Reference Number: RD-SOP-1216
Supplement Version: 14

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, 07 JUL 2026
IMPACT study number	22829
Study type / Study phase	Retrospective, non-interventional claims database study <☒ PASS> <Joint PASS: ☐ YES ☐ NO>
EU PAS register number	EUPAS1000000221

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.

Reference Number: RD-SOP-1216
Supplement Version: 14

	• 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 Real World Center of Excellence, Global Medical & Evidence Bayer AG Email: PPD PPD PPD InGef Email: PPD PPD PPD WIG2 Email: 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.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table of contents

Reference Number: RD-SOP-1216
Supplement Version: 14

List of Tables

Reference Number: RD-SOP-1216
Supplement Version: 14

List of Figures

Reference Number: RD-SOP-1216
Supplement Version: 14

1. Abstract

Acronym/Title	ROVER - Real World Outcomes of Patients Treated with Vericiguat in German Routine Care
Protocol version and date	V 1.0, 17 JUN 2026
IMPACT study number	22829
Study type / Study phase	Observational / Phase IV
Author	PPD Integrated Evidence Generation (IEG) Bayer AG Email: PPD PPD PPD InGef Email: PPD PPD PPD WIG2 Email: PPD
Rationale and background	Vericiguat is an oral soluble guanylate cyclase stimulator indicated for the treatment of symptomatic chronic heart failure in adults with reduced ejection fraction following a recent worsening heart failure event requiring intravenous therapy. In the Phase III VICTORIA trial, vericiguat reduced the composite endpoint of cardiovascular death or heart failure hospitalization compared with placebo. Vericiguat has been available in Germany since September 2021. However, evidence describing patient characteristics, treatment patterns, and clinical outcomes among vericiguat initiators in routine care in Germany has been limited.
Research question and objectives	This study aimed to describe mortality, hospitalization, demographic and clinical characteristics, and real-world drug use patterns among patients initiating vericiguat in Germany.

	Primary objective: To describe all-cause mortality, all-cause hospitalization, and heart failure-related hospitalization after initiation of vericiguat. **Secondary objectives:** To describe baseline sociodemographic and clinical characteristics, treatment patterns including adherence, titration, and persistence, and medication use in the 3 months before and after initiation of vericiguat. **Exploratory objective:** To describe the occurrence of hypotension after initiation of vericiguat.
Study design	This report describes a retrospective, single-arm cohort study of patients initiating vericiguat in Germany from September 2021 to June 2024.
Population	The study population comprised adults aged 18 years or older with a first observed vericiguat prescription after market availability in Germany.
Variables	Primary variables: all-cause mortality, all-cause hospitalization, and heart failure-related hospitalization. Secondary variables: baseline comorbidities, concomitant medication, and measures describing drug use patterns, including medication possession ratio, titration, and time to discontinuation. Exploratory variable: diagnoses indicating 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).
Study size	No formal sample size calculation was performed because the study was descriptive. A feasibility assessment based on the InGef database suggested that approximately 550 patients with at least one vericiguat prescription between 2021 and 2023 could be identified. The final number of included patients could vary depending on the applicable inclusion criteria and required observation periods.

Data analysis	Analyses were descriptive and exploratory. Mortality and hospitalization outcomes were summarized as incidence rates and with Kaplan–Meier methods. Adherence, titration, and persistence were assessed using dispensing-based measures and prespecified operational definitions. Baseline sociodemographic and clinical characteristics, as well as medication use before and after vericiguat initiation, were described. Exploratory regression models were used to examine associations between baseline characteristics and selected outcomes.
Milestones	Table 1 presents the planned and actual study milestones relevant to conduct and reporting of the study.

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

Reference Number: RD-SOP-1216
Supplement Version: 14

3. Investigators

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

Role: PPD
Name: PPD
Company: Bayer AG

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

4. Other responsible parties

Role: PPD
Name: PPD
Company: InGef

Role: PPD
Name: PPD
Company: InGef

Role: PPD
Name: PPD
Company: German Center for Heart Failure at the University Clinic Würzburg

Role:	PPD
Name:	PPD
Company:	German Center for Heart Failure at the University Clinic Würzburg

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.

5. Milestones

Table 1 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	Actual date
Study protocol approval	27 JUN 2024	27 JUN 2024
Start of analysis	05 JUL 2024	05 JUL 2024
End of analysis	31 AUG 2025	30 JAN 2026
Final report of study results	30 JUN 2026	07 JUL 2026

6. Rationale and background

Heart failure is associated with substantial morbidity, mortality, and healthcare utilization. In Germany, the burden of heart failure is particularly high among older adults. Vericiguat is a soluble guanylate cyclase stimulator approved for use in adults with symptomatic chronic heart failure and reduced ejection fraction following a recent worsening heart failure event.

The mechanism of action of vericiguat involves stimulation of soluble guanylate cyclase, a component of the nitric oxide–sGC–cyclic guanosine monophosphate pathway.

The Phase III VICTORIA trial evaluated vericiguat in patients with worsening heart failure and ejection fraction below 45% and reported a reduction in the composite outcome of cardiovascular death or heart failure hospitalization compared with placebo.

Vericiguat has been available in Germany since September 2021 in film-coated tablets of 2.5 mg, 5 mg, and 10 mg.

According to the Summary of Product Characteristics (SmPC), treatment was initiated at 2.5 mg once daily and titrated to a target dose of 10 mg, if tolerated. Meanwhile, after the period of this study, the SmPC recommends 5mg as the starting dose. Evidence on patient characteristics, treatment patterns, and outcomes among vericiguat initiators in routine clinical practice in Germany has been limited.

7. Research question 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.

7.1 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.

7.2 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.

7.3 Exploratory objective(s)

The exploratory objective(s) in this study are:

- Description of the occurrence of hypotension in patients initiating vericiguat

Reference Number: RD-SOP-1216
Supplement Version: 14

8. Amendments and updates

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
1	03.11.2025	9.2.1	Extension of the index identification period through 30 Jun 2024.	To increase the number of eligible patients available for descriptive analyses and to reflect the most recent period for which data were considered sufficiently complete for the main analyses.
2	03.11.2025	9.3	Refinement of subgroup characterization for patients without a recent worsening heart failure event by incorporating additional clinical and treatment-related variables.	To improve the descriptive characterization of patients without a recent worsening heart failure event and to support interpretation of subgroup results.
3	03.11.2025	9.3.2	Inclusion of oral diuretic intensification and intravenous diuretic treatment within 3 months before the index date as indicators of recent heart failure worsening.	To improve capture of clinically relevant recent worsening heart failure events in claims data, including treatment escalation not fully reflected by hospitalization diagnoses alone.
3	03.11.2025	9.3.2	Introduction of an exploratory VICTORIA-like subgroup definition based on recent worsening heart failure, operationalized as hospitalization with heart failure as the primary diagnosis or intravenous diuretic treatment within 3	To enable descriptive comparison of the study population with patients represented in the VICTORIA trial using a claims-based operational definition.

			months before the index date.	

9. Research methods

9.1 Study design

This study was a non-interventional, retrospective, single-arm cohort study of patients who initiated Verquvo (Vericiguat) in Germany. The study was based on anonymized patient data from a longitudinal claim database.

All adult patients (aged 18 years or older) who received an initial Vericiguat prescription (index date) between the 15th of September 2021 and the 30th of Jun 2024 (InGef - Index identification period) were included in the overall study population. Adherence, titration, persistence, as well as mortality, hospitalization, and other clinical and patient characteristics were described at index or within the pre-defined patient individual baseline and follow-up periods. Therefore, different pre-defined study cohorts were built according to different observation periods and further conditions.

Observation periods

Cohort entry: Each patient joined the cohort at the time of the first prescription of vericiguat. The earliest possible cohort entry date was on 15th Sep 2021, and the latest possible cohort entry date was on 30st Jun 2024 (Latest cohort entry InGef).

Cohort exit: Patients leave the cohort either at the time the insurance ends, at the time of their death or on 30st Jun (Latest cohort exit InGef).

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 was defined.

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

Sub Cohort 1a:

Follow-up: For the description of adherence, the follow-up period was 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 was defined.

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

9.2 Setting

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

The InGef Database included data from the years 2014 to 2025 and covered approximately 10 million persons. Because outpatient claims are available with a time delay, the database was considered sufficiently complete for the main analyses up to and including 30 JUN 2024 based on routine data availability assessments.

9.3 Subjects

Inclusion criteria Study Cohort 1

Study cohort 1: This population was used for the analysis of Vericiguat persistence, mortality rates, and hospitalization rates. Additionally, a "sub-cohort 1a" was extracted, consisting of patients with a second Vericiguat prescription to investigate adherence and titration patterns.

For all individuals from the InGef database, the following inclusion criteria applied:

- Patients with an initial prescription of Vericiguat (index date) according to ATC Code C01DX22.
- Patients aged at least 18 years at the time of the initial Vericiguat prescription.
- Patients with continuous insurance (allowing a one-month insurance gap, according to §19 SGB V) during the 365 days prior to the index date (one-year pre-observation period).
- Patients with continuous insurance (allowing a one-month insurance gap, according to §19 SGB V) from the index date until the end of their respective insurance period, death, or at the latest, until the 30th of Jun 2024 (InGef), whichever came 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.

Exclusion criteria Study Cohort 1

No exclusion criteria for any population were applied.

Inclusion criteria Study Cohort 2

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

- 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).

Exclusion criteria Study Cohort 2

No exclusion criteria for any population were applied.

9.4 Variables

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:

- Heart failure: Heart failure diagnosis (I50.-) with highest reached NYHA stage in baseline.
    - HF right (I50.0.-): NYHA I (I50.02); NYHA II (I50.03); NYHA III (I50.04); NYHA IV (I50.05)
    - HF left (I50.1.-): NYHA I (I50.11); NYHA II (I50.12); NYHA III (I50.13); NYHA IV (I50.14)
    - No HF: without any HF right or HF left diagnosis in baseline.
- 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 events: Number of patients with HF main or secondary hospitalization.
    - HF main hospitalization: *"full hospitalization case"* with a main 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.
    - HF secondary hospitalization: *"full hospitalization case"* with a 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.
- Time to Index since the last worsening event: 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. The same time-related categories will be calculated for HF hospitalization.
- Pre-defined comorbidities: All vericiguat new user with at least one ICD-10 GM Code according to *Table 2 (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 users with at least one prescription according to *Table 3 (see appendix)* within the respective pre-observation period of 12 months before the vericiguat index date.
- Guideline-Directed Medical Therapy (GDMT): Patients with at least one prescription of ACE / ARB / ARN-I, MRA, BB or SGLT2i. Further groups include:
    - ARN-I & SGLT2i
    - RAAS: ARB ore ACE or ARN-I)
    - Intravenous diuretics during the three months prior to index
    - Outpatient diuretic intensification (ODI) defined as the new initiation or dose increase of loop or thiazide diuretics during the three months prior to index
    - With at least 1 – 4 GDMT therapies within baseline

  - With at least 3 GMDT including ARN-I
  - With at least 3 GMDT including SGLT2i
- VICTORIA-like subgroup: patients with at least one recent worsening heart failure event, operationalized in claims data as an inpatient HF main diagnosis within 6 months before index date or intravenous diuretic treatment within 3 months before the vericiguat index date.
- VICTOR-like subgroup: patients without such recent worsening heart failure event prior to index date as defined above.

