Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	c37191900-03
BI Study Number:	1245-0259
BI Investigational product:	Jardiance®
Title:	**Empa**gliflozin fun**ct**ional capacity - Non-Inter**v**enti**o**nal S**t**ud**y**
Brief lay title:	**Emp-Activity**
Protocol version identifier:	Final 3.0
Date of last version of protocol:	14 Jun 2022
PASS	No
EU PAS register number:	Not applicable
Active substance:	Empagliflozin (ATC: A10BK03)
Medicinal Product:	Jardiance® film-coated tablet containing 10 mg empagliflozin
Product reference:	Jardiance EMEA/H/C/2677
Procedure number:	n.a.
Marketing authorisation holder(s):	MAH: [redacted] This study is initiated, managed and sponsored by: [redacted]

Joint PASS:	No
Research question and objectives:	Primary objective: To describe the change of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from baseline to 24 weeks in patients newly treated with empagliflozin according to routine practice. Secondary objectives: • To describe the change of the New York Heart Association (NYHA) Class from baseline to 24 weeks in patients newly treated with empagliflozin. • To capture real-world patterns of patient characteristics and clinical disease presentation according to therapeutic regimen chosen in participants with chronic HF
Country(-ies) of study:	Poland, Romania, Hungary, Switzerland, Czech Republic, Bulgaria, Slovenia, Serbia
Author:	[redacted]
In case of PASS, add: **MAH contact person:**	Not applicable
In case of PASS, add: **EU-QPPV**	Not applicable
In case of PASS, add: **Signature of EU-QPPV**	Not applicable
Date	30 Sep 2022

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CEE	Central Eastern Europe
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CSS	Clinical summary score
DMP	Data Management Plan
DMRP	Data Management and Review Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EF	Ejection Fraction
ENCePP	European network of Centers for Pharmacoepidemiology and Pharmacovigilance
FAS	Full Analysis Set
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HCP	Health Care Practitioner
HDL	High-density Lipoprotein
HF	Heart Failure
HFmrEF	Heart Failure with mildly reduced Ejection Fraction
HFpEF	Heart Failure with preserved Ejection Fraction
HFrEF	Heart Failure with reduced Ejection Fraction
ICD	International Statistical Classification of Diseases and Related Health Problems
IEC	Independent Ethics Committee
IRB	Institutional Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
LDL	Low-density Lipoprotein
LV	Left ventricular/ventricle
LVEF	Left ventricular ejection fraction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
NYHA	New York Heart Association
OSS	Overall Summary Score
PASS	Post-authorization safety study
PRO	Patient-reported Outcome
QoL	Quality of Life
SAP	Statistical Analysis Plan
SGLT2	Sodium-Glucose Co-Transporter 2
TSS	Total Symptom Score

3. RESPONSIBLE PARTIES

BI NIS [redacted], Regional Medical Affairs Manager	[redacted]
Trial Clinical Monitor (TCM)	[redacted]
Coordinating Investigator	[redacted]
Contract Research Organization (CRO)	[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance®			
Name of active ingredient: empagliflozin			
Protocol date: 24.Jan.2022	**Study number:** 1245-0259	**Version/Revision:** 3.0	**Version/Revision date:** 30 September 2022
Title of study:	**Empa**gliflozin fun**cti**onal capacity – Non-Inter**v**en**ti**onal S**tud**y		
Rationale and background:	The Emp-Activity study is a multinational, multi-center, non-interventional study conducted in CEE countries and based on newly collected data with the aim to close the gap between clinical trial data and available data regarding changes in patient-reporting outcomes after empagliflozin initiation in routine practice. QoL will be assessed by means of the complete version of KCCQ in real-world HF-patients treated with empagliflozin according to approval. Until now, limited data are available regarding PRO changes after empagliflozin initiation in routine practice. Since participants of clinical trials commonly differ from the broader population for whom a therapy may be used in clinical practice, there is a need to better characterize symptom changes and health related QoL more broadly following empagliflozin initiation in routine clinical practice. On the other hand, HF-patients treated initially with empagliflozin or with a different drug class (not including SGLT2i) will be included. Patients' characteristics, patient reported QoL, HF drugs used as well as physician's reason for not choosing empagliflozin for treatment will be collected at study index date 1 of these two cohorts. Hence, this NIS will additionally provide data regarding adoption of guidelines directed medical therapy in the real world.		
Research question and objectives:	This non-interventional study (NIS) will look at contemporary, real-world patterns of patient characteristics, clinical disease presentation, and therapeutic regimen chosen in participants with chronic heart failure (HF). Disease parameters recorded by the physician according to clinical routine as well as changes in patient-reported outcomes (PROs) will be evaluated through 24 weeks in HF patients treated with empagliflozin following the outpatient initiation of treatment.		

