ALDOSTERONE SYNTHASE INHIBITOR FOR TREATING HEART FAILURE

FIELD OF THE INVENTION

The invention relates to the use of a certain aldosterone synthase inhibitor for treating, reducing the risk of, or delaying the progression of certain disorders in patients with heart failure. The invention further relates to the use of the aldosterone synthase inhibitor in combination with sodium-glucose cotransporter-2 (SGLT2) inhibitors.

BACKGROUND

Heart failure (HF) is a clinical syndrome with symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and or objective evidence of pulmonary or systemic congestion (See B. Bozkurt et al., Universal Definition and Classification of Heart Failure, J Cardiac Failure; 27(4), 387-381 (2021). According to recent epidemiological reports, over 60 million people live with HF worldwide, and more than 1 million patients are admitted to hospitals with a primary diagnosis of HF. This makes HF the leading cause of hospitalisation and mortality, particularly among individuals aged 65 and above. (See Yancy CW, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol; 2013; 62(16); e147-e239.)

Among HF patients, 30-40% have a history of hospitalisation for HF (HHF), and 50% are readmitted within one year of their initial diagnosis. The prognosis after HHF is poor, with high reported mortality rates within 30 days (10%), 1 year (35%), and 5 years (75%). (See R.K Cheng et al., Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. Am Heart J; 168(5), p. 721-730.e3; 2014; and Shah KS, et al. Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. J Am Coll Cardiol; 2017; 70(20); 2476-2486; and GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990 - 2017: a

systematic analysis for the Global Burden of Disease Study 2017. Lancet; 2018; 392; 1789-1858.)

Current therapies for HF include the management of risk factors and concomitant diseases as well as lifestyle interventions and evidence-based medications. To date, several drug therapies have shown to provide a mortality benefit for patients who have HFrEF. These include SGLT2is, beta blockers, ACEis, ARBs, ARNis, and MRAs. (See Savarese G, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res; 2022; 118; 3272-3287.)

Epidemiological studies have reported that about 50% of patients with HF have a relatively normal or slightly reduced LVEF, in the range of 40% and above, also referred to as HF with mildly reduced (41-49%, HFmrEF) or preserved (≥50%) ejection fraction (HFpEF). (See Savarese G, et al.. Cardiovasc Res; 2022; 118; 3272-3287.) Despite recent advances in the management of HF, an unmet need for effective therapies remains, especially for HF with LVEF ≥40%. Established therapies for heart failure with mildly reduced and preserved ejection fraction include the management of risk factors and comorbidities, addressing weight loss for participants with obesity, as well as the control of signs and symptoms, including diuretics for fluid retention. SGLT2 inhibitors (SGLT2i) are currently the only therapeutic agents that demonstrated a significant reduction in the composite endpoint of cardiovascular (CV) death and HHF in this population and are recommended for the treatment of participants with symptomatic HF across the spectrum of LVEF. (See McDonagh TA, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC): with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur Heart J; 2023, 44(37):3627-3639.) Apart from SGLT2i, the clinical evidence supporting the efficacy of other therapies in reducing CV mortality or HF hospitalisations in HF and LVEF ≥40% remains elusive, suggesting either a modest level of efficacy overall or a benefit only for a subset of participants. In summary, this results in a high residual risk in participants suffering from HF with a mildly reduced and preserved ejection fraction indicating a great need for additional foundational therapies. (See S.D. Anker et al.

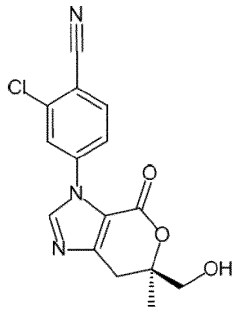
Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461.)

There is a need for new treatments for heart failure patients.

BRIEF SUMMARY OF THE INVENTION

The present invention relates to methods for treating patients with heart failure comprising administering a therapeutically effective amount of an aldosterone synthase inhibitor ("AS inhibitor") of the invention to a patient in need thereof, optionally in combination with an SLGT2 inhibitor ("the methods of the invention").

The AS inhibitor of the invention is a compound having the structure (**1**) shown below:



(**1**).

Compound **1** is a specific aldosterone synthase inhibitor (ASi) that effectively lowers aldosterone plasma concentrations in a dose dependent manner. As used herein, the terms "AS inhibitor of the invention," "the AS inhibitor," and "Compound **1**" are used interchangeably. Compound **1** is also known as 2-chloro-4-[(6R)-6,7-dihydro-6-(hydroxymethyl)-6-methyl-4-oxopyrano[3,4-d]imidazol-3(4H)-yl]-benzonitrile, BI 690517 and vicadrostat.

With the lack of long-term conclusive outcome studies examining whether new medications targeting aldosterone can prevent cardiovascular events, this is believed to be the first study to

investigate the efficacy and safety of an ASi in a heart failure population. Based on the beneficial effect of empagliflozin in participants with a history of HF, the combined use of Compound **1** and empagliflozin in participants with HF and LVEF ≥40% may have further beneficial effects on the efficacy and/or safety as compared to a monotherapy of Compound **1** or a SGLT2 inhibitor. (See Butler J, et al. Effect of empagliflozin in patients with heart failure across the spectrum of left ventricular ejection fraction. European Heart Journal; 2022, 43, 416–426.)