Adherence measurements:

- MPR: The treatment duration and the days of supply of the last prescription were not included in the treatment duration and the definition of the Medication Possession Ratio (MPR), as this last prescription would be considered as 100% adherence by definition, potentially leading to an overestimation of the MPR. The Patient MPR was 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 was divided into the following categories:
  - MPR $\geq$ 80%: Patients MPR $\geq$ 0.8

Titration:

- Titration pattern: Titration was calculated as logical variable for each patient according to the following titration pattern. If more than one strength of vericiguat was prescribed on the same day, the prescriptions are ordered in increasing strength, and the patient counts as up titrated. Continuous treatment wasn't 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 was 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 $\geq$ 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 $\geq (t_i)$.

Mortality:

- 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:

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 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 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)*.

Composite measurement:

A composite outcome based on all-cause mortality and HF hospitalization was 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.

Medications of interest before and after the Vericiguat index

- Pre-defined medications: All vericiguat new user with at least one prescription according to *Table 3 (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 per day in mg of each pre-defined medication.
- Reach of Target dose: All vericiguat new use reached with at least one prescription the pre-defined target dose or higher within the respective pre- and post-observation period of 3 months before and after the vericiguat index date.

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.

9.5 Data sources and measurement

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 3.

Table 3: 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)

9.6 Bias

9.6.1 Confounding

In association analyses based on observational data, careful consideration of covariate balance is important. Analytical approaches such as Propensity Score Matching (PSM) or regression adjustment can address differences in observed characteristics, but they do not capture unmeasured confounders. Unlike randomized designs, analyses of health insurance claims data are limited to variables that are routinely recorded, which may leave relevant factors unaccounted for and introduce potential bias in outcome estimates.

9.6.2 Selection Bias

Study Cohort 1a and Study Cohort 2 are potentially selective cohorts due to their respective selection criteria. In Study Cohort 1a, the requirement of a second prescription during the follow-up period may introduce immortal time bias, as inclusion necessitates survival until the second prescription can be observed. Consequently, individuals who died shortly after the first prescription are excluded from the cohort. In Study Cohort 2, a similar potential immortal time bias arises from the selection criteria requiring at least three months of observable data both before and after the index date, which likewise excludes individuals with early death or loss to follow-up.

9.6.3 Information Bias

Only outpatient prescriptions can be taken into account for the prescription of medication. Medications given during a hospital stay are not listed in the hospital billing data. This means that the analysis of prescribed medication may also be subject to bias if a patient spends a longer period of time in hospital and therefore no prescriptions are visible during this period (immeasurable time bias). In this study, we have attempted to take this into account by adding the hospital stays to the treatment time, assuming that the patients continued to receive the corresponding medication in hospital.

Observational studies based on claims data only capture the prescription and dispensing of a medication but not whether and how it is actually taken. This leads to uncertainties in estimating the duration of treatment, as patients may take their medication earlier or later than assumed or may even forgo it entirely. Additionally, analyses rely on standardized assumptions, such as Defined Daily Doses (DDD) or predefined treatment regimens, which do not always reflect real-world prescribing practices. Individual dose adjustments by the physician or the patient themselves remain unaccounted for.

Another issue is the lack of information on physician instructions regarding medication intake, which are not documented in claims data. Patients may deviate from standard dosing, take breaks in therapy, or use the medication only as needed, leading to discrepancies between dispensed medications and actual consumption. Furthermore, temporal gaps in claims data may arise when patients obtain medications from sources not captured in the analysis.

Simplified metrics such as the "Medication Possession Ratio" (MPR) or the "Proportion of Days Covered" (PDC) are therefore used to calculate persistence and adherence, but these are based on the assumption that all dispensed medications are consumed as prescribed. This assumption does not always align with reality, as irregular intake, self-medication, or intentional therapy interruptions can lead to misestimations.

In addition, the persistence outcome used a prespecified discontinuation definition requiring a treatment gap of more than 90 days. As a consequence, discontinuation could not be observed within the first 90 days after treatment initiation, which should be considered when interpreting early persistence patterns.

9.6.4 Other Bias

No other bias is expected.

9.6.5 Generalizability

The generalizability of findings may be limited due to the use of the InGef database, which primarily reflects the German healthcare system and may not represent other populations. Approximately 90% of German residents are covered by the statutory health insurance (SHI) system, which ensures broad representation in the database. However, individuals with private health insurance (PHI), comprising about 9% of the population, may have different healthcare access or treatment patterns, potentially influencing the applicability of findings. The PHI system primarily includes higher-income employees, civil servants, and self-employed individuals who meet specific eligibility criteria. Unlike SHI, private insurers are not obligated to accept all applicants, which may lead to selection bias based on health risk profiles (5). However, the InGef database has been demonstrated to have high external validity regarding overall measures of morbidity, mortality, and drug use dispensation (2).

9.7 Study size

No formal sample size calculation was performed because the study was descriptive. A feasibility assessment based on the InGef database suggested that approximately 550 patients with at least one vericiguat prescription between 2021 and 2023 could be identified.

The final number of included patients could vary depending on the applicable inclusion criteria and required observation periods.

9.8 Data transformation

Data relevant to the study objectives were extracted from the InGef research database for the defined observation period and used to derive the anonymized analysis dataset. The analysis dataset contained the variables required for the prespecified analyses described in Section 9.4. The data cut-off corresponds to the date on which the dataset was made available for analysis.

The data were analyzed by InGef staff using the open-source software R, version 4.0.2.

9.9 Statistical methods

9.9.1 Main summary measures

9.9.1.1 Description of socio-demographic and clinical characteristics at baseline

Socio-demographic characteristics at index were summarized using frequency tables and summary statistics. Continuous variables were additionally categorized and presented in frequency tables. Socio-demographic and clinical characteristics were described at the index date and during the respective baseline period before vericiguat initiation. For study cohort 1 (N), the number and proportion of patients with predefined characteristics were reported. Baseline characteristics were also summarized separately for patients initiating vericiguat at doses of 2.5 mg and 5 mg.

9.9.1.2 Adherence

This analysis is based on *"sub cohort 1a"*. Summary statistics were 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 was used to estimate the 95% CI as noted below given the mean and variance are both lambda (ƛ) in the following formula:

$$ƛ \pm Z(\alpha/2) * \sqrt{ƛ/n}$$

Additionally, the MPR was calculated for the following subgroups:

- Sex: Female, Male
- Age tertiles: Tertile 1, Tertile 2 and Tertile 3
- 5mg starter: Patients who started with a 5mg prescription

9.9.1.3 Titration

This analysis is based on Sub-cohort 1a. It evaluates the number of patients up-titrated to 5 mg and 10 mg, as well as the sector and physician specialty at the time of up-titration. Corresponding analyses are conducted for down-titration to 5 mg and 2.5 mg.

Descriptive summaries are provided for the starting dose of vericiguat, the maximum dose reached, and the time to first up-titration to 5 mg and 10 mg, respectively. Dose-specific treatment durations are calculated by summing the days of supply across prescribed packages for each dose strength. In addition, treatment pathways are described together with patient counts.

Only the first up-titration to 5 mg and 10 mg, and the first down-titration to 5 mg and 2.5 mg, if applicable, are considered. Treatment pathways are presented in chronological order. If more than one vericiguat strength is prescribed on the same day, prescriptions are ordered by increasing strength.

Therapy gaps between successive prescriptions are not considered. Patients up-titrated first to 5 mg and subsequently to 10 mg are counted in both up-titration categories. The same approach is applied to patients down-titrated to 5 mg and subsequently to 2.5 mg.

The number of patients following a given treatment pathway (for example, 2.5 mg → 5 mg → 10 mg → 5 mg) is reported as both absolute counts and patient proportions.

Analyses of starting dose, maximum dose reached, and time to up-titration are additionally stratified by the predefined subgroups. Separate analyses are also conducted for patients initiating treatment with 5 mg.

9.9.1.4 Persistence

Medication persistence was 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.

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:

$$\boldsymbol{Discontinuation\ Rate} = \frac{Number\ of\ patients\ with\ an\ event}{Number\ of\ person\ years, totaled\ for\ all\ persons} * 100$$

Discontinuation rate and corresponding 95% CIs were estimated per 100 person-years in the given assessment periods. The normal approximation method for a Poisson distribution was 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 was computed as mean (SD) and median (IQR) and was calculated according to the following formula:

Time to event = Date of event – Index date + 1

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

Furthermore, rates were be presented stratified by the following subgroups:

- Sex: Female, Male
- Age tertiles: Tertile 1, Tertile 2 and Tertile 3
- Worsening HF event: yes / no
- Time since last worsening HF event (days): 0 - 30 days, 30 – 59 days, ≥60 days
- Renal Impairment: Patients with at least one diagnosis according to ICD-10 GM Codes (I120; I1311; I132; N183; N184; N185; N170; N171; N172; N178; N179; N19; Z992; Z940).
- GDMT: yes / no
- GDMT Groups: with at least 1 – 4 GDMT, 3 GDMT incl. ARN-I, 3 GDMT incl. SGLT2i

Reference Number: RD-SOP-1216
Supplement Version: 14

9.9.1.5 Mortality and Hospitalization

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

$$\boldsymbol{Event\ Rate} = \frac{Number\ of\ patients\ with\ an\ event}{Number\ of\ person\ years, totaled\ for\ all\ persons} * 100$$

Rates and corresponding 95% CIs were estimated per 100 person-years in the given assessment periods. The normal approximation method for a Poisson distribution was 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 was computed as mean (SD) and median (IQR) among patients reaching the outcome after vericiguat initiation. Time to outcome was calculated according to the following formula:

Time to event = Date of event – Index date + 1

Additionally, event rates were computed using Kaplan-Meier estimator (survival curve including 50% estimator), in which censored observations were included.

Furthermore, rates were presented stratified by the following subgroups:

- Sex: Female, Male
- Age tertiles: Tertile 1, Tertile 2 and Tertile 3
- Worsening HF event: yes / no
- Time since last worsening HF event (days): 0 - 30 days, 30 – 59 days, ≥60 days
- Renal Impairment: Patients with at least one diagnosis according to ICD-10 GM Codes (I120; I1311; I132; N183; N184; N185; N170; N171; N172; N178; N179; N19; Z992; Z940).
- GDMT: yes / no
- GDMT Groups: with at least 1 – 4 GDMT, 3 GDMT incl. ARN-I, 3 GDMT incl. SGLT2i

9.9.2 Main statistical methods

9.9.2.1 Titration

Exploratory factors associated with reaching the maximum vericiguat dose of 10 mg were assessed using a logistic regression model including age, sex, starting dose, selected comorbidities, selected co-medications, and time since the most recent worsening heart failure event as covariates. Variables were prespecified based on baseline characteristics. Univariate models were fitted first, followed by a multivariable model including variables with $p<0.05$ in the univariate analysis. Odds ratios and 95% confidence intervals were reported.

9.9.2.2 Persistence

Exploratory factors associated with vericiguat discontinuation were assessed using a Cox proportional hazards model with time to discontinuation as the outcome and age, sex, selected comorbidities, selected co-medications, and time since the most recent worsening heart failure event as covariates. Variables were prespecified based on baseline characteristics. Univariate models were fitted first, followed by a multivariable model including variables with $p<0.05$ in the univariate analysis. Hazard ratios and 95% confidence intervals were reported.

9.9.2.3 Mortality and Hospitalization

Exploratory factors associated with mortality and hospitalization outcomes were assessed using Cox proportional hazards models including age, sex, selected comorbidities, selected co-medications, and time since the most recent worsening heart failure event as covariates. Variables were prespecified based on baseline characteristics. Univariate models were fitted first, followed by multivariable models including variables with $p<0.05$ in the univariate analysis. Hazard ratios and 95% confidence intervals were reported.

