional diagnosis (ICD-10-GM) Performed procedures and surgeries (OPS code) Date of hospital admission Reason for admission (e.g. accident, emergency) Date of end of hospital stay Reason of end of hospital stay (e.g. death in hospital, discharge) Type of hospital: psychiatric vs. somatic Costs of inpatient care (total costs per case)

9.4.2. WIG2 Database

This study will be conducted using the WIG2 database, an anonymized healthcare claims database with longitudinal data from approx. 4 million Germans/residents. Representativeness of the database has been demonstrated for the whole SHI population (which covers almost 90% of the German population (2022) with regard to age, gender and morbidity (Ständer et al. 2020). The database contains data from 1st January 2014 to 31st December 2022 and provides a longitudinal observation time of up to 9 years. It includes core data on insured persons and full billing information of utilized health services in hospitals, the ambulatory sector and pharmaceuticals. Information captured in the WIG2 database are similar to the information captured in the InGef database as described in Table 1.

9.5. Study size

Since no a priori hypotheses are specified and this study is only descriptive, sample size calculations are not applicable.

Within the InGef Database it can be expected to include about 550 patients with at least one vericiguat prescription between 2021 and 2023 in *"Study cohort 1"*.

Within the WIG2 Database it can be expected to include about 190 patients in study cohort 1.

The number of patients may vary according to further inclusion criteria in this study (e.g. observation periods to be fulfilled).

9.6. Data management

9.6.1. InGef

The most recent data will be extracted from the InGef research database for the selected observation period and saved locally for analysis. The extracted dataset contains all data described in Table 1 but limited to records from those persons with at least one documented ATC code for prescription C01DX22 during the observation period for reasons of data economy. As an exception, core data will be extracted from all insured persons in the InGef research database to properly calculate the proportion of patients with treatment. The data will be analyzed by InGef staff with R version 4.0.2.

9.6.2. WIG 2

The analytic datasets will be person-level and will contain with at least one prescription of vericiguat and the variables as specified above. Data will be extracted from the WIG2 database using data up to 2022.

All analyses must be conducted on the site of the data provider. Data management and analysis will be performed using Microsoft SQL Server 2016 and R Version 4.1.

9.7. Data analysis / statistical methods

Statistical analyses will be of explorative and descriptive nature only. The study is not intended to test any pre-defined statistical hypothesis. All variables will be analyzed descriptively with appropriate statistical methods: Categorical variables will be analyzed by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Missing data will not be imputed.

Results calculated in the different data sources will be pooled where possible.

The statistical software package R will be used in this study.

9.7.3. Analysis of the primary outcomes

9.7.3.1. Composite of HF hospitalization and all-cause mortality rates after vericiguat

The number and percentages of patients who reached the outcome during the given assessment period of the *"Study Cohort 1"* will be presented. The numerator will include the number of patients with an outcome within the assessment period and the denominator will include each patient's person time contributing to the assessment period as noted in the following formula:

$$Rate = \frac{Number\ of\ patients\ with\ an\ event}{Number\ of\ person\ years, totaled\ for\ all\ persons} * 10{,}000$$

Rates and corresponding 95% CIs will be estimated per 10,000 person-years in the given assessment periods. The normal approximation method for a Poisson distribution will be used to estimate the 95% CI as noted below given the mean and variance are both lambda (ƛ) in the following formula:

$$ƛ \pm Z(\alpha/2) * \sqrt{ƛ/n}$$

Time to outcome will be computed as mean (sd) and median (IQR) among patients reaching the outcome after vericiguat initiation. Time to outcome will be calculated according to the following formula:

$$Time\ to\ outcome = Date\ of\ outcome - Index\ date + 1$$

Additionally, the composite outcome will be computed using Kaplan-Meier estimator (survival curve), in which censored observations will be included.

Furthermore, rates will be stratified by the following variables:

- Sex: Female, Male
- Age tertiles: 20-69 (Tertile 1), 70-81 (Tertile 2) and ≥82 (Tertile 3)
- Worsening HF event:
    - HF caused hospitalization (via main or secondary diagnosis) or use of intravenous diuretics.
    - Single components of the abovementioned composite indicator.
- Time since last worsening HF event (days): 0-30, 30-60, 60-90, 90-180
- Renal Impairment:
- Number of GDMT: Patients with GDMT prescriptions (0; 1; 2; 3; 4).
- ARNI: At least one prescription of ARNI according to *Table 4* in appendix.
- SGLT2: At least one prescription of SGLT2 according to *Table 4* in appendix.
- ARNI & SGLT2: At least one prescription of ARNI and SGLT2 according to *Table 4* in appendix.