Accordingly, in its broadest embodiment, the invention relates to a method for treating a patient with heart failure and reduced ejection fraction (HFrEF), or heart failure with mildly reduced ejection fraction (HFmrEF), or heart failure with preserved ejection fraction (HFpEF), comprising administering a therapeutically effective amount of Compound 1, optionally in combination with a SGLT2 inhibitor, to a patient in need thereof.

In another embodiment, the invention relates to a method for treating a patient with heart failure and left ventricular ejection fraction ≥40% (LVEF ≥40%), the method comprising administering to the patient a pharmaceutically effective amount of Compound **1**, optionally, in combination with a SGLT2 inhibitor.

In another embodiment, the invention relates to the embodiment immediately above, wherein the method reduces the risk of cardiovascular death, hospitalization for heart failure and/or urgent heart failure visit in the patient.

In one embodiment, the invention relates to a method for reducing the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure in a patient, wherein the patient has heart failure and a left ventricular ejection fraction ≥40%, the method comprising administering to the patient a pharmaceutically effective amount of Compound **1** and, optionally, a SGLT2 inhibitor.

In another embodiment, the invention relates to the use of Compound **1**, optionally in combination with a SGLT2 inhibitor, for reducing the risk of cardiovascular death,

hospitalization for heart failure, and/or urgent heart failure visit in a patient, wherein the patient has heart failure and a left ventricular ejection fraction ≥40%.

In another embodiment, the invention relates to a method for preventing, reducing the risk of, and/or slowing the progression of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit in an adult patient with heart failure and left ventricular ejection fraction ≥40%, the method comprising administering to the patient a pharmaceutically effective amount of Compound **1** in combination with a SGLT2 inhibitor.

In another embodiment, the invention relates to the use of Compound **1** in combination with a SGLT2 inhibitor for preventing, reducing the risk of, an/or slowing the progression of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit in an adult patient with heart failure and left ventricular ejection fraction ≥40%.

In another embodiment, the invention relates to a method for treating a patient with symptomatic heart failure with a left ventricular ejection fraction ≥40%, the method comprising administering to the patient a pharmaceutically effective amount of Compound **1** in combination with a SGLT2 inhibitor.

In another embodiment, the invention relates to Compound **1** in combination with a SGLT2 inhibitor for the preparation of a medicament for treating a patient with heart failure; in another embodiment, the heart failure is chronic heart failure, symptomatic heart failure or urgent heart failure; and in another embodiment, the patient has a left ventricular ejection fraction ≥40%.

In another embodiment, the invention relates to the use of Compound **1** in combination with a SGLT2 inhibitor for treating a patient with heart failure; in another embodiment, the heart failure is chronic heart failure, symptomatic heart failure or urgent heart failure; and in another embodiment, the patient has a left ventricular ejection fraction ≥40%.

In another embodiment, the invention relates to any of the methods or uses described above, wherein the methods or uses prevent, slow the progression of, or reduce the risk of:

the time to first event of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit,

the total number of hospitalizations heart failure (first and recurrent),
the absolute change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS),
the time to cardiovascular (CV) death, and/or
the time to all-cause death.

In another embodiment, the invention relates to any of the embodiments described above wherein:

the patient has chronic heart failure, symptomatic heart failure, or urgent heart failure,
the patient is diagnosed with chronic heart failure at least 3 months prior to the start of treatment, and/or
the patient is diagnosed with chronic heart failure at least 3 months prior to the start of treatment and is classified in NYHA class II to IV at the start of treatment.

In one embodiment, the SLGT inhibitor when used in the methods or uses of the invention is selected from the group consisting of empagliflozin, dapagliflozin, sotagliflozin and canagliflozin.

In another embodiment, the SLGT inhibitor when used in the methods of uses of the invention is empagliflozin.

In one embodiment, the amount of the empagliflozin when used in the methods or uses of the invention is from 5 mg to 30 mg, or 10 mg to 25 mg, or 10 mg, or 25 mg.

In another embodiment, the amount of empagliflozin when used in the methods or uses of the invention is 10 mg.

In another embodiment, the amount of Compound **1** administered to the patient according to the methods or uses of the invention is from 0.5 to 30 mg; or from 1 to 25 mg; or from 3 to 20 mg; or 3 mg, 6 mg. or 10 mg, or 20 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 3 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 6 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 10 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 20 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 3 mg, and the amount of empagliflozin administered to the patient is 10 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 10 mg, and the amount of empagliflozin administered to the patient is 10 mg.

In another embodiment, the amount of Compound **1** administered to the patient is 20 mg, and the amount of empagliflozin administered to the patient is 10 mg.

In one embodiment, the invention relates methods for treating patients with heart failure and LVEF ≥40%, comprising administering to the patient a combination of 10 mg of Compound **1** and 10 mg empagliflozin.

In another embodiment, the invention relates to a method for treating patients with heart failure and LVEF ≥40%, comprising administering a combination of 10 mg of Compound **1** and 10 mg empagliflozin to the patient, wherein the treatment prevents, reduces the risk of, and/or slows the progression of first cardiovascular death and/or hospitalisation for heart failure in the patient.