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	• To capture patient characteristics, patient reported QoL, clinical disease presentation at the initiation of the given therapeutic regimen chosen in patients with HF • To describe the change in quality of life from visit 1 (=initiation of empagliflozin) to visit 2 (= 24 weeks after visit 1) by use of the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ) scores in HF patients newly treated with empagliflozin according to routine practice: clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS) • To describe the change from visit 1 to visit 2 (= 24 weeks after visit 1) in the New York Heart Association NYHA Class in HF patients newly treated with empagliflozin in real world conditions as evaluated by the treating health care practitioner (HCP)		
Study design:	This is a multinational non-interventional study based on newly collected data to assess demographics, disease, and treatment pattern of patients with HF in a two-cohort design: one cohort will receive first prescription of empagliflozin as routine therapy for HF, the other cohort will receive HF therapy with drugs with another mechanism of action. Treatment of HF according to routine practice is determined by the physician independent of the participation of the patient in this non-interventional study. Within the study there are 2 study-related visits: a visit 1 (= index date 1) and, for patients treated with empagliflozin, a second visit after approximately 24 weeks (visit 2 = index date 2). Thus, only patients receiving empagliflozin will be available for analysis regarding change in disease parameters and quality of life from index date 1 to index date 2. Patients treated with other drugs will not be followed up. These patients only have to fill in the KCCQ at index date 1.		

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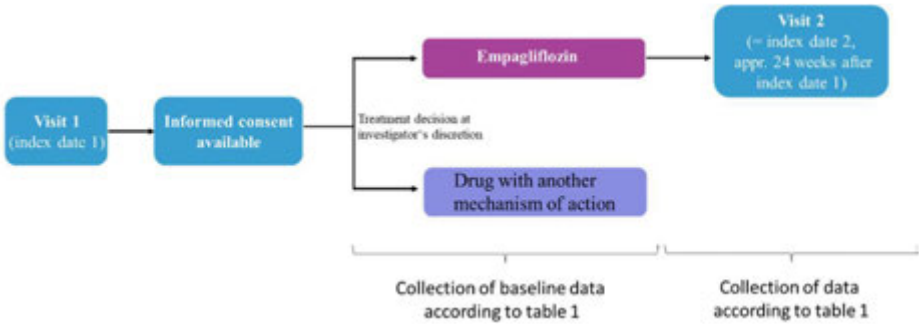
	On overview of the study is given in the following figure:  		
Population:	Indication Patients to be recruited within this study must have a physician diagnosed symptomatic chronic HF for which empagliflozin is an indicated treatment. Diabetic patients as well as non-diabetic patients can be enrolled. <u>Inclusion criteria</u> Patients can be included if all of the following criteria are met: • Written informed consent prior to study participation • Male and female patients ≥ 18 years at visit 1 • Patients must be contractually capable and mentally able to understand and follow the instructions of the study personnel • Patients with diagnosis of chronic heart failure NYHA Class 2-4 • Treatment-naïve for SGLT2i at visit 1 • Women of childbearing potential must take appropriate precautions against getting pregnant according to approval of chosen HF drug(s)		

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	Exclusion criteria • Missing physician's diagnosis of chronic heart failure • Patients hospitalized at visit 1 • Life expectancy ≤ 12 months according to physician's assessment • Lack of informed consent • Pregnant or lactating females • Participation in a parallel interventional clinical trial • Chosen treatment with another SGLT2i drug than empagliflozin • Having been enrolled into the non-empagliflozin-arm of this non-interventional study • Current or prior treatment with SGLT2i at visit 1 • Patients with dependency or relationship to the treating physician		
Variables:	Patient demographics (Year of birth, gender, height, weight) Date of first diagnosis of HF , etiology of HF Clinical parameters relevant for HF [LVEF, current NYHA Class according to treating physician, electrocardiogram (ECG), heart rate, blood pressure (systolic, diastolic), laboratory diagnostic according to clinical routine (last available value and date when it was collected), 6-min-walking test according to clinical routine Alcohol consumption and smoking status (non-smoker, previous smoker, current smoker) Concomitant diseases / Comorbidities Previous HF hospitalizations within the last 6 months HF related medication used in the last 6 months Current HF related and other relevant concomitant medication Newly prescribed treatment regime [Date of prescription, medication (empagliflozin and / or other drug), reason, if no prescription of empagliflozin] Patient reported outcomes (KCCQ 23 items) Date of discontinuation of empagliflozin treatment, reason (if applicable)		

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	Variables for safety evaluation: ADRs (serious and non-serious), fatal adverse events (AEs), pregnancies, HF related hospitalizations		
Data sources:	Medical records collected through routine clinical care will be used for patient demographic, disease relevant data and medication data. Patient reported outcome: All enrolled patients have to complete the KCCQ at index date 1, whereas only patients treated with empagliflozin were asked to fill in the KCCQ at index date 2.		
Study size:	It is planned that data of approximately 7000 HF patients in 8 countries will be collected (Poland, Romania, Hungary, Switzerland, Czech Republic, Bulgaria, Slovenia, Serbia).		
Data analysis:	Primary outcome - Change of each of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from index date 1 to 24 weeks after index date 1 in patients newly treated with empagliflozin according to routine practice. Subgroup analyses based on age at baseline, gender, country, baseline LVEF (reduced EF vs. preserved EF vs. mildly reduced EF), and status of diabetes mellitus at baseline. All recorded data for efficacy up to week 24 after index date 1 will be included. Secondary outcome: - Change of the New York Heart Association (NYHA) Class from index date 1 to 24 weeks after index date 1 in patients newly treated with empagliflozin - Real-world patterns at study index date 1 of patient characteristics, clinical disease presentation and therapeutic regimen chosen in participants with chronic HF		
Milestones:	Planned start of data collection: December 2022 Planned end of data collection: December 2023 Planned final study report: June 2024		