Factors associated with the composite outcome within vericiguat users will be explored with a Cox Proportional Hazard model with time until outcome as the outcome and variables such as age, sex, certain comorbidities (e.g. hypertension, ischemic heart disease, atrial fibrillation, diabetes mellitus, hyperlipidemia, CKD) certain co-medications (e.g. beta blockers, ACE inhibitors, Angiotensin II inhibitors, diuretics, antiarrhythmics) as well as the time from the worsening event as covariates. The final list of variables considered for the univariate analysis will be defined based on baseline characteristics. In addition to the univariate analysis, a multivariate model will be conducted comprised of variables showing a significant impact in the univariate model (p value <0.05). Hazard ratios and 95%-CI will be provided for all covariates.

All analyses will be repeated for the single components of the composite outcome.

9.7.4. Analysis of the secondary outcomes

9.7.4.1. Adherence

This analysis is based on *"sub cohort 1a"*. Summary statistics will be provided for the continuous variable MPR (mean, median, SD, Q1, Q3, min, max). Frequency tables for MPR categories as well as the number (n) and proportion (per 100 in %) of patients with MPR ≥80% will be provided including 95% CI. The normal approximation method for a Poisson distribution will be used to estimate the 95% CI as noted below given the mean and variance are both lambda (ƛ) in the following formula:

$$ƛ \pm Z(\alpha/2) * \sqrt{ƛ/n}$$

For definition of MPR, see *section 9.3.2.1 Outcomes*.

Additionally, the MPR will be calculated for all above defined subgroups.

9.7.4.2. Titration

This analysis is based on *"sub cohort 1a"*. The number of patients with an up-titration to 5mg and to 10mg, the up-titration sector and physician specialty are analysed, the same applies for down-titration to 5mg and 2.5mg, respectively.

Descriptive summaries will be provided for the starting dose of vericiguat, the maximum dose reached and the days until up-titration to 5mg and 10 mg respectively. The dose-specific treatment durations will be calculated by summing up the days of supply for the different prescribed packages. Different treatment pathways will be displayed together with patient counts.

Only the first increase in dose (up-titration) to 5mg and to 10mg and the first decrease in dose (down-titration) to 5mg and 2.5mg, if present, are considered in this analysis. Treatment dose pathways of patients are shown in successive treatment order. Please note that if more than one strength of vericiguat is prescribed on the same day, the prescriptions are ordered in increasing strength.

Therapy gaps between successive prescriptions are not considered in this analysis. The number of patients who are up titrated to 5mg and 10mg, respective, are also evaluated. Patients who are up-titrated first to 5mg and then to 10mg are counted in both categories. The same is implemented for patients who are down titrated to 5mg and 2.5mg, respectively.

The number of patients observed as having a certain treatment path (with respect to the change in dose over time, e.g. 2.5mg→5mg→ 10mg→5mg)) are shown in absolute numbers and patient shares.

For definition of Titration pattern, see *section 9.3.2.1 Outcomes*.

Analyses on starting dose, the maximum dose reached as well as the time until up titration will additionally be stratified by the above defined subgroups. Additionally, analyses will be done separately for patients starting on the 5mg dosage.

Factors associated with up-titration to the target dose within vericiguat users will be explored with a logistic regression model with reach of maximum dose of 10mg as the outcome and variables such as age, sex, vericiguat starting dose, certain comorbidities, certain co-medications as well as the time from the worsening event as covariates. The final list of variables considered for the univariate analysis will be defined based on baseline characteristics. In addition to the univariate analysis, a multivariate model will be conducted comprised of variables showing a significant impact in the univariate model (p value <0.05). Odds ratios and 95%-CI will be provided for all covariates.

9.7.4.3. Persistence

Medication persistence will be analyzed based on *"Study Cohort 1"* restricted to patients initiating vericiguat until 30-Dec-2023 based on the Kaplan – Meier method with ***discontinuation of vericiguat*** treatment as the ***event of interest***. For definition of continuation, discontinuation and censoring see *section 9.3.2.1 Outcomes*.