In another embodiment, In another embodiment, the invention relates to method for treating patients with heart failure and LVEF ≥40%, comprising administering a combination of 10 mg of Compound **1** and 10 mg empagliflozin to the patient, wherein the treatment prevents, reduces the risk of, and/or slows the progression of the time to first event of:

cardiovascular death, hospitalisation for heart failure or urgent heart failure visit,
the total number of hospitalisation for heart failure (first and recurrent), and
the absolute change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at Week 32.

In another embodiment, the invention relates to treatment of patients with heart failure and LVEF ≥40%, wherein the treatment prevents, slows the progression of, or reduces the risk of:

time to first event of cardiovascular death, hospitalisation for heart failure or urgent heart failure visit,

occurrence of hospitalisation for heart failures (first and recurrent,

absolute change from baseline in KCCQ-TSS at Week 32,

time to first hospitalization for heart failure,

time to cardiovascular death,

time to all-cause mortality, or

time to first occurrence of or death from:

kidney failure,

chronic dialysis (defined as dialysis continuing for at least 30 days),

renal transplant,

sustained* reduction of ≥50% eGFR using the (CKD-EPI)cr equation,

sustained* eGFR (CKD-EPI)cr <10 mL/min/1.73 m2 (composite renal endpoint),

absolute change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ (KCCQ-CSS) at Week 32, and/or

absolute change from baseline in KCCQ-TSS at Week 52,

wherein *sustained' is either (a) measured at two consecutive scheduled study visits; or (b) measured at the final Follow-up visit or the last scheduled visit before death, loss to follow-up, or withdrawal of consent.

In another embodiment, the invention relates to treatment of patients with heart failure and LVEF ≥40%, wherein the treatment prevents, slows the progression of, or reduces the risk of:

time to first HHF or urgent HF visit,

time to first CV death, HHF, urgent HF visit or urgent outpatient visit for HF,

time to first urgent HF visit,

occurrences of all-cause hospitalisations (first and recurrent),

time to first all-cause hospitalization,

time to all-cause mortality or first event of all-cause hospitalization,

time to first event of all-cause mortality or HHF,
time to first myocardial infarction (MI) (fatal or non-fatal),
time to first stroke (fatal or non-fatal),
time to first transient ischemic attack (TIA),
time to first stroke (fatal or non-fatal) or transient ischemic attack (TIA),
time to first atrial fibrillation (Afib) or atrial flutter (Aflutter) episode,
time to first CV death or non-fatal MI,
time to first CV death or non-fatal stroke,
time to first CV death, non-fatal MI or non-fatal stroke (3-point major adverse cardiovascular events [MACE]),
time to first event of CV death, HHF, non-fatal MI or non-fatal stroke (4-point major adverse cardiovascular events [MACE]),
time to first event of ventricular tachycardia,
time to sudden cardiac death,
time to first composite renal endpoint or cardiovascular death,
time to first composite renal endpoint, HHF or Cardiovascular death,
time to first composite renal endpoint or all-cause hospitalization,
absolute change from baseline in KCCQ overall summary score (KCCQ-OSS) at Week 32,
absolute change from baseline in KCCQ overall summary score (KCCQ-OSS) at Week 52,
absolute change from baseline in KCCQ clinical symptom score (KCCQ-CSS) at Week 52,
win ratio for all-cause mortality, total number of HHF and KCCQ TSS at Week 32,
absolute change from baseline to off-treatment follow-up visit in eGFR,
absolute change from end of treatment to off-treatment follow-up visit in eGFR,
change in NYHA class from baseline to Week 32 and 52 (see Table 2),
change in health economic analyses using health care resource utilization data ,
relative change in UACR from baseline over time,
absolute change from baseline in body weight over time,
absolute change from baseline in systolic blood pressure (SBP) over time,

absolute change from baseline in diastolic blood pressure (DBP) over time,
absolute change from baseline in systolic blood pressure (SBP) [mmHg] at Week 32 in participants with baseline SBP greater than or equal to 130 mmHg,
absolute chance from baseline in diastolic blood pressure (DBP) [mmHg] at Week 32 in participants with baseline DBP ⩾80 mmHg,
absolute change from baseline in pulse rate over time,
increase in eGFR (CKD-EPI)cr slope of change from baseline (on-treatment), and/or
absolute change from baseline in eGFR during treatment.

In another embodiment, the invention relates to treatment of patients with heart failure and LVEF ≥40%, wherein the treatment prevents, slows the progression of, or reduces the risk of:
adverse events of special interest (AESI),
incidence of clinically relevant hyperkalemia,
incidence of hyperkalemia > 5.5 mmol/L, or > 6.0mmol/L,
incidence of adverse events (AEs) leading to discontinuation,
absolute change from baseline in potassium over time,
incidence of acute renal failure (based on narrow standardized Medical Dictionary for Regulatory Activities [MedDRA] standardized MedDRA query [SMQ]), and/or
time to first acute kidney injury.

In one embodiment, the combination of Compound **1** and empagliflozin are administered as a free combination.