5. AMENDMENTS AND UPDATES

V 1.0 dated 24 Jan 2022

V 2.0 dated 14 Jun 2022

- Changes of participating countries

V 3.0 dated 30 Sep 2022

- Changes in timelines, number of patients and number of participating countries
- Change of responsible Trial Clinical Monitor
- Due to approval extension for empagliflozin adaptation of wording, patients with HF irrespective of EF will be included, update of inclusion and exclusion criteria and update of section 7.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Q3 2022
Start of data collection	Q4 2022
End of data collection	Q4 2023
Study progress report 1	Q2 2023
Study progress report 2	Q2 2024
Final report of study results	Q2 2024

7. RATIONALE AND BACKGROUND

Heart failure (HF) is a chronic disease which is characterized by reduced pumping capacity of the heart and / or elevated intracardial pressure. Clinical symptoms are often not present in the early stages of this disease. Underlying cardiac reasons are myocardial abnormalities resulting in systolic and/or ventricular dysfunction, and or abnormalities of the valves, pericardium, endocardium, heart rhythm and conduction [1].
HF is a major cause of hospitalizations, impaired health status, and deaths. Among the risks for developing HF are hypertension, obesity, and diabetics. Worldwide, prevalence increases due the ageing population and improvements in medical treatment [2].
Based on left ventricular ejection fraction (LVEF), HF can be classified into 3 subtypes with different underlying aetiologies, demographics, co-morbidities and response to therapies: 1) HF with reduced ejection fraction (LVEF ≤ 40%), 2) HF with preserved ejection fraction (LVEF ≥ 50%) and 3) HF with mildly reduced LV systolic function (LVEF = 41-49%). Until 2022, only in HF patients with reduced ejection fraction (HFrEF therapies have been approved to reduce both morbidity and mortality[1]. Nevertheless, there is no cure of HF; therefore, there is further need for improvement of therapies leading to higher quality of life in patients with HF.

Recently, a new drug class, which originally was developed to treat diabetes was approved for treatment of HFrEF. The new agent, available as film-coated tablets, promote glucose excretion in urine by inhibiting a transport protein, the sodium-glucose cotransporter 2 (SGLT2), thereby reducing renal glucose reabsorption.

The agent empagliflozin is a reversible, highly, and selective competitive inhibitor of SGLT2. Due to results of clinical trials that demonstrated its potential of lowering blood glucose levels in diabetic patients, empagliflozin was approved in Europe in June 2014 for the treatment of patients with type 2 diabetic as an adjunct to diet and exercise as monotherapy when metformin is considered inappropriate due to intolerance or in addition to other medicinal products for the treatment of diabetes [1],[4],[5].
An unexpected finding of the clinical trials with diabetes patients was that empagliflozin additionally reduces hospitalizations due to HF and cardiac death. The EMPA-REG OUTCOME study which randomly assigned type 2 diabetes patients to receive 10 mg or 25 mg of empagliflozin or placebo once daily focused on cardiovascular outcomes. Results showed that patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the cardiovascular outcomes and of death from any cause when the study drug was added to standard care [6], [7].

Thus, the EMPEROR-Reduced randomized clinical trial tested 10 mg empagliflozin or placebo in diabetic and non-diabetic patients additionally to appropriate treatment with e.g. diuretics, inhibitors of the renin-angiotensin system, beta-blockers. It was designed to evaluate the effect of empagliflozin on the risk of cardiovascular death or hospitalization for heart failure in patients with established symptoms of HF accompanied by evidence of systolic dysfunction [8]. Empagliflozin reduced the risk of hospitalization for HF in patients regardless of the presence or absence of diabetes [9]. Given the positive results of this trial, the therapeutic indication for use of empagliflozin (Jardiance®) has been extended by the European Medicine Agency (EMA) in July 2021. In addition to treatment of type 2 diabetes mellitus, empagliflozin is also indicated in adults for the treatment of symptomatic chronic heart failure with reduced ejection fraction. The recommended dose for this new indication is 10 mg once daily [10]. Since August 2021, empagliflozin is also approved in the USA in adults with HFrEF.

In 2022, EMA and FDA both expanded the approval of empagliflozin for use in adults with HF, regardless of ejection fraction, to reduce the risk of cardiovascular death and HF hospitalization.

Approval was based on results of the EMPEROR-Preserved study, a randomized, double-blind, international trial. 5988 patients with class II-IV heart failure and an ejection fraction of more than 40% were randomized to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure. Results showed that Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for HF in patients with heart failure and a preserved ejection fraction [11].