9.9.3 Missing values

Not applicable

9.9.4 Sensitivity analyses

All analyses describing persistence of drug use with vericiguat via the indicator time until discontinuation as approximation were 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 were conducted.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

The analyses were conducted in accordance with relevant good practice principles for epidemiology and secondary data analysis. Quality assurance of the analysis code included independent review by a second data scientist.

Study information and analytical documentation were maintained to support accurate reporting, interpretation, and verification of the analyses. Supporting documentation is retained in accordance with applicable requirements.

External partners participating in the study-maintained study-relevant documentation in accordance with applicable local requirements.

10. Results

10.1 Participants

10.1.1 Study Population 1

Study Cohort 1 was defined by applying the prespecified inclusion and exclusion criteria to the InGef research database. Adult patients aged 18 years or older with at least one vericiguat prescription (ATC C01DX22) were included, with cohort entry defined as the date of the first observed vericiguat prescription and the latest possible cohort entry date being 30 Jun 2024. In addition, patients were required to have continuous insurance coverage, allowing for a one-month gap in accordance with §19 SGB V, during the 365 days before the index date. This baseline period was used to assess demographic and clinical characteristics at cohort entry.

After cohort entry, patients were followed over their individual observation time until end of insurance, death, or end of study, whichever occurred first. The study design for Study Cohort 1 is shown in Figure 1.

Overall, 732 patients aged 18 years or older met the eligibility criteria for Study Cohort 1 and had the required 365-day baseline observation period before their first observed vericiguat prescription.

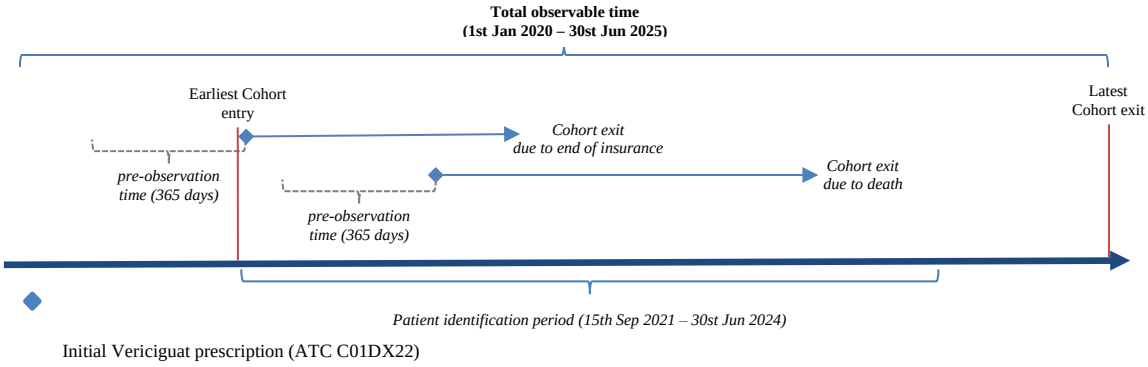

Figure 1 - Schematic overview of the Cohort Selection 1

Table 4: Number of eligible persons for study cohort 1

Selection criteria	N	%
Patients with an initial prescription of vericiguat (index date) according to ATC Code C01DX22 on earliest cohort entry (15th Sep 2020)	753	100
At least 18 years or older on the initial prescription of Vericiguat.	753	100
Patients with continuous insurance (with an allowed one-month insurance gap, according to §19 SGB V) within 365 days prior to the respective index date (one year pre-observation time).	732	97.2

Reference Number: RD-SOP-1216
Supplement Version: 14

10.1.2 Study Population 1a

For the analysis of the two outcomes adherence and titration patterns, a sub cohort of study cohort 1 (N = 732) was selected. In addition to the inclusion criteria from study cohort one all patients needed at least one second Vericiguat prescription within the follow-up.

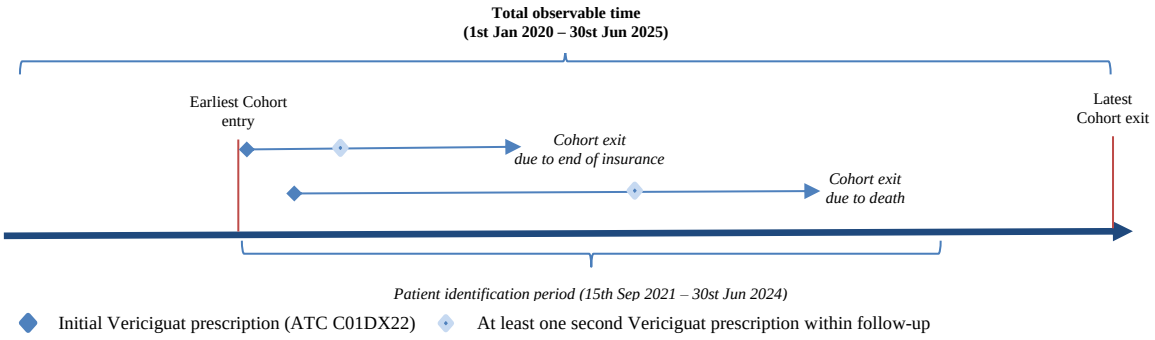

Figure 2 - Schematic overview of the Cohort Selection 1a

In Total we identified **611** (83.5%) 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.

Table 5: Number of eligible persons for study cohort 1a

Selection criteria	N	%
Patients least 18 years or older with an initial prescription of vericiguat (index date) according to ATC Code C01DX22 on earliest cohort entry (15th Sep 2020) and 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).	732	100
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.	611	83.5

10.1.3 Study Population 2

Study Cohort 2 was defined to compare medication use in the 3 months before and after vericiguat initiation. In addition to the inclusion criteria for Study Cohort 1, patients were required to have continuous insurance coverage, allowing for a one-month gap in accordance with §19 SGB V, during the 3 months before and the 3 months after the index date. The study design for Study Cohort 2 is shown in Figure 3.

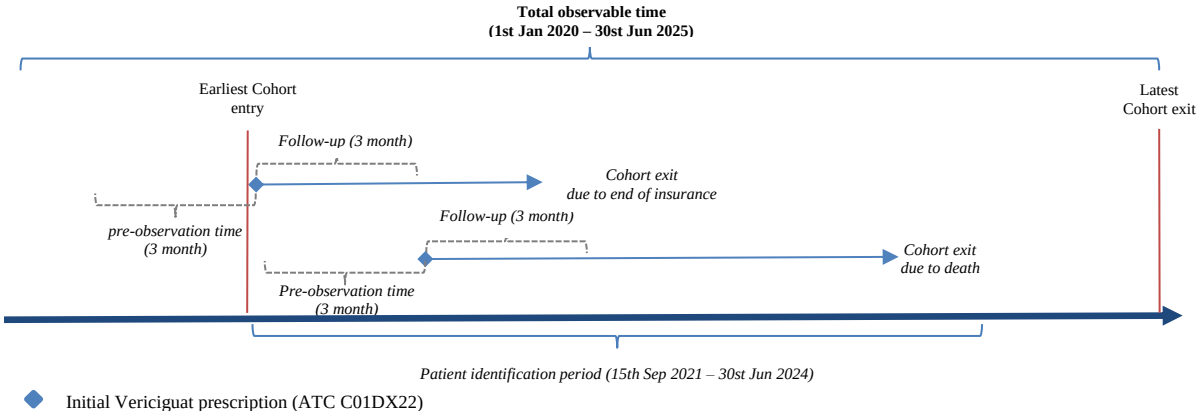

Figure 3 - Schematic overview of the Cohort Selection 2

Of the 732 patients included in Study Cohort 1, 673 (91.9%) met the additional requirement of continuous insurance coverage, allowing for a one-month gap in accordance with §19 SGB V, during the 3 months before and the 3 months after the first observed vericiguat prescription and were therefore included in Study Cohort 2.

Table 6: Number of eligible persons for study cohort 2

Selection criteria	N	%
Patients least 18 years or older with an initial prescription of vericiguat (index date) according to ATC Code C01DX22 on earliest cohort entry (15th Sep 2020) and 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).	732	100
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.	673	91.9

10.2 Descriptive data

Study Cohort 1 was further characterized according to predefined socio-demographic and clinical variables assessed during the 365 days before the first observed vericiguat prescription. Absolute and relative frequencies were calculated for each characteristic. Socio-demographic variables included sex and age, presented as age groups and tertiles. Clinical characteristics included prior hospitalizations, selected pre-existing conditions, and baseline drug therapies. The most relevant baseline characteristics are summarized below.

10.2.1 Socio-demographic variables

The sex and age distribution indicates that vericiguat was prescribed predominantly to men and older patients. Men accounted for 77.7% of the cohort, and the median age at treatment initiation was 71 years (Q1: 62.8; Q3: 80.0).

Table 7: Socio-demographic characteristics of Study Cohort 1 at baseline (N = 732)

Variable	n (%)
Sex	
Female	163 (22.3%)
Male	569 (77.7%)
Age Groups (categ.)	
18 - 50	52 (7.1%)
51 - 60	101 (13.8%)
61 - 70	206 (28.1%)
71 - 80	200 (27.3%)
81 - 90	160 (21.9%)
>90	13 (1.8%)
Age Tertiles (categ.)	
18 - 65 (Tertile 1)	223 (30.5%)
66 - 75 (Tertile 2)	243 (33.2%)
> 76 (Tertile 3)	266 (36.3%)

10.2.2 Worsening HF event at baseline

Overall, 89.5% of patients had at least one all-cause hospitalization before vericiguat initiation.

Before vericiguat initiation, 78.6% of patients had at least one hospitalization with or because of heart failure. Most of these patients (62.8% of the total cohort) had such a hospitalization within 6 months before treatment initiation, whereas 21.4% initiated vericiguat without any prior heart failure-related hospitalization. In addition, 38.5% had received at least one intravenous diuretic prescription before starting vericiguat.

Using the prespecified claims-based operational definition, 70.9% of patients were classified in the VICTORIA-like subgroup, defined by a recent worsening heart failure event within 6 months before first vericiguat prescription or intravenous diuretic treatment within 3 months before the first observed vericiguat prescription.

Table 8: Clinical characteristics of Study Cohort 1 at baseline (N = 732)

Variable	Groups	n (%)
Number of all-cause hospitalized patients	Total	655 (89.5%)
Number of Patients with at least one wHF event	Total	575 (78.6%)
thereof patients with wHF event within:	0 - 6 months	460 (62.8%)
thereof patients with wHF event within:	6 - 24 months	64 (8.7%)
thereof patients with wHF event:	> 24 months	51 (7%)
Number of Patients without wHF event before Vericiguat	never	157 (21.4%)
Number of Patients with i.v. Diuretics	Total	282 (38.5%)
Number of Patients with wHF event or i.v. Diuretics, within 3 months before index (VICTORIA-like)	Total	519 (70.9%)

10.2.3 Comorbidities at baseline

The study cohort was highly multimorbid, with 99.7% of patients having at least one predefined comorbidity. Hypertension was the most common comorbidity and was recorded in 93.0% of patients. Other ischemic heart disease was present in 82.0%, atrial fibrillation in 60.7%, and diabetes mellitus in 58.1% of patients.