In another embodiment, the combination of Compound **1** and empagliflozin are administered as a fixed-dose combination.

In one embodiment, the patient with heart failure and LVEF ≥40% is a type 2 diabetes mellitus patient.

In another embodiment, the patient with heart failure and LVEF ≥40% is a type 1 diabetes patient.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations:

ACEi	Angiotensin-converting enzyme inhibitor
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
AS	Aldosterone synthase
ASi	Aldosterone synthase inhibitor
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BMI	Body mass index
BNP	Brain natriuretic peptide
CA	Competent Authority
CI	Confidence interval
CKD	Chronic kidney disease
(CKD-EPI)cr	Chronic Kidney Disease Epidemiology Collaboration creatinine equation
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CRA	Clinical research associate

CRF	Case report form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organization
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Cardiovascular
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
EC	Ethics Committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EMPA	Empagliflozin
EoS	End of study (corresponds with end of trial)
EoT	End of treatment
EPC	Established pharmacologic class
EPHESUS	Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
ER	Emergency room

ES	Entered set
ExC	Executive Committee
FEV1	Forced expiratory volume in one second
FOT	Fully outsourced trial
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health authority
HDL	High-density lipoprotein
HF	Heart failure
HFE	Heart failure event
HFmrEF	Heart failure with mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
Hb	Haemoglobin
HbA1c	Glycated Haemoglobin
HHF	Hospitalisation for heart failure
hsCRP	High sensitivity C-reactive protein
hsTnT	High-sensitivity troponin T
i.v.	Intravenous
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICD	Implantable cardioverter defibrillator
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonizations of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product

INN	International non-proprietary name
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator site file
ITT	Intention to treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K+	Potassium
KCCQ	Kansas City Cardiomyopathy Questionnaire
KDIGO	Kidney Disease: Improving Global Outcomes
LC-MS	Liquid chromatography tandem mass spectrometry
LDL	Low density lipoprotein
LPLT	Last participant last treatment
LPLV	Last participant last visit
LVAD	Left ventricular assist device
LVEF	Left ventricular ejection fraction
LVMI	Left ventricular mass index
MACE	Major adverse cardiovascular events
MATE2-K	Multidrug and toxin extrusion 2
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MMRM	Mixed model repeated measures
MR	Mineralocorticoid receptor
MRA	Mineralocorticoid receptor antagonist

MRI	Magnetic resonance imaging
Na+	Sodium
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OAT3	Organic anion transporter 3
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic set
p.o.	Per os (oral)
PPARγ	Peroxisome proliferator-activated receptor gamma
PRO	Participant-reported outcome
QD	Quaque die (once a day)
RA	Regulatory authority
RAAS	Renin-angiotensin-aldosterone-system
RDW	Red cell distribution width
REP	Residual effect period
RS	Randomized set
SAE	Serious adverse event
SD	Standard deviation
SGLT-1/2	Sodium-glucose co-transporter 1/2
SGLT2	Sodium-dependent glucose co-transporter 2
SMQ	Standardized MedDRA query
SoA	Schedule of assessments
SOC	Standard of care
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Terminal half-life of the analyte in plasma
T2DM	Type 2 diabetes mellitus

TIA	Transient ischemic attack
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist trial
TRT	Therapy or treatment
TS	Treated set
TSAP	Trial statistical analysis plan
UACR	Urine albumin-to-creatinine ratio
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

As used herein, the term “heart failure event” or “HFE” is refers to an event of worsening HF that requires augmentation of therapy for HF. For example, the assessment of the participant and treatment augmentation may require HHF or may be undertaken during an ER, urgent care, or other urgent outpatient visit.

The term “heart failure hospitalization” or “HHF” as used herein means an event that meets all of the following criteria:

- The primary diagnosis is admission to the hospital for HF (i.e., The question “Did the treating physician assess that worsening of HF required new or augmentation of existing treatment?” is answered yes)
- The participant’s length-of-stay in the hospital or emergency room extends for at least 12 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
- The participant exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following:

- Dyspnea (dyspnoea with exertion, dyspnoea at rest, orthopnoea, paroxysmal nocturnal dyspnoea),
- Decreased exercise tolerance,
- Fatigue,
- Edema,
- Other symptoms of worsened end-organ perfusion or volume overload
- At least one physical examination finding OR one laboratory criterion as objective evidence of new or worsening HF Physical examination findings considered to be due to HF include new or worsened:
    - peripheral edema,
    - increased abdominal distention or ascites (in the absence of primary hepatic disease),
    - pulmonary rales/crackles/crepitations,
    - Increased jugular venous pressure and/or hepatojugular reflux,
    - S3 gallop, and/or
    - Clinically significant or rapid weight gain thought to be related to fluid retention
- Laboratory criteria of new or worsening HF, if obtained in close temporal relationship of presentation, including:
    - increased BNP or NT-proBNP concentrations consistent with decompensation of HF (in participants with chronically elevated natriuretic peptides, a significant increase should be noted above baseline,
    - radiological or ultrasonographic evidence of pulmonary congestions,
    - non-invasive or implantable diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output,
    - Invasive evidence of new or worsening HF including right heart catheterization showing elevated pulmonary capillary wedge pressure (pulmonary artery occlusion pressure), elevated central venous pressure, and/or