However, the mechanism of action on HF is still not fully understood. More evidence is needed regarding the effects of SGLT2 inhibitors in patients across the broad spectrum of HF.

Besides improvements in clinical endpoints such as survival or risk of hospitalization, improvements in quality of life (QoL) as recorded by the patients in form of symptoms or physical function have become an independent factor which is also underlined by the guidance statements from regulatory agencies and the recognition of Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire by the Food and Drug Administration as a clinical trial endpoint, or component of a combined endpoint to evaluate devices or drugs for heart failure [12][13].

The KCCQ is a 23-item (15 question) self-administered questionnaire designed to quantify physical limitations, symptoms (frequency, severity and recent change over time), social limitations, self-efficacy, and quality of life. To facilitate interpretability, two summary scores were developed. Combining the physical limitation and symptom domains (excluding symptom stability) forms a functional status score. A clinical summary core can be calculated by combining the functional status with the QoL and social limitation domains [14].

QoL data during empagliflozin therapy have been examined in a double-blind, placebo- controlled trial with nondiabetic HFrEF patients who received either 10 mg empagliflozin daily or placebo [15]. Within this clinical trial the short form of KCCQ (KCCQ-12) was used. Results showed a significant improvement in QoL in empagliflozin-treated patients compared to placebo-treated ones. In the EMPEROR-Preserved trial the KCCQ-23 was used to assess QoL. Results revealed meaningful improvement of patients who received empagliflozin compared to placebo [16].

However, since patients in clinical trials are selected by several inclusion and exclusion criteria with regard to organ function or comorbidities, and receive medication as stated in the protocol, these patients are not necessarily representative of patients in routine practice.

As shown in a contemporary US outpatient HFrEF registry, most patients did not receive target doses of medical therapy at any point during longitudinal follow-up and few patients had doses increased over time. Patients did not receive optimum doses of medication for many reasons, including medication intolerance, patient preference, clinician preference, healthcare systems-based reasons, and clinical inertia [17].

The Emp-Activity study is a multinational, multi-center, non-interventional study conducted in CEE countries and based on newly collected data with the aim to close the gap between clinical trial data and available data regarding changes in patient-reporting outcomes after empagliflozin initiation in routine practice. QoL will be assessed by means of the complete version of KCCQ in real-world HF-patients treated with empagliflozin according to approval. Until now, limited data are available regarding PRO changes after empagliflozin initiation in routine practice. As mentioned before, participants of clinical trials commonly differ from the broader population for whom a therapy may be used in clinical practice. Thus, there is a need to better characterize symptom changes and health related QoL more broadly following empagliflozin initiation in routine clinical practice.

On the other hand, HF-patients treated initially with or without empagliflozin will be included. Patients' characteristics, HF drugs used as well as physician's reason for not choosing empagliflozin for treatment will be collected at baseline of these two cohorts. Hence, this NIS will additionally provide data regarding adoption of guidelines directed medical therapy in the real world.

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8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

To describe the change of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from baseline to 24 weeks in patients newly treated with empagliflozin according to routine practice.

Secondary objectives:

- To describe the change of the New York Heart Association (NYHA) Class from baseline to 24 weeks in patients newly treated with empagliflozin.
- To capture real-world patterns of patient characteristics and clinical disease presentation according to therapeutic regimen chosen in participants with chronic HF

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a multinational non-interventional study based on newly collected data to assess demographics and treatment pattern of patients with HF in a two-cohort design: One cohort will receive first prescription of emagliflozin as routine therapy for HF, the other cohort not. Treatment of HF according to routine practice is determined by the physician independent of the participation of the patient in this non-interventional study.
During visit 1 (= index date 1), a routine visit in the clinical practice, patients will be recruited. All patients fulfilling the inclusion/exclusion criteria can be enrolled, irrespective of the HF-treatment they will receive. Patients will be enrolled consecutively by the participating physicians until the sample size requirement is met. The treating physician will make the decision on the medications which will be prescribed to their patients, either Empagliflozin or a drug with different mechanism of action. For all enrolled patients, demographic data, disease data, and treatment data will be collected at baseline.
All patients irrespective of treatment in addition of standard of care shall fill in the KCCQ at visit 1. Additionally, only for patients receiving empagliflozin a second time point of data collection is planned 24 weeks after visit 1 (= visit 2). At this time point, HF disease parameters will be collected as specified in table 1, and patients have to fill in the KCCQ for the second time.

A study overview is given Figure 1.