Renal impairment was also common: 62.0% of patients had some degree of kidney dysfunction, and 55.9% met the criteria for chronic kidney disease (CKD). Overall, 50.0% had CKD stage 3 or higher, including 10.1% with CKD stage 5.

Other relevant comorbidities were also frequently observed. Myocardial infarction was documented in 42.5% of patients, and 8.2% had a history of stroke. Pulmonary comorbidities were common, with COPD recorded in 31.4% and respiratory infection in 41.5% of patients. In addition, anemia (22.8%), depression (23.6%), and hypothyroidism (23.2%) were frequently documented.

Table 9: Comorbidities of Study Cohort 1 at baseline (N = 732)

Variable	n (%)
Any pre-defined comorbidity	730 (99.7%)
Anemia	167 (22.8%)
Atrial fibrillation	444 (60.7%)
Cancer	126 (17.2%)
Renal impairment	454 (62%)
Acute kidney injury (AKI)	203 (27.7%)
Chronic kidney disease (CKD)	409 (55.9%)
Highest CKD stage 1	7 (1%)
Highest CKD stage 2	36 (4.9%)
Highest CKD stage 3	196 (26.8%)
Highest CKD stage 4	96 (13.1%)

Highest CKD stage 5	74 (10.1%)
CKD stage 3 or higher	366 (50%)
COPD	230 (31.4%)
Depression	173 (23.6%)
Diabetes mellitus	425 (58.1%)
Genitourinary infection	156 (21.3%)
Hyperkalemia	117 (16%)
Hypertension	681 (93%)
Hypotension	147 (20.1%)
Hypothyroidism	170 (23.2%)
Myocardial infarction	311 (42.5%)
Other ischemic heart disease	600 (82%)
Respiratory infection	304 (41.5%)
Sleep apnea	142 (19.4%)
Stroke	60 (8.2%)
Venous thromboembolism	55 (7.5%)

10.2.4 Guideline-Directed Medical Therapy at baseline

As expected for patients initiating vericiguat as add-on therapy, almost all patients (98.8%) had already received at least one component of guideline-directed medical therapy (GDMT) before treatment initiation. In addition, most patients had been treated with at least three individual GDMT components at baseline.

Table 10: Guideline-Directed Medical Therapy at baseline (N = 732)

Variable	n (%)
Guideline-Directed Medical Therapy (GDMT)	723 (98.8%)
ACE Inhibitor	179 (24.5%)
Aldosteron Antagonists / Mineralcorticoid Receptor Antagonists (MRA)	561 (76.6%)
Angiotensin Receptor Blocker (ARB)	149 (20.4%)
Angiotensin Receptor Neprilysin Inhibitor (ARN-I)	559 (76.4%)
Beta-Blocker (BB)	677 (92.5%)
SGLT-2 Inhibitor	626 (85.5%)
ARNI & SGLT2i	503 (68.7%)
RAS Medications (ARB or ACE or ARNI)	695 (94.9%)
Intravenous diuretics	114 (15.6%)
Outpatient diuretic intensification	178 (24.3%)
GDMT Groups	723 (98.8%)
with 1 GDMT	13 (1.8%)
with 2 GDMT	57 (7.8%)
with 3 GDMT	180 (24.6%)
with 4 GDMT	473 (64.6%)

10.3 Outcome data

Adherence and Persistence

Adherence was estimated using the medication possession ratio (MPR), a dispensing-based measure. Approximately 91% of patients had an MPR of at least 0.8. Estimates were broadly similar across sex and age groups, with some variation by starting dose. These findings should be interpreted in light of the limitations of claims data, as dispensing does not confirm actual intake.

Persistence was evaluated using a claims-based operational definition of discontinuation. During follow-up, approximately 17% of patients met the discontinuation definition. No discontinuations were identified within the first 90 days after initiation under the prespecified algorithm, and the cumulative discontinuation proportion at 12 months was approximately 12%. Estimates were broadly similar across age and sex strata and were not clearly associated with time since the most recent worsening heart failure event. These findings should be interpreted with consideration of the assumptions used to estimate treatment duration.

The absence of discontinuation events within the first 90 days should be interpreted in light of the prespecified persistence definition, which required a treatment gap of more than 90 days before discontinuation was classified.

Dose Titration

Most patients initiated vericiguat at the recommended starting dose of 2.5 mg. More than half of the population underwent at least one dose up-titration during follow-up, and approximately one third achieved the target dose of 10 mg. Patients with a recent wHF event were less likely to reach the maximum dose.

Clinical Outcomes

During follow-up, the all-cause mortality rate was 20 per 100 patient years. Mortality estimates were higher in older patients and in patients with renal impairment or a recent worsening heart failure event. In exploratory multivariable Cox regression analyses, shorter time since the most recent worsening heart failure event showed the strongest association with mortality, whereas no clear independent associations were observed for several other baseline characteristics after adjustment.

The rate of heart failure-related hospitalization was 46 per 100 person years. Hospitalization estimates were higher among patients with a recent worsening heart failure event, particularly when vericiguat was initiated within six months of that event. Estimates also increased with age and were higher in patients with renal impairment. Adjusted analyses showed an association between recency of worsening heart failure events and subsequent heart failure hospitalization.

For the composite endpoint of all-cause mortality or heart failure hospitalization, the rate was 57 per 100 person years. Composite event estimates were higher in men than in women and increased across age tertiles. Patients in the VICTORIA-like subgroup had higher observed composite event rates than patients not meeting that subgroup definition. In exploratory multivariable models, recent worsening heart failure events, renal impairment, atrial fibrillation, and intravenous diuretic use were associated with a higher risk of the composite outcome.

10.4 Main results

10.4.1 Vericiguat starting dose and follow-up time

Patients with Vericiguat (N = 732) were followable for an average of 639.4 days (SD = 352.5 days) from the date of the first vericiguat prescription. Approximately 77% of patients started their treatment with vericiguat with a 2.5 mg prescription. A total of 233 (32%) received a 10 mg prescription at least once during the study period.

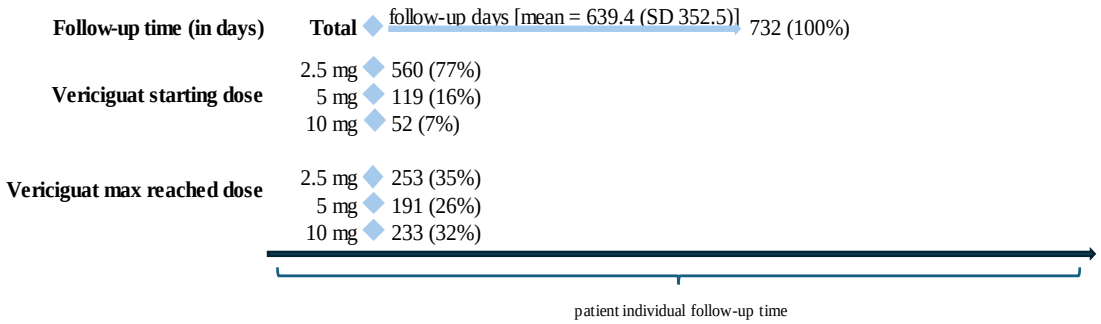

Figure 4 - Description of the vericiguat initiation and the maximum reached dose

10.4.2 Adherence

Adherence to vericiguat was estimated using MPR and appeared broadly similar across the study population. Estimates were generally consistent across age groups, sex, and starting-dose categories, although some differences were observed. Because adherence was derived from dispensing records, the results should be interpreted as estimates of medication availability rather than confirmed medication intake.

Table 11: Medication Possession Ratio (MPR) of patients treated with vericiguat (N = 611)

	n (%)
Patients with MPR ≥ 0.8	555 (90.8%)
Female	116 (87.2%)
Male	439 (91.8%)
Age Tertile 1	172 (93%)
Age Tertile 2	177 (87.2%)
Age Tertile 3	206 (92.4%)
5 mg starter	79 (84%)

10.4.3 Titration

Table 12 summarizes starting dose, dose escalation, and maximum dose reached among patients included in the titration analysis. Most patients initiated vericiguat at the lowest available dose. More than half had at least one observed dose increase during follow-up, and the highest dose was reached in a substantial proportion of patients. Time to dose escalation varied across patients.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table 12: Description of Vericiguat Titration pattern with time to titration

		Number of Patients		Time until Treatment							
		n	(%)	Sum	Min	Q1	Median	Mean	SD	Q3	Max
Total	**Total**	**611**	**100**								
Vericiguat starting dose	2.5 mg	479	78.40								
	5 mg	94	15.38								
	10 mg	37	6.06								
Up-titration (yes/no)*	**Total**	351	57.45	25,154	2	15.0	28.0	71.7	106.7	76.5	866
with at least one up-titration to	5 mg	265	43.37	18,134	2	14.0	23.0	68.4	111.6	68.0	889
with at least one up-titration to	10 mg	223	36.50	23,717	7	29.0	55.0	106.4	132.6	128.0	970
with at least one up-titration to	5 mg without 10 mg	127	20.79	10,467	4	16.5	36.0	82.4	105.5	97.5	518
with at least one up-titration to	10 mg without 5 mg	40	6.55	4,084	7	23.0	45.5	102.1	159.8	90.8	866
Down-titration (yes/no)*	**Total**	94	15.38	23,051	4	69.3	176.0	245.2	233.9	323.5	1,203
with at least one down-titration to	5 mg	34	5.56	10,157	4	119.3	171.0	298.7	298.1	412.0	1,203
with at least one down-titration to	2.5 mg	61	9.98	13,201	8	65.0	176.0	216.4	183.0	308.0	882
with at least one down-titration to	5 mg without 2.5 mg	9	1.47	3,661	4	148.0	415.0	406.8	324.3	711.0	903
with at least one down-titration to	2.5 mg without 5 mg	12	1.96	3,045	8	41.5	135.5	253.8	262.1	382.3	778
Vericiguat maximum reached dose	2.5 mg	172	28.15	-	-	-	-	-	-	-	-
	5 mg	166	27.17	9,063	-	-	18.0	54.6	92.8	55.8	517
	10 mg	218	35.68	19,378	-	20.0	43.0	88.9	123.5	100.3	969

Table 13 summarizes observed titration pathways and time to first dose adjustment. Among patients starting at 2.5 mg, up-titration to 5 mg and, for some patients, subsequently to 10 mg was observed. Among patients starting at 5 mg, a subset reached 10 mg, whereas dose reductions were less frequent. Only a small number of patients initiated treatment at 10 mg, and down-titration from this starting dose was uncommon.

Overall, the titration findings indicate heterogeneous dose adjustment patterns in routine care. The tabulated results provide the detailed distributions and time summaries.

Table 13: Description of Vericiguat titration patterns with time to titration

		Number of Patients		Time until Treatment*						
Patient pathway	**Dose in mg**	**n**	**(%)**	**Min**	**Q1**	**Median**	**Mean**	**SD**	**Q3**	**Max**
Vericiguat starting dose	**2.5 mg**	479	78.4							
up-titration to max. reached dose	5 mg	127	20.8	4	16.5	36.0	86.7	120.9	97.5	760
up-titration to max. reached dose	10 mg	179	29.3	7	30.5	56.0	112.1	140.7	140.0	970
Vericiguat starting dose	**5 mg**	94	15.4							
up-titration to max. reached dose	10 mg	44	7.2	8	22.0	46.0	91.5	107.6	98.3	431
down-titration to min. reached dose	2.5 mg	5	0.8	40	48.0	234.0	174.4	120.3	270.0	280
Vericiguat starting dose	**10 mg**	37	6.1							
down-titration to min. reached dose	5 mg	<5	-	-	-	-	-	-	-	-
down-titration to min. reached dose	2.5 mg	<5	-	-	-	-	-	-	-	-

** First up/down titration of each patient after index with time until patient is up/down-titrated for the first time*

Logistic regression analysis of factors associated with achieving the maximum Vericiguat dose (10 mg)

In the adjusted logistic regression analysis, shorter time since the most recent worsening heart failure event was associated with lower odds of reaching the maximum vericiguat dose of 10 mg. Other variables included in the multivariable model did not show clear independent associations in this exploratory analysis.