The number and percentages of patients with an event during the given assessment period of the "*Study Cohort 1"* will be presented. The numerator will include the number of patients with event within the assessment period and the denominator will include each patient's person time contributing to the assessment period as noted in the following formula:

$$Discontinuation\ Rate = \frac{Number\ of\ patients\ with\ an\ event}{Number\ of\ person\ years, totaled\ for\ all\ persons} * 10{,}000$$

Discontinuation rate and corresponding *95% CIs* will be estimated per 10,000 person-years in the given assessment periods. The normal approximation method for a Poisson distribution will be used to estimate the 95% CI as noted below given the mean and variance are both lambda (ƛ) in the following formula:

$$ƛ \pm Z(\alpha/2) * \sqrt{ƛ/n}$$

Time to event will be computed as mean (sd) and median (IQR) and will be calculated according to the following formula:

$$Time\ to\ event = Date\ of\ event - Index\ date + 1$$

Additionally, *discontinuation rates* will be computed using Kaplan-Meier estimator (survival curve including 50% estimator), in which censored observations are included.

Furthermore, results will be presented stratified by above defined subgroups and additionally bv starting dose.

Factors associated with vericiguat discontinuation will be explored with a Cox Proportional Hazard model with time until discontinuation as the outcome and variables such as age, sex, certain comorbidities, certain co-medications as well as the time from the worsening event as covariates. The final list of variables considered for the univariate analysis will be defined based on baseline characteristics. In addition to the univariate analysis, a multivariate model will be conducted comprised of variables showing a significant impact in the univariate model (p value <0.05). Hazard ratios and 95%-CI will be provided for all covariates.

9.7.4.4. Description of socio-demographic and clinical characteristics at baseline

Socio-demographic characteristics at index will be described by frequency tables or summary statistics for *"Study cohort 1"*. Continuous variables will be categorized and presented in frequency tables in addition to summary statistics.

Clinical characteristics will be described at index within the respective baseline period before vericiguat. Numbers (n) and proportion (per 100 in %) of patients with the pre-defined medications, comorbidities, hospitalization (see *section 9.3.2.2 Outcomes*) are presented within *"study cohort 1"* (N).

Additionally, characteristics will be calculated stratified by sex, age terciles, worsening HF status as well as separately for patients starting with the 5mg dose.

9.7.4.5. Comedications before and after vericiguat

This analysis is based on *"Study Cohort 2"*. The number of subjects and frequency of subjects on drugs and drug classes of interest three month prior and three months after index date will be summarized by a frequency table, together with the mean amount (in mg) and associated standard deviation, where applicable. This does not apply to combination therapies.

9.7.5. Exploratory outcome

9.7.5.1. Hypotension

The number and percentages of patients who reached the outcome during the given assessment period of the *"Study Cohort 1"* will be presented. The numerator will include the number of patients with an outcome within the assessment period of 3 months and the denominator will include each patient's person time contributing to the assessment period as noted in the following formula:

$$Rate = \frac{Number\ of\ patients\ with\ an\ event}{Number\ of\ person\ years, totaled\ for\ all\ persons} * 10{,}000$$

Rates and corresponding 95% CIs will be estimated per 10,000 person-years in the given assessment periods. The normal approximation method for a Poisson distribution will be used to estimate the 95% CI as noted below given the mean and variance are both lambda (ƛ) in the following formula:

$$ƛ \pm Z(a/2) * \sqrt{ƛ/n}$$

Time to outcome will be computed as mean (sd) and median (IQR) among patients reaching the outcome after discharge. Time to outcome will be calculated according to the following formula:

$$Time\ to\ outcome = Date\ of\ outcome - Index\ date + 1$$

Additionally, the composite outcome will be computed using Kaplan-Meier estimator (survival curve), in which censored observations will be included.

Furthermore, rates will be stratified by the following variables:

- Sex: Female, Male
- Age tertiles

9.7.6. Sensitivity analysis

All analyses describing persistence of drug use with vericiguat via the indicator time until discontinuation as approximation will be repeated with varying allowed treatment gaps. Whereas the main analysis included a treatment gap of 90 days, sensitivity analyses with treatment gaps of 30, 60 and 180 days will be conducted.

9.8. Quality control

The analyses follow the guidelines for Good Epidemiological Practice (GEP) (3) and Good Practice for Secondary Data Analysis (GPS) (4). In addition, quality assurance of the analysis code produced is carried out by a second data scientist.