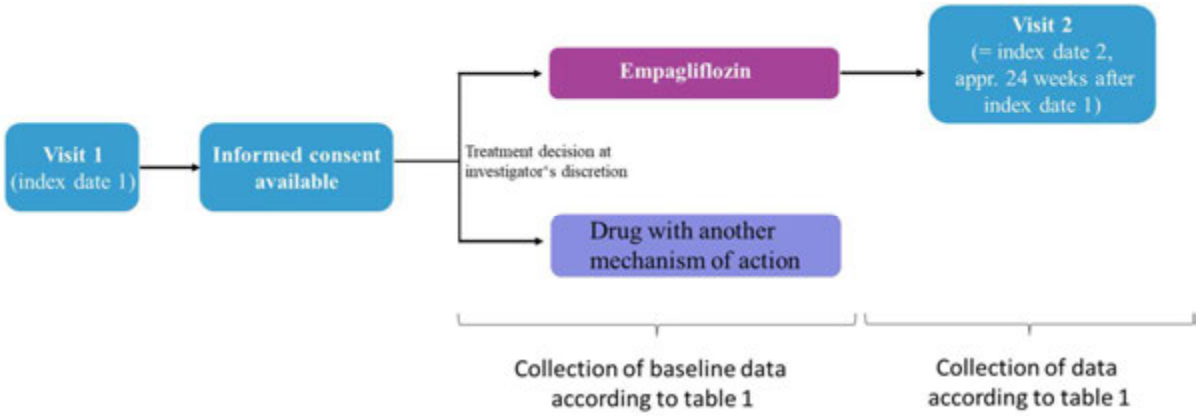

Figure 1: Overview study design

9.2 SETTING

In this NIS, data in a total of about 4600 HF patients will be collected during routine clinical practice by private practice and clinics in 8 countries.

There will be no procedure outside routine clinical practice except for handing out the KCCQs to the enrolled patients by the study stuff. The physician's decision to initiate treatment with empagliflozin or

HF drug(s) with another mechanism of action is independent of the registration of the patient in this study. Empagliflozin and all other HF drugs will be prescribed according to approval.

This study is planned to observe patients treated with empagliflozin for approximately 24 weeks, whereas data of patients without empagliflozin prescription are collected at visit 1 exclusively.
In addition to data collected by the physician, all patients should fill in the KCCQ-questionnaire at visit 1, whereas only patients receiving empagliflozin must fill in the questionnaire after approximately 24 weeks to address the change in disease specific symptoms and items regarding physical functioning and self-care during empagliflozin therapy in a real-world patient population.

Since this is a real-world study, there are no specifical eligibility criteria other than life expectancy ≤ 12 months and hospitalization at visit 1; patients having been enrolled into the non-empagliflozin arm must not be enrolled into the empagliflozin-arm afterwards. The contraindications and recommendations as stated in the SmPCs of empagliflozin and the other HF drugs have to be adhered to. For ethical and / or medical reasons, pregnant or lactating women, patients not willing to consent and patients with dependency relationship to the treating physician will be excluded.

9.2.1 Study sites

It is planned to collect data of approximately 4600 patients by approximately 1000 sites in 8 countries located in central east Europe (CEE): Switzerland, Poland, Romania, Hungary, Czech Republic, Bulgaria, Slovenia and Serbia). It is strived to include a minimum of about 3300 patients starting with empagliflozin treatment.

It is expected that each participating site will enroll 5 patients to ensure country-specific representativeness of collected data, so that a minimum target number of 100 patients per country will be reached.

9.2.2 Study population

Indication
Patients to be recruited within this study must have a physician diagnosed symptomatic chronic HF for which empagliflozin is an indicated treatment. Diabetic patients as well as non-diabetic patients can be enrolled.
Patients fulfilling the following eligibility criteria will be enrolled consecutively into the empagliflozin or the non-empagliflozin arm according to the physician's choice of HF treatment.

Inclusion criteria
Patients can be included if all of the following criteria are met:

- Written informed consent prior to study participation
- Male and female patients ≥ 18 years at Visit 1
- Patients must be contractually capable and mentally able to understand and follow the instructions of the study personnel
- Patients with diagnosis of chronic heart failure NYHA Class 2-4

- Treatment-naïve for SGLT2i at visit 1
- Women of childbearing potential must take appropriate precautions against getting pregnant according to approval of chosen HF drug(s)

Exclusion criteria

Patients cannot be included if any of the following criteria is met:

- Missing physician's diagnosis of chronic heart failure
- Patients hospitalized at visit 1
- Life expectancy ≤ 12 months according to physician's assessment
- Lack of informed consent
- Pregnant or lactating females
- Participation in a parallel interventional clinical trial
- Chosen treatment with another SGLT2i drug than empagliflozin
- Having been enrolled into the non-empagliflozin-arm of this non-interventional study
- Current or prior treatment with SGLT2i at visit 1
- Patients with contraindications according to current SmPC
- Patients with dependency or relationship to the treating physician

9.2.3 Study visits

Table 1 presents all data collected and assessments performed at each visit.

Table 1: Planned visits and data collected

Parameter	**Visit 1**	**Visit 2**
	Day 0 = index date 1 = Day of newly prescribed HF drug	24 weeks (±2 weeks) after index date 1 = End of observation [index date 2]
	All patients	**Only patients treated with empagliflozin**
Informed Consent	X	
Inclusion / Exclusion Criteria	X	
Patient demographics (age, gender, height, and weight)	X	X (weight only)
Medical history	X	
Alcohol consumption / Smoking status	X	
LVEF	X	X
Current NYHA Class	X	X

Table 1: Planned visits and data collected (cont.)