    - depressed cardiac index, or left heart catheterization showing elevated left ventricular end-diastolic pressure consistent with decompensation of HF
- Intensification of therapy (significant augmentation of a current therapy for HF, or addition of a new therapy for HF).
- Significant augmentation in oral diuretic therapy (for example, the doubling of loop diuretic dose; initiation of maintenance loop diuretic therapy; or initiation of combination diuretic therapy to relieve congestion).
- Initiation of intravenous diuretic (a single dose is sufficient).
- Initiation of an intravenous vasoactive agent (catecholamine, phosphodieaterase-3 inhibitor, other vasopressor, vasodilator).
- Mechanical fluid removal (ultrafiltration, hemofiltration, initiation of dialysis for what is felt to be a primary cardiac rather than renal cause)

As used herein, the term "urgent heart failure visit" or "UHFV" means any visit meeting the above criteria for UHF, but where the patient spends less than 12 hours in an emergency room or any other urgent care setting. It is understood that urgent care visits due to complications of oral diuretics will not be considered sufficient to fulfill the criterion of intensification of treatment.

As used herein, the term "chronic heart failure" or "CHF" generally refers to the inability of the heart to pump blood effectively caused by, for example, weak muscle function (e.g., HFrEF)) or the inability of the heart to relax properly (e.g., HFpEF). Clinical symptoms for CF include shortness of breath, fatigue during normal activities, and swelling of the feet, ankles, and abdomen.

As used herein, the term "symptomatic heart failure" refers to a current or previous symptoms of heart failure.

As used herein, the term "cardiovascular death" or "CV" death means death resulting from an acute MI, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV haemorrhage, and death due to other CV causes. For the analysis of the primary endpoint, CV death will include death of undetermined cause.

As used herein, the term "death due to acute myocardial infarction" refers to a death by any CV mechanism (e.g., arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤ 30 days after a MI related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. There may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤ 30 days of the MI, it will be considered a death due to MI. Acute MI should be verified to the extent possible by the diagnostic criteria for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention, coronary artery bypass graft surgery), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

As used herein, the term "sudden cardiac death" refers to a death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

- Death witnessed and occurring without new or worsening symptoms
- Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI
- Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
- Death after unsuccessful resuscitation from cardiac arrest (e.g., ICD) unresponsive sudden cardiac death, pulseless electrical activity arrest)
- Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology
- Unwitnessed death in a subject seen alive and clinically stable ≤ 72 hours prior to being found dead without any evidence supporting a specific non-CV cause of death

As used herein, the term "death due to heart failure" refers to a death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

As used herein, the term "death due to stroke" refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria for stroke.

As used herein, the term "death due to cardiovascular procedures" refers to death caused by the immediate complications of a cardiac procedure.

As used herein, the term "death due to cardiovascular haemorrhage" refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.

As used herein, the term "death due to other cardiovascular causes" refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arterial disease).

As used herein, the term, the term "non-cardiovascular death" means as any death with a specific cause that is not thought to be CV in nature such, for examples,

- Death from pulmonary causes
- Death from renal causes. Evidence of renal death requires:
    - Evidence of CKD stage 5 (i.e., eGFR <15 mL/min/1.73m2 [and usually <10 mL/min/1.73m2] or ESKD); AND
    - Evidence of:
        - Conservative management of ESKD: the participant or their representatives had decided that, despite a clinical need, renal replacement therapy [RRT] was not to be provided. This includes progression to ESKD before RRT can be provided; OR

  - Withdrawal from RRT: the participant or their representative has chosen to discontinue RRT (e.g., personal choice, intolerant of dialysis therapy); AN
  - No evidence that other major pathology led: (a) to death, or (b) to the decision to withdraw from RRT (e.g., cancer or stroke), or (c) made dialysis infeasible. Such deaths should be ascribed to the underlying condition.
- Death from any of the following causes: gastrointestinal, hepatobiliary, pancreatic, infection (includes sepsis), inflammatory (e.g., Systemic Inflammatory Response Syndrome (SIRS) / Immune(including autoimmune) (may include anaphylaxis from environmental (e.g., food) allergies), haemorrhage that is neither CV bleeding or a stroke, non-CV procedure or surgery, trauma, suicide, non-prescription drug reaction or overdose, prescription drug reaction or overdose (may include anaphylaxis), neurological (non-CV), malignancy, and other non-CV causes

As used herein, the term "undetermined cause of death" refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Occasionally, it may not be possible to determine exact causality when 2 lethal conditions contribute to death equally. In this circumstance all events not due solely to non-CV causes should be classified as CV-related.

As used herein, the term "lack of information" when use to describe a cause of death (e.g., the only available information is "participant died") refers to a death when there is insufficient supporting information or detail to assign the cause of death. Such death is classified as undetermined cause of death.

Unless otherwise specified, the terms "patient" and "participant" are given the same meaning.

The terms "treatment" and "treating" comprise therapeutic treatment of patients having already developed said condition. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus

the compositions and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy.