Bayer will ensure that study information is handled and stored to allow for accurate reporting, interpretation and verification of that information. The analytical dataset and statistical programs used to generate the data included in the final report will be kept in electronic format and available for audit and inspection. All relevant study documents will be stored after the end or discontinuation of the study for at least 15 years.

The external partners participating in the study are required to archive documents and datasets, statistical programs and study relevant documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to store documents for a retention period of at least 15 years, unless local regulations define otherwise.

9.9. Limitations of the research methods

The analysis dataset obtained from the InGef database covers approximately 10 million insured members of SHIs all over Germany. Representativeness for SHI and the whole German population cannot be guaranteed with regard to age and sex.

Because of the inclusion criteria defined for study cohort 2 (continuous observability post index) a selection bias can be expected since patients dying during this period cannot enter this analyses population potentially impacting results.

Furthermore, the analysis might be subject to the immeasurable time bias, as medications during a hospital stay cannot be identified in German claims data. However, this can be counteracted to the extent that the time spent in hospital is taken into account and reported when calculating individual outcome parameters such as persistence.

In addition to the billing information relevant to a treatment case used in this analysis, no further information such as individual patient records or disease-specific laboratory values are available.

The definition of the exploratory safety outcome hypotension is based on ICD codes. While clinical trials in the HF area usually included *symptomatic hypotension* as an outcome, such detailed ICD codes do not exist. Thus, comparisons between real world evidence and clinical trials regarding the occurrence of hypotension need to be made cautiously.

9.10. Other aspects

Not applicable

10. Protection of human subjects

10.1. InGef Database

Claims data are transferred directly from healthcare providers to a specialized data center owned by the SHIs, which provides data warehouse and IT services (in conformity with §284 in combination with §70 and §71 SGB V). In the data center (acting as a trust center), data are anonymized before entering the InGef database. Data are anonymized with respect to individual insured members, healthcare providers (e.g. physicians, doctors' offices, hospitals, pharmacies), and the respective SHI. As all patient-level data in the InGef research database are de-identified and are not social data anymore in the sense of §67 Abs. 2 SGB X in combination with Art. 4 Nr. 1 DSGVO, use of the study database for healthcare services research is therefore fully compliant with German federal law and, accordingly, Institutional Review Board or ethical approval for this study is not needed. Since this study is based on anonymized claims data, no informed consent of the patient is required.

10.2. WIG2 Database

As this study involves anonymized data from the WIG2 database, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent is not required. Furthermore, their use for scientific purposes conforms with German law and no additional permission by an IRB or IEC is needed.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products [Revision 2 from 2017) for these studies, the submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarized in the final study report unless the protocol provides for different reporting with a due justification.

12. Plans for disseminating and communicating study results

This study will be registered at “www.clinicaltrials.gov" and in in the EU PAS register at “http://www.encepp.eu/encepp_studies/indexRegister.shtml”. Results will be disclosed in a publicly available database within the standard timelines.

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the MAH. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines(1), STROBE(2)). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the MAH.

13.References

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Annex 1: List of stand-alone documents

Document Name

- 22829_Table_Shells*;* v 1.0, 14-JUN-2024

Annex 2: Additional information

Table 2 Comorbidities of interest

Comorbidities	ICD-10-GM Codes
Hypertension	O16; I10; I110; I119; I120; I129; I130; I1310; I1311; I132; I150; I158; I159; I674; O100; O101; O102; O103; O104; O109; O11
Myocardial infarction	I21; I210; I211; I212; I213; I214; I219; I22; I220; I221; I228; I229; I23; I230; I231; I232; I233; I234; I235; I236; I238
Other ischemic heart disease	I20; I200; I201; I208; I209; I24; I241; I248; I249; I25; I251; I2510; I2511; I253; I254; I255; I258; I259
Diabetes mellitus	E1021; E1041; E11; E114; E13; E1301; E1321; E135; E1011; E103; E104; E1101; E131; E1311; E1331; E136; E10; E102; E109; E1131; E115
CKD	I120; I1311; I132; N183; N184; N185; N170; N171; N172; N178; N179; N19; Z992; Z940
CKD stage 1	N181
CKD stage 2	N182
CKD stage 3	N183
CKD stage 4	N184
CKD stage 5	N185; I120; I1311; I132
COPD	J41; J410; J411; J418; J42; J43; J439; J44; J440; J441; J449
Cancer	C000; C001; C002; C003; C004; C005; C006; C008; C009; C020; C021; C022; C023; C024; C028; C029; C030; C031; C039; C040; C041
Sleep apnea	G4730; G4731; G4732; G4738; G4739
Atrial fibrillation	I480; I481; I482; I483; I484; I489
Stroke	I60; I600; I601; I602; I603; I604; I605; I606; I607; I608; I609; I61; I610; I611; I612; I613; I614; I615; I616; I618; I619
Anemia	D509; D530; D531; D532; D538; D539; D593; D594; D599; D610; D618; D630; D638; D644; D648; D649
Hypotension	I951; I952; I953; I958; I959
Depression	F313; F314; F315; F317; F320; F321; F322; F323; F328; F329; F330; F331; F332; F333; F334; F338; F339
Hyperkalemia	E875