These model results should be interpreted as exploratory because they are based on observational claims data and prespecified baseline covariates.

10.4.4 Persistence

Using the prespecified claims-based discontinuation definition, 123 patients (16.8%) were classified as having discontinued vericiguat during follow-up, corresponding to an event rate of 11.1 per 100 patient-years (95% CI 9.2–13.2). These estimates reflect dispensing-based treatment continuity and should be interpreted in light of the assumptions used to estimate treatment duration and account for hospital stays.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table 14: Persistence rates after vericiguat

Baseline Characteristics	n patients with discontinuation (%)	Cumulative event rate in %	Patient time in years	Event rate per 100 patient years (with 95% CI)
Total	123 (16.8%)	16.8	1108.4	11.1 (CI: 9.2; 13.2)
Sex				
Female	34 (20.9%)	20.9	243.8	13.9 (CI: 9.7; 19.5)
Male	89 (15.6%)	15.6	864.5	10.3 (CI: 8.3; 12.7)
Age Tertile				
Tertile 1 (18 - 65)	50 (22.4%)	22.4	369.8	13.5 (CI: 10; 17.8)
Tertile 2 (66 - 75)	35 (14.4%)	14.4	387.7	9 (CI: 6.3; 12.6)
Tertile 3 (> 76)	38 (14.3%)	14.3	350.9	10.8 (CI: 7.7; 14.9)
Worsening HF event (inpatient HF main diagnosis) within 6 months before index	76 (16.5%)	16.5	651.9	11.7 (CI: 9.2; 14.6)
Time to Vericiguat Index, since the last wHF event				
1 - 29 days	56 (17%)	17.0	471.0	11.9 (CI: 9; 15.4)
30 - 59 days	8 (12.3%)	12.3	88.4	9 (CI: 3.9; 17.8)
> 60 days	12 (18.2%)	18.2	92.4	13 (CI: 6.7; 22.7)
Patients with renal impairment diagnosis	69 (15.2%)	15.2	663.0	10.4 (CI: 8.1; 13.2)
Patients with GDMT in Baseline	120 (16.6%)	16.6	1100.4	10.9 (CI: 9; 13)
ACE Inhibitor	25 (14%)	14.0	276.7	9 (CI: 5.8; 13.3)
MRA (Mineralcorticoid Receptor Antagonists)	95 (16.9%)	16.9	842.8	11.3 (CI: 9.1; 13.8)
ARB (Angiotensin Receptor Blocker)	39 (26.2%)	26.2	224.8	17.4 (CI: 12.3; 23.7)
ARNI (Angiotensin Receptor Neprilysin Inhibitor)	86 (15.4%)	15.4	858.6	10 (CI: 8; 12.4)
BB (Beta-Blocker)	114 (16.8%)	16.8	1034.9	11 (CI: 9.1; 13.2)
SGLT-2 Inhibitor	104 (16.6%)	16.6	955.6	10.9 (CI: 8.9; 13.2)
ARNI & SGLT2i	80 (15.9%)	15.9	770.9	10.4 (CI: 8.2; 12.9)
GDMT Groups				
with 1 GDMT	<5	-	14.0	-
with 2 GDMT	7 (12.3%)	12.3	80.1	8.7 (CI: 3.5; 18)
with 3 GDMT	30 (16.7%)	16.7	300.2	10 (CI: 6.7; 14.3)
with 4 GDMT	80 (16.9%)	16.9	706.1	11.3 (CI: 9; 14.1)
VICTORIA-like: Patients with wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	85 (16.4%)	16.4	748.0	11.4 (CI: 9.1; 14.1)
VICTOR-like: Patients without wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	38 (17.8%)	17.8	360.3	10.5 (CI: 7.5; 14.5)

Under the prespecified claims-based discontinuation algorithm, no discontinuation events were identified within the first 90 days after treatment initiation, because discontinuation required a treatment gap of more than 90 days. Thereafter, discontinuation accumulated gradually over follow-up.

Discontinuation rates by worsening heart failure status are also presented in Table 14, with corresponding Kaplan-Meier curves in Figure 6. Persistence patterns were broadly similar in patients with and without recent worsening heart failure events.

In the exploratory Cox regression analysis of time to first discontinuation, no strong or consistent independent associations were identified across the evaluated baseline characteristics. These model results should be interpreted cautiously because they are based on observational claims data and prespecified baseline covariates.

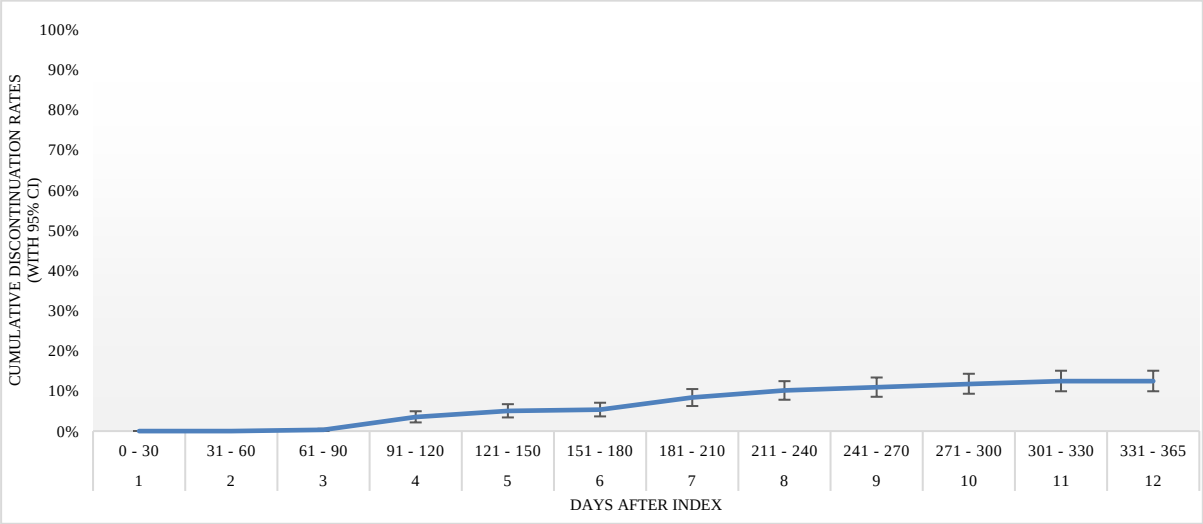

Figure 5 - Time to first treatment discontinuation of Vericiguat

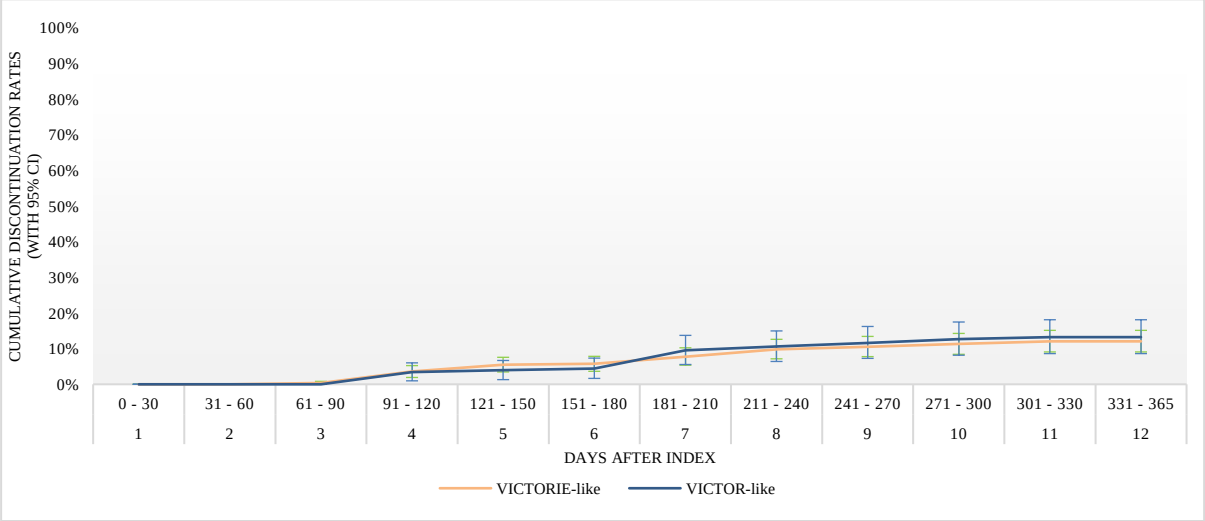

Figure 6 - Time to first treatment discontinuation of Vericiguat in patients with and without recent worsening heart failure events

10.4.5 Mortality

Mortality rates after initiation of Vericiguat

All-cause mortality following initiation of vericiguat was assessed across prespecified baseline characteristics. In the overall cohort, 258 deaths were observed, corresponding to a cumulative mortality rate of 35.2% and an event rate of 20.1 deaths per 100 patient-years (95% CI 17.7–22.7).

Mortality rates were broadly similar between women and men. Higher mortality was observed in older patients, in patients with renal impairment, and in patients with a recent worsening heart failure event before treatment initiation. Mortality was also higher in patients meeting the prespecified VICTORIA-like subgroup definition than in those who did not. Detailed subgroup estimates are provided in Table 15.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table 15: Mortality rates after vericiguat