The terms "prophylactically treating", "preventively treating" and "preventing" are used interchangeably and comprise a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

GENERAL SYNTHETIC METHODS

Compound **1** used in the methods of the invention may be prepared by the methods and examples described in WO 2016/014736 and U.S. provisional application no. 63/553234, filed February 14, 2024.

Mono-tablets containing Compound **1** or empagliflozin can be made by conventional mono-tablet formulations. The mono-tablets contain standard pharmaceutical excipients, for example, mannitol, microcrystalline cellulose, copovidone, croscarmellose sodium, magnesium stearate, and a film coating (containing a colorant, hypromellose, macrogol, talc and titanium dioxide). Mono-tablets containing empagliflozin are also commercially available under the tradename JARDIANCE®.

Placebo tablets are developed to mimic the appearance of the tablets containing the AS inhibitor. The placebo tablets contain standard pharmaceutical excipient, for example, microcrystalline cellulose, mannitol, and magnesium stearate. The coating of the placebo tablet is generally the same as the tablet containing the AS inhibitor described above.

Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)).

Fixed-dose combinations of Compound **1** and empagliflozin can be prepared from granules of the actives using conventional twin-Screw granulation and fluid-Bed granulation.

METHODS OF THERAPEUTIC USE

As noted above, one embodiment of the invention relates to methods for treating a patient with heart failure and left ventricular ejection fraction ≥40% (LVEF ≥40%), the method comprising administering to the patient a pharmaceutically effective amount of Compound **1,** optionally in combination with an SGLT2 inhibitor; in another embodiment, Compound **1** and an SGLT2 inhibitor are administered to the patient; and in another embodiment, Compound **1** and an SGLT2 inhibitor are administered to the patient, wherein the SGLT2 inhibitor is empagliflozin.

While empagliflozin has a different mechanism of action, the co-administration of SGLT2 inhibitors, which have shown improving outcomes in heart failure with preserved ejection fraction, employs a dual pharmacological approach. This strategy may mitigate the risk of hyperkalaemia and provide synergistic and complementary therapeutic benefits. By leveraging two distinct mechanisms of action, this combined treatment approach may enhance the overall efficacy and safety profile of the therapeutic regimen.

The mitigation of hyperkalaemia may allow for a higher dose of Compound **1** with balanced safety for hyperkalaemia. This dual mechanism may provide a greater therapeutic benefit than (steroidal or non-steroidal) mineralocorticoid receptor (MR) antagonists, with less risk of hyperkalaemia because efficacy should be elicited at doses corresponding to a lesser impact on MR-dependent electrolyte regulation.

Accordingly, another embodiment of the invention relates to the treatment of heart failure with Compound **1** in combination with a SGLT2 inhibitor; and in another embodiment, the SGLT2 inhibitor is empagliflozin.

Compound **1**, and optionally the SGLT2 inhibitor, may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compound **1** may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition.

Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 5%, but more preferably at least about 20%, of Compound **1** (w/w) or a combination thereof. The optimum percentage (w/w) of Compound **1** may vary and is within the purview of those skilled in the art. Alternatively, Compound **1** and the conventional therapeutics or other adjuvants may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regimen.

As mentioned above, each of the dosage forms of Compound **1** and the optional SGLT2 inhibitor may include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art and suitable to the dosage form. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred or dosage forms include tablets and capsules. Dosage levels and requirements for Compound 1 and the optional SGLT2 inhibitor may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In one embodiment, the amount of the empagliflozin is from 5 mg to 30 mg, or 10 mg to 25 mg, or 10 mg, or 25 mg. Specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

Within this invention, it is to be understood that the combinations or combined uses of Compound **1** and SGLT2 inhibitor according to this invention may envisage the simultaneous, sequential or separate administration of the therapeutic components.

In this context, “combination” or “combined” within the meaning of this invention may include, without being limited, fixed and non-fixed (e.g., free) forms (including kits, or other administration, application or dosage forms) and uses, such as e.g., the simultaneous, sequential or separate use of Compound **1** and SGLT2 inhibitor.

The combined administration or application of this invention may take place by administering the therapeutic components together, such as e.g., by administering them simultaneously in one single or in two separate formulations. Alternatively, the administration may take place by

administering the therapeutic components sequentially, such as e.g., successively in two separate formulations.

For the combination therapy of this invention the therapeutic components may be administered separately (which implies that they are formulated separately) or formulated altogether (which implies that they are formulated in the same preparation). Hence, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination.

In another aspect of the invention, patients may optionally be treated with a third therapeutic agent. Non limiting examples of optional third therapeutic agents include loop diuretics (for example, furosemide, bumetanide, ethacrynic acid, and torsemides) or thiazide diuretics (for example, metolazone, hydrochlorothiazide, chlorthalidone, indapamide, methyclothiazide, and chlorothiazide).

In one embodiment, the methods of the invention relate to the methods or uses described herein where Compound **1** and the SGLT2 inhibitor are administered as a fixed dose combination. The fixed-dose combination of the compounds is expected to offer a new class of foundational therapy with a beneficial efficacy and safety profile. In another embodiment, the SGLT2 inhibitor is empagliflozin.