Respiratory infection	J00; J01; J010; J011; J012; J013; J014; J018; J019; J02; J020; J028; J029; J03; J030; J038; J039; J04; J040; J041; J042
Genitourinary infection	N390
Venous thromboembolism	I26; I260; I269; I80; I800; I801; I802; I8020; I8028; I803; I808; I809; I81; I822; I829
Hypothyroidism	E018; E032; E038; E039; E890

Table 3 Medications of interest

Category	***Measure***	**WHO ATC Code**	**5-digit ATC**
Co-medications (Covariate)	Antiarrhythmics	C09BB1 C01EB10	C01BG; C01BB; C01BA; C01BA; C01BA; C01BC; C01BB; C01BA; C01BB; C01BD; C01BD; C01BD; C01BD; C08DB; C08DA; C08DA;
Co-medications (Covariate)	Antidiabetics (including SGLT2 inhibitors)		A10A; A10AB; A10AB; A10AB; A10AB; A10AB; A10AB; A10AB; A10AB; A10AC; A10AC; A10AC; A10AC; A10AC; A10AC; A10AD; A10AD; A10AD; A10AD; A10AD; A10AD; A10AD; A10AD; A10AD; A10AE; A10AE; A10AE; A10AE; A10AE; A10AE; A10AE; A10AE; A10AE; A10AF; A10AF; A10B; A10BA; A10BA; A10BA; A10BA; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BB; A10BC; A10BC; A10BD; A10BF; A10BF; A10BF; A10BF; A10BG; A10BG; A10BG; A10BG; A10BH; A10BH; A10BH; A10BH; A10BH; A10BH; A10BH; A10BH; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10BX; A10X; A10XA; A10XA
Co-medications (Covariate)	Calcium channel blocker	C08CA01; C07FB07; C07FB12; C07FB13; C08CA17; C08CA51; C08GA02; C09BB03; C09BB04; C09BB07; C09BX01; C09BX03; C09BX04; C09DB01;	

		C09DB02; C09DB04; C09DB05; C09DB06; C09DB07; C09DB09; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53; C09XA54; C10BX03; C10BX07; C10BX09; C10BX11; C10BX14; C10BX18; C08CA02; C07FB02; C09BB05; C08CA13; C09BB02; C09DB08; C08CA08; C09BB06; C08CA04; C08CA05; C07FB03; C08GA01	
Co-medications (Covariate)	Lipid-lowering drugs	A08AB01; A10BH51; A10BH52	C10AA; C10AB; C10AC; C10AD; C10AX; C10BA; C10BX; 0
Co-medications (Covariate)	Nitrates	C01DA08; C01DA14; C01DA58; C01DA02; C01DA52	
Co-medications (Covariate)	NOACs	B01AF02; B01AE07; B01AF01; B01AF03	
Co-medications (Covariate)	Platelet aggregation inhibitors (incl. aspirin)		B01AC
Co-medications (Covariate)	Vitamin K antagonists (VKA)		B01AA
HF Treatment	ACE Inhibitor	C10BX04; C10BX06; C10BX07; C10BX11; C10BX12; C10BX13; C10BX14; C10BX15 ; C10BX17 ; C10BX18;	C09AA; C09BA; C09AA; C09BA; C09AA; C09BA; C09BB; C09BB; C09AA; C09BA; C09AA; C09BA; C09BB; C09AA; C09BA; C09BB; C09BX; C09BX; C09BX; C09AA; C09BA; C09AA; C09BA; C09BB; C09BB; C09BX; C09BX; C09AA; C09BB; C09BA; C09BB; C09BB; C09BA; C09BA; C09BB; C09BX
HF Treatment	Angiotensin Receptor Blocker (ARB)		C09CA; C09DA; C09DB; C09CA; C09DA; C09DB; C09DX; C09CA; C09DA; C09CA; C09DA; C09DB; C09DB; C09DX; C09DX; C09DX; C10BX; C09CA; C09DA; C09DB; C09DX; C09CA; C09DA; C09DB; C09CA; C09DA; C09CA; C09DA; C09DB; C09DX; C09DA; C09DA; C09DB; C09DX; C09DX;