Baseline Characteristics	n deaths (%)	Cumulative event rate in %	Patient time in years	Event rate per 100 patient years (with 95% CI)
Total	258 (35.2%)	35.2	1282.4	20.1 (CI: 17.7; 22.7)
Sex				
Female	55 (33.7%)	33.7	296.2	18.6 (CI: 14; 24.2)
Male	203 (35.7%)	35.7	986.2	20.6 (CI: 17.8; 23.6)
Age Tertile				
Tertile 1 (18 - 65)	49 (22%)	22.0	439.2	11.2 (CI: 8.3; 14.7)
Tertile 2 (66 - 75)	72 (29.6%)	29.6	441.2	16.3 (CI: 12.8; 20.6)
Tertile 3 (> 76)	137 (51.5%)	51.5	402.0	34.1 (CI: 28.6; 40.3)
Worsening HF event (inpatient HF main diagnosis) within 6 months before index	191 (41.5%)	41.5	756.9	25.2 (CI: 21.8; 29.1)
Time to Vericiguat Index, since the last wHF event				
1 - 29 days	139 (42.2%)	42.2	548.2	25.4 (CI: 21.3; 29.9)
30 - 59 days	30 (46.2%)	46.2	99.9	30 (CI: 20.3; 42.9)
> 60 days	22 (33.3%)	33.3	108.7	20.2 (CI: 12.7; 30.6)
Patients with renal impairment diagnosis	195 (43%)	43.0	756.7	25.8 (CI: 22.3; 29.7)
Patients with GDMT in Baseline	255 (35.3%)	35.3	1270.6	20.1 (CI: 17.7; 22.7)
ACE Inhibitor	72 (40.2%)	40.2	314.0	22.9 (CI: 17.9; 28.9)
MRA (Mineralcorticoid Receptor Antagonists)	195 (34.8%)	34.8	982.8	19.8 (CI: 17.2; 22.8)
ARB (Angiotensin Receptor Blocker)	48 (32.2%)	32.2	277.0	17.3 (CI: 12.8; 23)
ARNI (Angiotensin Receptor Neprilysin Inhibitor)	185 (33.1%)	33.1	981.1	18.9 (CI: 16.2; 21.8)
BB (Beta-Blocker)	234 (34.6%)	34.6	1198.0	19.5 (CI: 17.1; 22.2)
SGLT-2 Inhibitor	218 (34.8%)	34.8	1100.7	19.8 (CI: 17.3; 22.6)
ARNI & SGLT2i	164 (32.6%)	32.6	880.1	18.6 (CI: 15.9; 21.7)
Intravenous diuretics	51 (44.7%)	44.7	177.3	28.8 (CI: 21.4-37.8)
Outpatient diuretic intensification	67 (37.6%)	37.6	315.2	21.3 (CI: 16.5-27.0)
GDMT Groups				
with 1 GDMT	7 (53.8%)	53.8	17.4	40.2 (CI: 16.2; 82.9)
with 2 GDMT	24 (42.1%)	42.1	88.4	27.2 (CI: 17.4; 40.4)
with 3 GDMT	63 (35%)	35.0	344.7	18.3 (CI: 14; 23.4)
with 4 GDMT	161 (34%)	34.0	820.2	19.6 (CI: 16.7; 22.9)
VICTORIA-like: Patients with wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	208 (40.1%)	40.1	868.2	24 (CI: 20.8; 27.4)

VICTOR-like: Patients without wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	50 (23.5%)	23.5	414.1	12.1 (CI: 9; 15.9)

Mortality rates over time in new users of Vericiguat

Cumulative all-cause mortality over time is shown in Figure 7. Mortality accumulated gradually during follow-up, reaching approximately one fifth of patients by 12 months after vericiguat initiation.

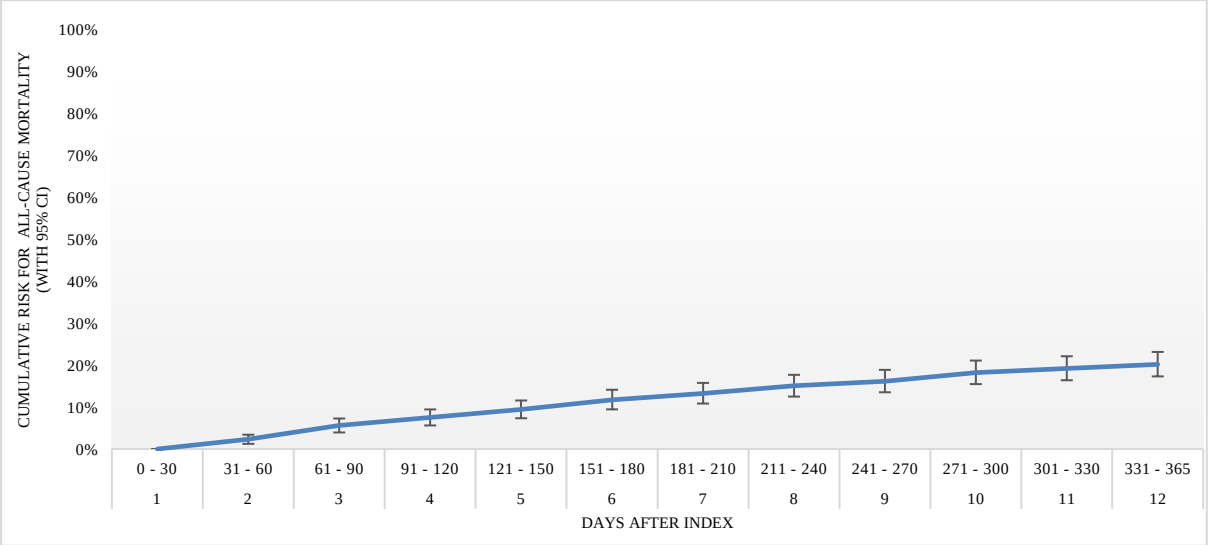

Figure 7 - Time to all-cause mortality in new users of Vericiguat

Mortality rates by worsening heart failure status

Figure 8 shows cumulative mortality by worsening heart failure status according to the prespecified VICTORIA-like subgroup definition. Mortality was consistently higher over follow-up in patients with a recent worsening heart failure event or intravenous diuretic treatment before initiation than in patients not meeting this definition.

Figure 8 - Cumulative mortality risk in VICTORIA-like vs. VICTOR-like patients

These findings indicate a substantially higher cumulative risk of death in patients with recent worsening heart failure or intravenous diuretic use prior to Vericiguat initiation.

Cox regression analysis of time to death

In the adjusted Cox regression analysis, a worsening heart failure event within 0–6 months before vericiguat initiation was associated with a higher risk of death compared with no prior worsening heart failure event. More remote worsening heart failure events were not clearly associated with mortality risk in this exploratory analysis. An ODI was associated with an increased mortality risk while the use of i.v. diuretics appeared to have no effect.

10.4.6 Hospitalization

Heart failure hospitalization rates after initiation of Vericiguat

Heart failure hospitalization following initiation of vericiguat was assessed across prespecified baseline characteristics. In the overall cohort, 387 patients experienced at least one heart failure hospitalization, corresponding to a cumulative event rate of 52.9% and an event rate of 46.2 hospitalizations per 100 patient-years (95% CI 41.7–51.0).

Hospitalization rates were broadly similar by sex. Higher rates were observed in older patients, in patients with renal impairment, and in patients with a recent worsening heart failure event before treatment initiation. Rates were also higher in patients meeting the prespecified VICTORIA-like subgroup definition than in those who did not. Detailed subgroup estimates are provided in Table 16.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table 16: Heart Failure Hospitalization Rates after Vericiguat

Baseline Characteristics	n deaths (%)	Cumulative event rate in %	Patient time in years	Event rate per 100 patient years (with 95% CI)
Total	387 (52.9%)	52.9	838.4	46.2 (CI: 41.7; 51)
Sex				
Female	76 (46.6%)	46.6	195.4	38.9 (CI: 30.7; 48.7)
Male	311 (54.7%)	54.7	643.0	48.4 (CI: 43.1; 54.1)
Age Tertile				
Tertile 1 (18 - 65)	105 (47.1%)	47.1	294.6	35.6 (CI: 29.2; 43.2)
Tertile 2 (66 - 75)	133 (54.7%)	54.7	274.0	48.5 (CI: 40.6; 57.5)
Tertile 3 (> 76)	149 (56%)	56.0	269.8	55.2 (CI: 46.7; 64.8)
Worsening HF event (inpatient HF main diagnosis) within 6 months before index	282 (61.3%)	61.3	430.8	65.5 (CI: 58; 73.6)
Time to Vericiguat Index, since the last wHF event				
1 - 29 days	207 (62.9%)	62.9	304.5	68 (CI: 59; 77.9)
30 - 59 days	42 (64.6%)	64.6	50.9	82.5 (CI: 59.5; 111.5)
> 60 days	33 (50%)	50.0	75.4	43.8 (CI: 30.1; 61.5)
Patients with renal impairment diagnosis	267 (58.8%)	58.8	452.2	59 (CI: 52.2; 66.6)
Patients with GDMT in Baseline	385 (53.3%)	53.3	827.3	46.5 (CI: 42; 51.4)
ACE Inhibitor	91 (50.8%)	50.8	208.2	43.7 (CI: 35.2; 53.7)
MRA (Mineralcorticoid Receptor Antagonists)	302 (53.8%)	53.8	626.9	48.2 (CI: 42.9; 53.9)
ARB (Angiotensin Receptor Blocker)	76 (51%)	51.0	181.5	41.9 (CI: 33; 52.4)
ARNI (Angiotensin Receptor Neprilysin Inhibitor)	301 (53.8%)	53.8	635.3	47.4 (CI: 42.2; 53)
BB (Beta-Blocker)	359 (53%)	53.0	776.4	46.2 (CI: 41.6; 51.3)
SGLT-2 Inhibitor	336 (53.7%)	53.7	720.7	46.6 (CI: 41.8; 51.9)
ARNI & SGLT2i	271 (53.9%)	53.9	569.4	47.6 (CI: 42.1; 53.6)
Intravenous diuretics	119 (66.9%)	66.9	180.4	66.0 (CI: 54.6-78.9)
Outpatient diuretic intensification	53 (46.5%)	46.5	121.9	43.5 (CI: 32.6-56.9)
GDMT Groups				
with 1 GDMT	<5	-	15.0	-
with 2 GDMT	28 (49.1%)	49.1	63.2	44.3 (CI: 29.4; 64)
with 3 GDMT	106 (58.9%)	58.9	216.0	49.1 (CI: 40.2; 59.4)
with 4 GDMT	247 (52.2%)	52.2	533.2	46.3 (CI: 40.7; 52.5)
VICTORIA-like: Patients with wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	314 (60.5%)	60.5	514.0	61.1 (CI: 54.5; 68.2)

VICTOR-like: Patients without wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	73 (34.3%)	34.3	324.4	22.5 (CI: 17.6; 28.3)

Reference Number: RD-SOP-1216
Supplement Version: 14

Heart failure hospitalization rates over time in new users of Vericiguat

Cumulative heart failure hospitalization over time is shown in Figure 9. Hospitalizations accumulated predominantly during the first three months of follow-up reaching approximately two fifths of patients by 12 months after vericiguat initiation.

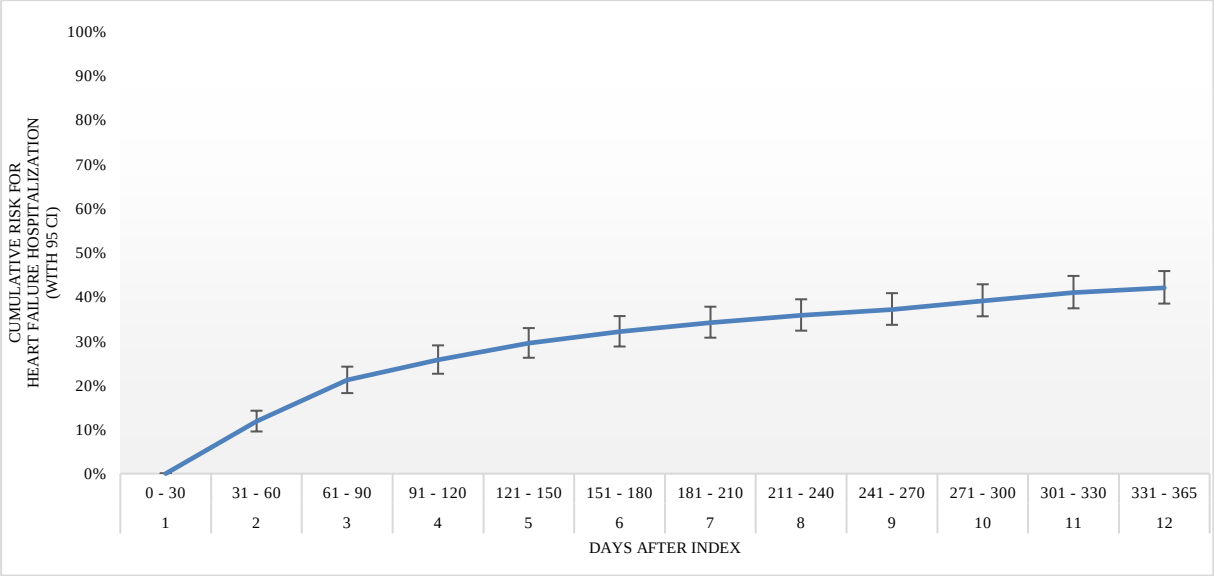

Figure 9 - Time to heart failure hospitalization in new users of Vericiguat

Heart failure hospitalization rates by worsening heart failure status

Figure 10 shows cumulative heart failure hospitalization by worsening heart failure status according to the prespecified VICTORIA-like subgroup definition. Hospitalization rates were consistently higher over follow-up in patients with a recent worsening heart failure event or intravenous diuretic treatment before initiation than in patients not meeting this definition.