In another embodiment, the combination of Compound **1** and the SGLT2 inhibitor may prevent or reduce the risk of hyperkalaemia events as compared to monotherapy with Compound **1**. In another embodiment, the SGLT2 inhibitor is empagliflozin.

Clinical Trial Protocol

1. OVERVIEW

The clinical trial protocol described below is designed to address the unmet need for effective therapies for HF, especially for HF with LVEF ≥40%. Inhibiting aldosterone production with Compound **1**, rather than blocking the mineralocorticoid receptor (MR), may avoid adverse effects associated with MR antagonists, such as hyperkalaemia and antiandrogenic- and

progestogenic-related side effects. Blocking both MR pathways with the combination of Compound **1** and empagliflozin may enable greater efficacy with a better safety profile.

2. TRIAL OBJECTIVES

The efficacy and safety of Compound **1** in combination with a SGLT2 inhibitor is studied according to the clinical trial study protocol described below. The goal of the study is to provide substantial evidence of the efficacy, safety, and tolerability of the combination of Compound **1** (10 mg) and empagliflozin (10 mg) in comparison to placebo and empagliflozin (10 mg) on top of standard of care in patients with HF and LVEF ≥40%. Table 1 shows the classification of HF by Left Ventricular Ejection Fraction (LVEF)

Table 1. Classification of HF by Left Ventricular Ejection Fraction (LVEF)

Type of HF	LFEV
HF with reduced ejection fraction (HFrEF)	≤40%
HF with mildly reduced ejection fraction (HFmrEF)	41% - 49%
HF with preserved ejection fraction (HFpEF)	≥50%

The primary objective is to demonstrate the efficacy of the combination of Compound **1** (10 mg) and empagliflozin (10 mg) as compared to placebo and empagliflozin (10 mg) for the time to first CV death, hospitalisation for heart failure (HHF), or urgent HF visit in patients with HF and LVEF ≥40%, based on hazard ratios as described herein.

Key secondary objectives are to demonstrate the efficacy of the combination of Compound **1** (10 mg) and empagliflozin (10 mg) as compared to placebo and empagliflozin (10 mg) for the time to first event of CV death or HHF, the total number of HHF (first and recurrent), the absolute change from baseline in Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS) at Week 32, time to CV mortality, and time to all-cause mortality. (See C.P Green et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35(5):1245-1255.)

Other secondary objectives are to demonstrate the efficacy for the time to first HHF, time to first occurrence of composite renal endpoint, as well for the absolute change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) at Week 32, the total symptom score (KCCQ-TSS) at Week 52, the absolute change from baseline in the KCCQ overall summary score (KCCQ-OSS) at Weeks 32 and 52, the absolute change from baseline in systolic blood pressure (SBP) [mmHg] at Week 32 in participants with baseline SBP ≥130 mmHg, and the absolute chance from baseline in diastolic blood pressure (DBP) [mmHg] at Week 32 in participants with baseline DBP ≥80 mmHg.

All primary analyses will be based on treatment comparisons as randomized, including information after any changes of study treatment or concomitant medications until the end of the study.

This trial includes participants with an LVEF of 40% or above. An LVEF of ≥50% constitutes HFpEF; an LVEF of 41-49% is considered HFmrEF. The range for LVEF was broadened to include those who have recovered their LVEF and frequently present with a value of exactly 40% due to known digit preference of rounding the final outcome.

Trial participants should receive best possible SOC in accordance with applicable HF local/international guidelines and should not be required to receive MRAs. This includes symptom control, diuretics, and management of comorbidities. Among participants with an LVEF of ≥41%, beta-blockers, ARNI, ACEI or ARB may be considered for the treatment of HF or its comorbidities; whereas, with HF and a LVEF of exactly 40% these drugs are recommended. Participants, who based on investigator judgement, require an ASi or MRA, are not eligible.

The main endpoints are as follows:

Primary endpoint

- The composite primary endpoint is the time to first event of CV death, HHF, or urgent HF visit. Death, HHF, and urgent HF visit will be categorized by the investigator according to pre-specified criteria.

Key secondary endpoints

- Time to first event of CV death, or HHF
- Occurrence of HHF (first and recurrent)
- Absolute change from baseline in KCCQ-TSS at Week 32
- Tine to CV death
- Time to all-cause mortality

Other secondary endpoints:

- Time to first HHF
- Time to first occurrence of or death from kidney failure, chronic dialysis (defined as dialysis continuing for at least 30 days) or renal transplant or sustained* reduction of ≥50% estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation (CKD-EPI)cr or sustained eGFR (CKD-EPI)cr <10 mL/min/1.73 m2 (composite renal endpoint)*

  *"sustained" is either (a) measured at two consecutive scheduled study visits; or (b) measured at the final Follow-up visit or the last scheduled visit before death, loss to follow-up, or withdrawal of consent.
- Absolute change from baseline in clinical summary score (HF symptoms and physical limitations domains) of the KCCQ (KCCQ-CSS) at Week 32
- Absolute change from baseline in KCCQ-TSS at Week 52
- Absolute change from baseline in KCCQ-OSS at Week 32
- Absolute change from baseline in KCCQ-OSS at Week 52
- Absolute change from baseline in systolic blood pressure (SBP) [mmHg] at Week 32 in participants with baseline SBP ≥ 130 mmHg
- Absolute chance from baseline in diastolic blood pressure (DBP) [mmHg] at Week 32 in participants with baseline DBP ≥ 80 mmHg

Further objection and further endpoints

Further objectives include the additional efficacy, safety, and biomarker evaluations with Compound **1** (10 mg) and empagliflozin (10 mg) as compared to placebo and empagliflozin (10 mg) as well as PK evaluations in participants receiving Compound **1** (10 mg) and empagliflozin (10 mg).