Parameter	Visit 1	Visit 2
	Day 0 = index date 1 = Day of newly prescribed HF drug	24 weeks (±2 weeks) after index date 1 = End of observation [index date 2]
	All patients	**Only patients treated with empagliflozin**
HF related examinations according to clinical routine*	X	X
HF related Hospitalizations in the last 6 months	X	
HF medication used in the last 6 months	X	
Current HF related or other relevant concomitant medication	X	X
Prescribed HF drug at Day 0	X	X
Patient questionnaire: 23 items-KCCQ	X	X
Safety: Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancy, HF-related hospitalizations		X
Discontinuation of treatment with empagliflozin during study treatment (yes/no)		X
Intention to continue or discontinue treatment with empagliflozin after study period (yes/no)		X
Rationale for treatment discontinuation, if applicable		X

* Last available value and date when it was collected

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study

3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

The patients have the right to stop study participation at any time and for any reason, without affecting their further treatment. Study participation may be stopped for a given patient in case of individual safety issues.

9.3 VARIABLES

The following parameters will be collected at **visit 1** (= index date 1) of all registered patients:

1. Patient demographics:
   - Year of birth
   - Gender
   - Height, weight, BMI (will be calculated from height and weight)
2. Date of first diagnosis of HF
3. Etiology of heart failure
   - Coronary artery disease
   - Hypertension
   - Valve disease
   - Cardiomyopathy
   - Congenital heart disease
   - Drug induced
   - Infective
   - Storage disorders
   - Diabetes
   - Obesity
   - Other
4. Clinical parameters relevant for HF (last available value and date when it was collected) as valid at baseline and performed during clinical routine:
   - LVEF
   - Current NYHA Class according to treating physician
   - Electrocardiogram (ECG)
   - Heart rate
   - Blood pressure (systolic, diastolic)
   - Laboratory diagnostic according to clinical routine (last available value and date when it was collected):
     - BNP (B-type natriuretic peptide) and/or pro-BNP (N-terminal pro–B-type natriuretic peptide)
     - Lipids (cholesterol, HDL, LDL)
     - Blood urea nitrogen (BUN)
     - Serum creatinine

    - Sodium, potassium
    - Complete blood count
  - 6-min-walking test according to clinical routine
5. Alcohol consumption and smoking status (non-smoker, previous smoker, current smoker)
6. Concomitant diseases / Comorbidities
   - Disease according to ICD-10 (diabetes, hypertension, coronary artery disease, infarction, chronic kidney disease, atrial fibrillation, cancer, other)
   - Date of first diagnosis
7. Previous HF hospitalizations within the last 6 months
8. HF related medication used in the last 6 months
   - Medication
   - Indication
   - Application
   - Dose
   - Start date, end date, continuing
9. Current HF related and other relevant concomitant medication
   - Medication
   - Indication
   - Application
   - Dose
   - Start date, end date, continuing
10. Newly prescribed treatment regime:
    - Date of prescription
    - Medication (empagliflozin and / or other drug)
    - Reason, if no prescription of empagliflozin
11. Patient reported outcomes:
    - KCCQ (23 items) completed by patients during the visit

The following parameters will be collected at routine **visit 2** [= index date 2: 24 weeks (±2 weeks) after index date 1] only of registered patients treated with empagliflozin:

1. Weight, BMI (will be calculated from height and weight)
2. Clinical parameters relevant for HF performed during clinical routine (last available value and date when it was collected):
   - LVEF
   - Current NYHA Class according to treating physician
   - Electrocardiogram (ECG)
   - Heart rate
   - Blood pressure (systolic, diastolic)
   - Laboratory diagnostic according to clinical routine (last available value and date when it was collected):
     - BNP (B-type natriuretic peptide) and/or pro-BNP (N-terminal pro–B-type natriuretic peptide)

  - Lipids (cholesterol, HDL, LDL)
  - Blood urea nitrogen (BUN)
  - Serum creatinine
  - Sodium, potassium
  - Complete blood count
- 6-min-walking test according to clinical routine

3. Current HF related or other relevant concomitant medication
4. HF drug(s) prescribed at visit 2
5. Patient reported outcomes:
   - KCCQ (23 items) completed by patients during the visit
6. Safety: ADRs (serious and non-serious), fatal adverse events (AEs), pregnancies, HF related hospitalizations
7. Discontinuation of treatment with empagliflozin during study period (yes/no)
   - If yes: date of discontinuation, reason (if applicable)
8. Continuation or discontinuation of treatment with empagliflozin after study period (yes/no)
   - In case of discontinuation: date of discontinuation, reason (if applicable)

9.3.1 Exposures

The drug of interest is Jardiance® with the active ingredient empagliflozin. Within this study, there are two HF patient cohorts: patients receiving first prescription of empagliflozin and those who have been prescribed a drug with a different mechanism of action for the treatment of HF.
During this study, it is planned to observe for each patient who receives a first prescription of empagliflozin a treatment period of approximately 24 weeks. Patients not treated with empagliflozin will not be observed further after visit 1.
The recommended daily dose of empagliflozin for treatment of heart failure is 10 mg once daily.