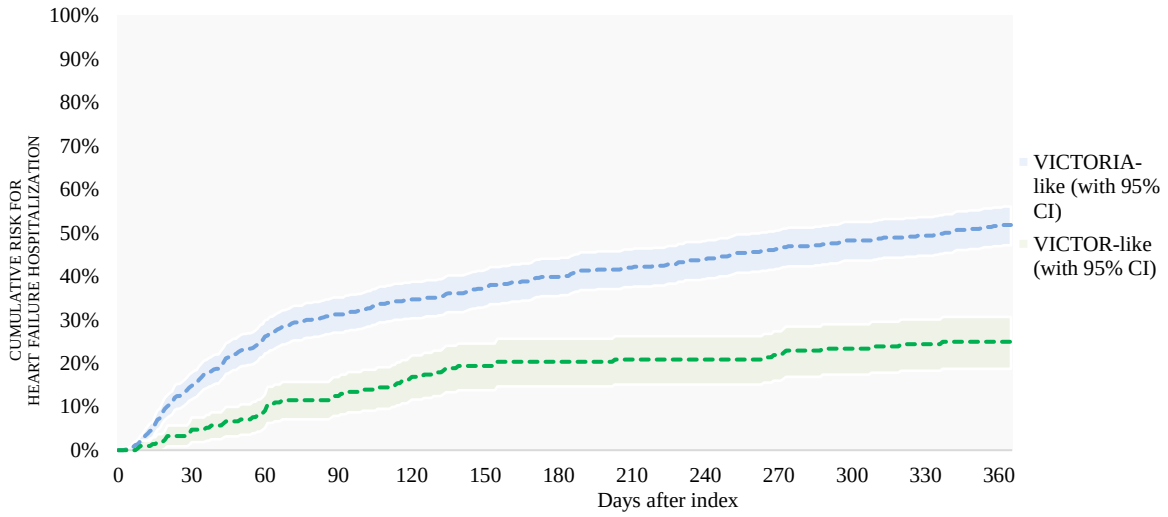

Figure 10 - Cumulative risk for heart failure hospitalization in VICTORIA-like vs. VICTOR-like patients

Cox regression analysis of heart failure hospitalization

In the adjusted Cox regression analysis, worsening heart failure events before vericiguat initiation were associated with a higher risk of heart failure hospitalization, particularly when these events occurred more recently. Intravenous diuretic use and renal impairment were also associated with higher hospitalization risk in this exploratory analysis, while ODI was not associated with risk for heart failure hospitalizations. Other baseline covariates did not show clear independent associations after adjustment.

10.4.7 Composite

All-cause mortality or heart failure hospitalization after initiation of Vericiguat

The composite outcome of all-cause mortality or heart failure hospitalization was assessed across prespecified baseline characteristics. In the overall cohort, 478 patients experienced a composite event, corresponding to a cumulative event rate of 65.3% and an event rate of 57.0 events per 100 patient-years (95% CI 52.0–62.4).

Composite event rates were broadly similar by sex. Higher rates were observed in older patients, in patients with renal impairment, and in patients with a recent worsening heart failure event before treatment initiation. Rates were also higher in patients meeting the prespecified VICTORIA-like subgroup definition than in those who did not. Detailed subgroup estimates are provided in Table 17.

Reference Number: RD-SOP-1216
Supplement Version: 14

Table 17: All-Cause Mortality or Heart Failure Hospitalization Rates after Vericiguat

Baseline Characteristics	n deaths (%)	Cumulative event rate in %	Patient time in years	Event rate per 100 patient years (with 95% CI)
Total	478 (65.3%)	65.3	838.4	57 (CI: 52; 62.4)
Sex				
Female	97 (59.5%)	59.5	195.4	49.7 (CI: 40.3; 60.6)
Male	381 (67%)	67.0	643.0	59.3 (CI: 53.5; 65.5)
Age Tertile				
Tertile 1 (18 - 65)	121 (54.3%)	54.3	294.6	41.1 (CI: 34.1; 49.1)
Tertile 2 (66 - 75)	157 (64.6%)	64.6	274.0	57.3 (CI: 48.7; 67)
Tertile 3 (> 76)	200 (75.2%)	75.2	269.8	74.1 (CI: 64.2; 85.1)
Worsening HF event (inpatient HF main diagnosis) within 6 months before index	342 (74.3%)	74.3	430.8	79.4 (CI: 71.2; 88.3)
Time to Vericiguat Index, since the last wHF event				
1 - 29 days	251 (76.3%)	76.3	304.5	82.4 (CI: 72.5; 93.3)
30 - 59 days	51 (78.5%)	78.5	50.9	100.2 (CI: 74.6; 131.7)
> 60 days	40 (60.6%)	60.6	75.4	53.1 (CI: 37.9; 72.3)
Patients with renal impairment diagnosis	337 (74.2%)	74.2	452.2	74.5 (CI: 66.8; 82.9)
Patients with GDMT in Baseline	475 (65.7%)	65.7	827.3	57.4 (CI: 52.4; 62.8)
ACE Inhibitor	118 (65.9%)	65.9	208.2	56.7 (CI: 46.9; 67.9)
MRA (Mineralcorticoid Receptor Antagonists)	369 (65.8%)	65.8	626.9	58.9 (CI: 53; 65.2)
ARB (Angiotensin Receptor Blocker)	93 (62.4%)	62.4	181.5	51.2 (CI: 41.4; 62.8)
ARNI (Angiotensin Receptor Neprilysin Inhibitor)	366 (65.5%)	65.5	635.3	57.6 (CI: 51.9; 63.8)
BB (Beta-Blocker)	442 (65.3%)	65.3	776.4	56.9 (CI: 51.7; 62.5)
SGLT-2 Inhibitor	413 (66%)	66.0	720.7	57.3 (CI: 51.9; 63.1)
ARNI & SGLT2i	329 (65.4%)	65.4	569.4	57.8 (CI: 51.7; 64.4)
Intravenous diuretics	137 (77.0%)	77.0	180.4	75.9 (CI: 63.8; 90.0)
Outpatient diuretic intensification	72 (63.2%)	63.2	121.9	59.1 (CI: 46.2; 74.4)
GDMT Groups				
with 1 GDMT	8 (61.5%)	61.5	15.0	53.4 (CI: 23.1; 105.3)
with 2 GDMT	36 (63.2%)	63.2	63.2	57 (CI: 39.9; 78.9)
with 3 GDMT	125 (69.4%)	69.4	216.0	57.9 (CI: 48.2; 69)
with 4 GDMT	306 (64.7%)	64.7	533.2	57.4 (CI: 51.1; 64.2)
VICTORIA-like: Patients with wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	380 (73.2%)	73.2	514.0	73.9 (CI: 66.7; 81.7)

VICTOR-like: Patients without wHF event (as hospitalization with HF main diagnosis) or i.v. Diuretics, within 3 months before index	98 (46%)	46.0	324.4	30.2 (CI: 24.5; 36.8)

Composite event rates over time in new users of Vericiguat

Cumulative composite event rates over time are shown in Figure 11. Composite events accumulated progressively during follow-up, reaching approximately half of patients by 12 months after vericiguat initiation.

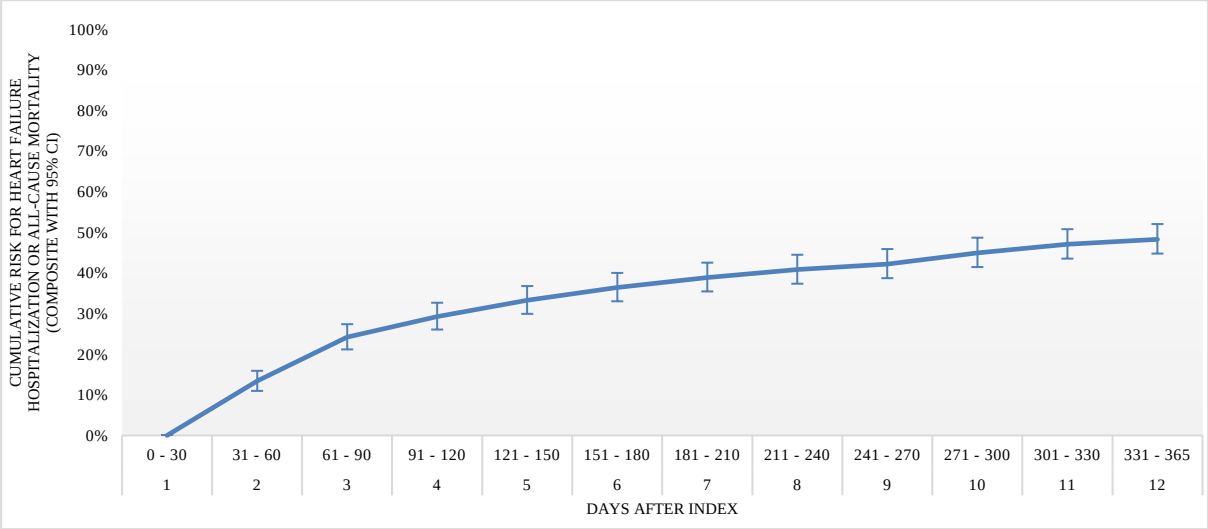

Figure 11 - Time to all-cause mortality or heart failure hospitalization in new users of Vericiguat

Composite event rates by worsening heart failure status

Figure 12 shows cumulative composite event rates by worsening heart failure status according to the prespecified VICTORIA-like subgroup definition. Composite event rates were consistently higher over follow-up in patients with a recent worsening heart failure event or intravenous diuretic treatment before initiation than in patients not meeting this definition.