			C09XA; C09CA; C09DA; C09DA; C09DB; C09DB; C09DX
HF Treatment	Angiotensin Receptor Neprilysin Inhibitor (ARNI)	C09DX04	
HF Treatment	Beta-Blocker (BB)		C07AA; C07AA; C07AA; C07AA; C07AA; C07AA; C07AA; C07AB; C07AB; C07AB; C07AB; C07AG; C07BA; C07BA; C07BB; C07BG; C07CB; C07CG; C07DB; C07FB; C07FB; C07FX; C07FX; C07FX; C09BX; C09BX; C09BX; C09DX; C07AB; C07AB; C07AB; C07AB; C07AG; C07BA; C07BA; C07BB; C07BB; C07BB; C07BB; C07BB; C07CA; C07CA; C07CB; C07CB; C07DA; C07FB; C07FB; C07FB; C07FX; C07FX; C07FX; C07FX; C07BA; C07BA; C07BB; C07BB; C07CB; C07FB; C07FB; C07FX
HF Treatment	Digoxin/Digitoxin	C01AA05; C01AA04	
HF Treatment	Ivabradine	C07FX06; C01EB17; C07FX05	
HF Treatment	Loop Acting Diuretic (High-Ceiling)		C03CA; C03CB; C03EB
HF Treatment	Mineralcorticoid Receptor Antagonists (MRA) / Aldosteron Antagonists	C03DA01; C03DA04	
HF Treatment	SGLT-2 Inhibitor	A10BD15; A10BD16; A10BD2A10BD21; A10BD24; A10BD25; A10BD27; A10BK02; A10BK03; A10BK04; A10BD19; A10BD23; A10BK01	
HF Treatment	Thiazide Diuretics (Low-Ceiling)		C03AA; C03AX; C03AA; C03AA; C03AB; C03AB; C03AB; C03AH; C03EA; C03EA

HF Treatment	i.v. iron preparations	B03AC	B03AC

Annex 3: ENCePP checklist for post-authorization safety study (PASS) protocols

Study title: ROVER – Real World Outcomes in Patients Treated with Vericiguat in German Routine Care

EU PAS Register® number: Not yet registered **Study reference number (if applicable): Not applicable**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☒	☐	
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9
	4.2.2 Age and sex	☐	☐	☒	
	4.2.3 Country of origin	☒	☐	☐	9
	4.2.4 Disease/indication	☒	☐	☐	9
	4.2.5 Duration of follow-up	☒	☐	☐	9
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorised according to time windows?	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	9

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9
9.1.3 Covariates and other characteristics?	☒	☐	☐	9
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9
9.3.3 Covariates and other characteristics?	☒	☐	☐	9
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	9
10.4 Are stratified analyses included?	☒	☐	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9
11.2 Are methods of quality assurance described?	☒	☐	☐	9
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	9
12.1.2 Information bias?	☐	☐	☒	9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☐	☒	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Annex 4: Signature pages

Signature Page

This protocol is electronically signed in the study management system

Title	ROVER – Real World Outcomes of Patients Treated with Vericiguat in German Routine Care
Protocol version and date	*V1.0, 04 JUL 2024*
Gemstone study number	*22829*
Study type / Study phase	Retrospective, non-interventional claims database study <☒ PASS> <Joint PASS: ☐ YES ☐ NO>
Medicinal product / Active substance	*Verquvo / Vericiguat*
Study Initiator and Funder	*Bayer AG*

The signatory(ies) agree(s) that the study will be conducted under the conditions described in the protocol.

Signatories

PPD