9.3.2 Outcomes

This NIS will describe contemporary, real-world patterns of patient characteristics, clinical disease presentation, and therapeutic regimen chosen in participants with chronic HF in CEE countries. Additionally, PRO is assessed by use of the disease specific KCCQ. These data will be collected at visit 1 of all registered patients.

The primary objective is to document and analyze QoL data from patients with HF receiving first treatment with empagliflozin in daily routine care. For this approach, the disease specific KCCQ is used to examine changes from index date 1 to index date 2 (= 24 weeks after study index date 1) in these patients. The primary outcome will be evaluated on patients receiving initial prescription of empagliflozin at visit 1 and who have filled in the KCCQ at visit 1 and visit 2.

The primary and secondary outcomes do not touch any safety questions.

9.3.2.1 Primary outcomes

Change of each of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin according to routine practice

9.3.2.2 Secondary outcomes

- Change of the New York Heart Association (NYHA) Class from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin
- Capture of real-world patterns of patient characteristics, clinical disease presentation and therapeutic regimen chosen in participants with chronic HF as well as of patient reported outcome at visit 1.

[redacted]

9.3.3 Covariates

Covariates for adjustment will include patient demographics and disease characteristics. These will be discussed in the Statistical Analysis Plan (SAP).

9.4 DATA SOURCES

Medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients as well as for patient demographics, collection of current HF medication, concomitant diseases, and concomitant medication, as well as for the health data of the patient at visit 2.

The KCCQ will be provided as paper version by the treating physician or trained site stuff to the patient to be filled out in writing at visit 1 (all patients) and visit 2 (patients with initial empagliflozin treatment only).

9.5 STUDY SIZE

With no formal a-priori hypotheses, this observational study uses a hypothesis-free approach focused on descriptive analyses. Thus, no formal sample size calculation is provided. The study is designed to describe the use of empagliflozin and PRO in clinical routine. In the 8 participating countries sites in urban as well as rural areas will be included. The nationwide distribution of the participating sites and the number of 4600 patients enrolled are intended to ensure that the data

collected are representative. Based on random identification, it is expected that about 3300 patients will receive empagliflozin. The large sample size overall was chosen to support a large range of analyses from general scientific questions to specific regional or subgroup questions with sufficient precision. A minimum target number of 100 patients per country is chosen to provide reasonable sample size for scientific questions applicable across countries and subgroups of interest. The sample size will ensure that the descriptive data are sufficiently precise and meaningful at a country or subgroup level.

9.6 DATA MANAGEMENT

The data management plan (DMP) is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

The NIS-DMRP will describe all functions, processes, and specifications for data collection, cleaning and validation. The contract research organization (CRO) [redacted]) is assigned for electronic data capture (EDC) system development. The electronic Case Report Forms (eCRF) are part of the EDC system which allows documentation of the relevant study variables by all participating sites in a standardized manner. The eCRF will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review by personnel of data management of the CRO may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution.
The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling and the safety requirements of the FDA (US Food & Drug Administration) concerning systems for the data acquisition of clinical studies in accordance with "Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic Records; Electronic Signatures. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

Statistical analysis will be performed by [redacted]).
The statistical analysis plan (SAP) for the study is summarized below. Full details of the statistical analysis will be documented in the SAP, which will be finalized before the end of data collection.

In general, all analyses will be carried out by using descriptive and exploratory statistical methods including exploratory confidence intervals and p-values. For the analyses SAS® software version 9.4 or higher will be used.

All data captured at visit 1 will be analyzed on all registered patients [Full analysis set (FAS)]. All patients who have received at least one dose of empagliflozin for HF and have filled in KCCQ at time points ‘index date 1’ and ‘index date 2 (= week 24 after index date 1)’ will be included in the ‘primary endpoint set’ which will be used for primary endpoint analysis.
Safety set: All patients who received empagliflozin at least once will be used for safety and further analyses.

9.7.1 Main analysis

Analysis of the primary outcome

- Change of each of the Kansas City Cardiomyopathy Questionnaire (KCCQ) scores [clinical summary score (CSS), total symptom score (TSS), overall summary score (OSS)] from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin according to routine practice

will be performed according to the analysis manual for the KCCQ. Changes in the KCCQ scores will be calculated for each patient. Results will be presented as N, mean, standard deviation, median, minimum and maximum values as well as number of missings as extra column. A change of 5 points of OSS will be considered as clinically meaningful.
Change from index date 1 in clinical summary score for HF symptoms and physical limitations domains of the KCCQ at week 24 will be evaluated further by subgroup analyses based on age at index date 1, gender, country, baseline LVEF (rEF, mpEF pEF), and status of diabetes mellitus at visit 1. All recorded data for efficacy up to week 24 will be included.

Analysis of the secondary outcome

- Change of the New York Heart Association (NYHA) Class from index date 1 to index date 2 (= 24 weeks after index date 1) in patients newly treated with empagliflozin

tabulation of relative and absolute frequencies will be presented.