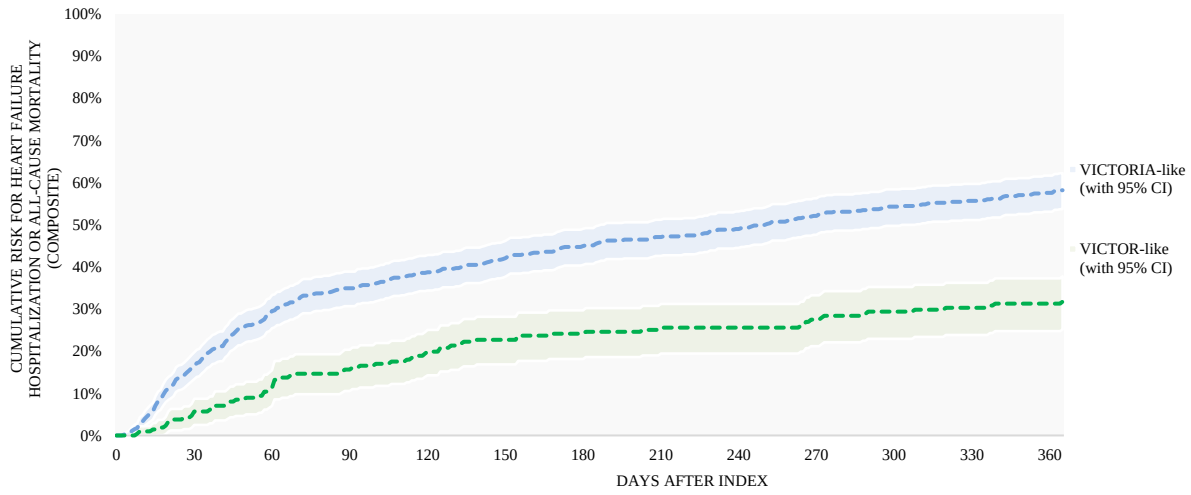

Figure 12 - Cumulative risk of all-cause mortality or heart failure hospitalization in VICTORIA-like versus VICTOR-like patients

Cox regression analysis of all-cause mortality or heart failure hospitalization

In the adjusted Cox regression analysis, worsening heart failure events before vericiguat initiation were associated with a higher risk of the composite outcome, particularly when these events occurred more recently. Renal impairment, atrial fibrillation, and intravenous diuretic use were also associated with higher risk in this exploratory analysis, while ODI was not associated with the risk for the composite outcome. Other baseline covariates did not show clear independent associations after adjustment.

10.5 Other analyses

10.5.1 Hypotension

Within 90 days after vericiguat initiation, 75 of 732 patients (10.25%) had a recorded diagnosis indicating hypotension. Most recorded events were identified in the inpatient setting rather than outpatient care. Patients using vericiguat aged 18-65 more frequently experienced hypotension than vericiguat users with older age. Recorded hypotension was more frequent among patients with a baseline history of hypotension and among patients with a worsening heart failure event before treatment initiation. Events were also more commonly observed among patients initiating vericiguat at 2.5 mg than among those initiating at 5 mg. Detailed subgroup proportions are shown in Table 18.

Table 18: Hypotension in vericiguat new user

	n with Hypotension	N Vericiguat new user per subgroup	Proportion %
Overall	75	732	10.25
thereof, with Hypotension diagnosis in the **outpatient Sector**	26	732	3.55
thereof, with Hypotension diagnosis in the **inpatient Sector**	53	732	7.24
Age Tertiles			
Tertile 1 (18 - 65)	26	223	11.66
Tertile 2 (66 - 75)	23	243	9.47
Tertile 3 (> 76)	26	266	9.77
Sex			
Female	19	163	11.66
Male	56	569	9.84
Patients with hypotension during baseline	38	147	25.85
Patients without hypotension during baseline	37	585	6.32
Worsening HF event, with HF main diagnosis in baseline	51	460	11.09
Vericiguat starting dose			
2.5 mg	60	560	10.71
5 mg	10	119	8.40

10.6 Adverse events/adverse reactions

Not applicable.

11. Discussion

11.1 Key results

This study describes real-world use patterns and selected clinical outcomes among patients initiating vericiguat in Germany. Adherence, estimated using a dispensing-based medication possession ratio, was high in the analyzed subcohort, and most patients initiated treatment at the 2.5 mg starting dose. More than half of patients included in the titration analysis had at least one observed dose increase, while patients with a more recent worsening heart failure event were less likely to reach the maximum dose of 10 mg in exploratory analyses.
Persistence estimates based on the prespecified claims-based discontinuation definition suggested continued treatment in most patients over follow-up. The absence of discontinuation events within the first 90 days should be interpreted in light of the outcome definition, which required a treatment gap of more than 90 days before discontinuation was classified.
Mortality, heart failure hospitalization, and the composite outcome of death or heart failure hospitalization were higher in patients with older age, renal impairment, and more recent worsening heart failure events. Patients meeting the prespecified VICTORIA-like subgroup definition also showed higher observed event rates than patients not meeting this definition. Exploratory regression analyses indicated that the recency of worsening heart failure before treatment initiation was associated with these outcomes.
Recorded diagnoses indicating hypotension within 90 days after treatment initiation were observed in a minority of patients. These findings should be interpreted cautiously because the analysis was based on claims-recorded diagnoses and descriptive subgroup summaries.
Overall, the study provides descriptive evidence on vericiguat use, treatment patterns, and recorded clinical outcomes in routine care in Germany. The findings should be interpreted in light of the observational design, the use of claims data, and the operational definitions applied for treatment patterns and outcomes.

11.2 Limitations

Despite these findings, several limitations should be acknowledged. First, the observational nature of the study introduces the potential for confounding. Although regression methods were used to adjust for observed covariates, analyses based on health insurance claims data are limited to routinely recorded variables; therefore, residual confounding due to unmeasured or incompletely captured factors cannot be excluded. Second, selection bias may be present because the study population was derived from a specific insured population and may not fully represent the broader patient population. Third, information bias is possible because claims data capture prescriptions and dispensings rather than confirmed medication intake. As a result, adherence, persistence, and treatment duration are estimated based on operational assumptions and may not fully reflect actual drug use, including dose adjustments, treatment interruptions, or physician instructions that are not observable in claims data. In addition, medications administered during hospital stays are not captured in outpatient prescription data, which may lead to exposure misclassification and immeasurable time bias, particularly among patients with prolonged hospitalizations, although attempts were made to account for this in the analysis. Finally, some study outcomes depended on prespecified operational definitions, which may influence the timing and frequency of observed events and should be considered when interpreting the findings.

11.3 Interpretation

Overall Interpretation of Results

This study provides relevant real-world evidence on the use of vericiguat in patients with heart failure, with a particular focus on adherence, dose titration, persistence, and clinical outcomes. Overall, the findings suggest that vericiguat is being used in routine clinical practice with generally high adherence and structured titration patterns, consistent with label-based use in a heterogeneous patient population.

Most patients initiated treatment at the recommended low starting dose, and more than half underwent dose escalation during follow-up. Persistence appeared relatively high during the early treatment phase and declined gradually over time, consistent with long-term therapy in chronic heart failure, although these estimates were based on claims-derived operational definitions. Clinical outcomes were strongly associated with markers of disease severity, particularly advanced age and recent worsening heart failure, which were consistently linked to higher risks of mortality, hospitalization, and the composite endpoint.

Safety analyses did not indicate any new or unexpected findings. Overall, the observed safety profile of vericiguat was consistent with its known and labeled risks, and no new safety signals were identified in this real-world setting.

Comparison with Prior Research

The results of this real-world analysis are broadly consistent with findings from randomized controlled trials and previous observational studies. High adherence and structured titration observed in this cohort align with data from pivotal trials such as VICTORIA, suggesting that some treatment-use patterns observed under trial conditions are also seen in routine care.

At the same time, the higher absolute rates of hospitalization observed in this study likely reflect differences in patient selection. In routine clinical practice, vericiguat appears to be prescribed to patients with more advanced disease and a greater comorbidity burden than those typically enrolled in randomized trials. These differences in baseline risk may explain the higher event rates observed after treatment initiation.

Overall, the present findings extend the existing evidence base by showing how vericiguat is used in a broader and clinically more complex population in routine care.

Safety Concerns and Benefit-Risk Balance

Safety analyses did not reveal any new or unexpected findings. The observed safety profile of vericiguat was consistent with its established and labeled risks. In this context, the overall benefit–risk balance of vericiguat remains unchanged.

Strength of Evidence for Risk

While randomized controlled trials remain the gold standard for causal inference, this study adds important real-world evidence on the use and outcomes of vericiguat in routine clinical practice. The general consistency of adherence patterns, titration behavior, and associations between disease severity markers and clinical outcomes with prior evidence supports the overall plausibility of the findings.

Nevertheless, the observational design limits causal interpretation, and residual confounding cannot be excluded. In addition, several measures particularly adherence, persistence, and treatment duration were based on claims-derived operational assumptions rather than confirmed medication use. Further research in specific high-risk subgroups may help refine the

understanding of treatment patterns and outcomes, but the present findings do not suggest any change in the known safety profile of vericiguat.

11.4 Generalizability

The generalizability of the findings is potentially limited by the use of the InGef database, which reflects the German healthcare system. While the database covers a large proportion of patients under statutory health insurance, differences in treatment patterns among privately insured individuals and populations in other countries may affect the applicability of these results.

12. Other information

Not applicable.

13. Conclusion

In conclusion, this study provides real-world evidence on the use of vericiguat in patients with heart failure in Germany. Vericiguat use was characterized by generally high adherence, structured dose titration, and persistence patterns consistent with long-term treatment in routine clinical practice, although these measures were based on claims-derived operational definitions. Clinical outcomes were primarily associated with markers of disease severity, particularly recent worsening heart failure and older age. No new safety signals were identified, and the observed safety profile was consistent with the known and labeled risks of vericiguat. Overall, these findings add to the available evidence on vericiguat use in a broad, clinically complex heart failure population in routine care.

14. References

1. FDA, Code of Federal Regulations, 21 CFR 11: Electronic records; electronic signatures, 01 April 2020
2. EU, Commission implementing regulation (EU) No 520/2012 of 19 Jun 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council, Official Journal of the European Union, 20 Jun 2012
3. EFPIA HCP Code, Code on the Promotion of Prescription-Only Medicines to and Interactions with Healthcare Professionals, 06 Jun 2014
4. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology; EMA/95098/2010 (Revision 8, Jul 2020)
5. EMA, Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2); EMA/873138/2011_Rev 2, 28 Jul 2017
6. EMA, Guideline on good pharmacovigilance practices (GVP) – Product- or population-specific considerations IV: paediatric population; EMA/572054/2016, 25 Oct 2018
7. EMA, Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (Rev 3); EMA/813938/2011_Rev 3, 09 Oct 2017
8. EMA, Guideline on good pharmacovigilance practices (GVP) Module VIII Addendum I – Requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies (Rev 3); EMA/395730/2012_Rev 3, 15 Jun 2020
9. EU, Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (latest consolidated version 01 Jan 2011)
10. EU, Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (latest consolidated version 20 Jan 2011)
11. W. P. Battisti, E. Wager, L. Baltzer, D. Bridges, A. Cairns. C. I. Carswell, L. Citrome, J. A. Gurr, L. A. Mooney, B. J. Moore, T. Peña, C. H. Sanes-Miller, K. Veitch, K. L. Woolley and Y. E. Yarker, Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3, Ann Intern Med., 2015

12. E. von Elm, D. G. Altman, M. Egger, S. J. Pocock, P. C. Gøtzsche and J. P. Vandenbroucke, STROBE-Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies. J Clin Epidemiol. 2, J Clin Epidemiol., 2008
13. Ludwig M, Enders D, Basedow F, Walker J, Jacob J: Sampling strategy, characteristics and representativeness of the InGef research database. Public Health 2022. doi: 10.1016/j.puhe.2022.02.013
14. Ständer, S., Ketz, M., Kossack, N., Akumo, D., Pignot, M., Gabriel, S., & Chavda, R. (2020). Epidemiology of Prurigo Nodularis compared with Psoriasis in Germany: A Claims Database Analysis. Acta dermato-venereologica; DOI: 10.2340/00015555-3655 , 199.

Appendices

Annex 1: List of stand-alone documents

Table 19: List of stand-alone documents

Document Name	Final version and date (if available)
Initial study protocol	v1.0, 04 JUL 2024
Study protocol amendment	v1.1, 20 NOV 2024