For the analysis of the secondary outcome

- Capture of real-world patterns of patient characteristics, clinical disease presentation and therapeutic regimen chosen in participants with chronic HF as well as of patient reported outcome at visit 1

tabulations of relative and absolute frequencies will be presented. Comparison of data at visit 1 between patients receiving empagliflozin or not for treatment of HF will be performed by Chi-quadrat-test or Mann-Whitney-U-test.

[redacted]

9.7.3 Safety analysis

All adverse drug reactions (ADRs) (serious and non-serious), all AEs with fatal outcome, hospitalizations due to HF as collected per study protocol will be included and summarized in the final study report.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All patients treated with empagliflozin for HF will be included in the safety analysis. In general, safety analyses will be descriptive in nature.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events.

All adverse events occurring on empagliflozin treatment plus 7 days will be considered 'treatment-emergent'. Deterioration of pre-existing conditions will also be considered 'treatment- emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

All participating sites will receive a comprehensive study site file with all information on the NIS. Site staff will be trained on the study procedures and on handling of the eCRF before documentation of the first patient by a mandatory webinar or on-site, whatever will be more feasible (e.g. influenced by pandemic situation). Training will be documented in the study site file.

To improve and secure data quality, automatic data checks (eChecks) upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail. Data management activities by means of manual query processes might be implemented as defined in the DMP to increase data integrity.

To provide further quality assurance of the documented patient observations, routine monitoring will take place at the site with the highest number of patients currently enrolled two months after the First Patient In (FPI) in the respective country. If on-site visits are not possible due to pandemic situation, remote quality review may be performed. Risk-based monitoring or for-cause audit will be performed based on the key risk indicators in case of decreasing data quality (i.e. of missing data, data discrepancies, protocol violations, etc.). Details will be specified in the study monitoring plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This is a single arm non-interventional study based on newly collected data with the aim to gather data of HF treatment as well as PRO in clinical routine. Generally, a NIS is the most suitable instrument for obtaining information about the use of medicines in everyday clinical practice. The eligibility criteria are non-restrictive which will permit the enrolment of a broad patient population. Thus, patients are more different in baseline characteristics and disease data than patients enrolled into a clinical trial. The choice of treatment and performance of examinations is at the discretion of the investigator. Therefore, results of disease specific examinations recorded may comprise various time periods. There may also be more missing values as in clinical trials, since the non-interventional nature means that no specification is provided on examinations to be carried out.

Selection bias could occur at the site level and the patient level. The site of the patient selection may affect the outcomes given patient differences across practice sites. To minimize the site level selection

bias, the goal is to have a great number of participating centers. To minimize selection bias at the patient level, consecutive enrolment is performed. Additionally, a non-empagliflozin treated cohort is added in order to get an overview of the HF patients at the respective sites.

Information bias will be minimized by the use of standard eCRF and validated patient questionnaire as well as by physicians' training on the study protocol.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor, via remote data capture.
All study relevant data will be captured via a web-based Electronic Data Capturing system. The delegated site staff will enter and edit the data via a secure network, with secure access features (i.e. electronic password system with username and password and secure identification). A complete electronic audit trail will be maintained.

9.10.3 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.
For eCRFs, all data must be derived from source documents.

9.10.4 Direct access to data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). BI study staff and auditor may

review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.1.

9.10.5 Completion of study

The EC/competent authority in each participating EU member state needs to be notified about the end of the study (last patient/patient out, unless specified differently in Section 9.2 or early termination of the study.
After completion of the study, the CRO will transfer all study documents to BI for archiving.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) per GPP and according to the regulatory and legal requirements of the participating country.

The patient must be informed orally and in writing that his/her personal study-related data will be recorded pseudonymized and used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.
The patients' study participation is voluntary and the patients have the right to stop study participation any time and for any reason, without any disadvantage on their further treatment.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. The identification key is kept confidentially by the physician at the study site.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities, i.e. the competent authority. The medical and personal patient data may be inspected by dedicated study site staff and by dedicated monitors (CRAs) for quality assurance reasons. All these personnel are obligated to confidentiality. For those quality checks and authority inspection the patient releases the treating physician from the medical confidentiality.

During the study, medical results and reports and personal information from the patients will be collected in patient files at the study sites. Those data important for the study will be collected pseudonymized via an eCRF.
Before analysis, the data will be anonymized and the reports from this analysis will be provided to the sponsor of the study, Boehringer Ingelheim. After analysis and finalization of the study report, the anonymized data will be transferred to Boehringer Ingelheim.

Study data will be kept according to local requirements and then be destroyed.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug, For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reactions (ADRs) (serious and non-serious),
- all AEs with fatal outcome,
- HF-related hospitalizations.

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance
The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provide to BI unique entry point:

All **serious ADRs** associated with the studied medical product empagliflozin	Immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to studied medical product empagliflozin	Immediately within 24 hours
All **non-serious ADRs** associated with the studied medical product empagliflozin	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required
For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF page and the NIS AE form.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov and a study specific publication plan will be developed to describe planned publications.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

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13.2 UNPUBLISHED REFERENCES

Not applicable.

14. ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable

15. ANNEX 2 ADDITIONAL INFORMATION

None.