Further efficacy endpoints:

- Time to first HHF or urgent HF visit
- Time to first CV death, HHF, urgent HF visit or outpatient oral diuretic intensification for HF
- Time to first event of HHF, urgent HF visit, or outpatient oral diuretic intensification
- for HF
- Time to first urgent HF visit
- Occurrences of all-cause hospitalisations (first and recurrent)
- Time to first all-cause hospitalisation
- Time to first event of all-cause mortality or all-cause hospitalisation
- Time to first event of all-cause mortality or HHF
- Time to first myocardial infarction (MI) (fatal or non-fatal)
- Time to first stroke (fatal or non-fatal)
- Time to first transient ischemic attack (TIA)
- Time to first stroke (fatal or non-fatal) or transient ischemic attack (TIA)
- Time to first atrial fibrillation (Afib) or atrial flutter (Aflutter) episode in participants without history of AFF (atrial fibrillation or flutter)
- Time to first CV death or non-fatal MI
- Time to first CV death or non-fatal stroke
- Time to first CV death, non-fatal MI or non-fatal stroke (3-point major adverse cardiovascular events [MACE])
- Time to first event of CV death, HHF, non-fatal MI or non-fatal stroke (4-point major adverse cardiovascular events [MACE])
- Time to first event of ventricular tachycardia

- Time to sudden cardiac death
- Time to first composite renal endpoint or cardiovascular death
- Time to first composite renal endpoint, HHF or Cardiovascular death
- Time to first composite renal endpoint or all-cause hospitalisation
- Absolute change from baseline in KCCQ overall summary score (KCCQ-OSS) at Week 32
- Absolute change from baseline in KCCQ overall summary score (KCCQ-OSS) at Week 52
- Absolute change from baseline in KCCQ clinical symptom score (KCCQ-CSS) at Week 52
- Win ratio for all-cause mortality, total number of HHF and KCCQ TSS from baseline at Week 32 (see Pocock SJ, Ariti CA, Collier TJ, et al. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J; 2012; 33; 176-182)
- Absolute change from baseline to off-treatment follow-up visit in eGFR [mL/min/1.73 m2]
- Absolute change from end of treatment to off-treatment follow-up visit in eGFR [mL/min/1.73 m2]
- Change in NYHA class from baseline to Week 32 and 52 (see Table 2)
- Health economic analyses using health care resource utilization data
- Relative change in UACR [mg/g] from baseline over time
- Absolute change from baseline in body weight [kg]over time
- Absolute change from baseline in systolic blood pressure (SBP) [mmHg]over time
- Absolute change from baseline in SBP [mmHg] over time in participants with baseline SBP ≥130 mmHg
- Absolute change from baseline in diastolic blood pressure (DBP) [mmHg] over time
- Absolute change from baseline in DBP [mmHg] over time in participants with
- baseline DBP ≥ 80 mmHg
- Absolute change from baseline in pulse rate [bpm]over time

- Time to new onset of diabetes mellitus
- eGFR (CKD-EPI)cr [mL/min/1.73 m2] slope of change from week 12 onwards (on-treatment chronic slope)
- Absolute change from baseline in eGFR [mL/min/1.73 m2] on-treatment over time. Time to first occurrence of death from kidney failure, chronic dialysis (defined as dialysis continuing for at least 30 days) or renal transplant or onset of sustained* reduction of ≥ 40% eGFR from baseline using the (CKD-EPI)cr equation or onset of sustained eGFR (CKD-EPI)cr < 10 mL/min/1.73 m2 (composite renal endpoint-40)
- Time to first occurrence of death from kidney failure, chronic dialysis (defined as dialysis continuing for at least 30 days) or renal transplant or onset of sustained* reduction of ≥ 57% eGFR from baseline using the (CKD-EPI)cr equation or onset of sustained eGFR (CKD-EPI)cr < 10 mL/min/1.73 m2 (composite renal endpoint-57)
  *"Sustained" is either (a) measured at two consecutive visits at least 30 days apart; or (b) measured at the final Follow-up visit or the last scheduled visit before death, loss to follow-up, or withdrawal of consent.

Safety objectives

- Adverse events of special interest (AESI)
- Incidence of clinically relevant hyperkalemia (as per investigator judgement)
- Incidence of hyperkalemia with serum potassium > 5.5 mmol/L, or > 6.0mmol/L (based on central laboratory)
- Incidence of adverse events (AEs) leading to discontinuation of vicadrostat/vicadrostat matching placebo
- Occurrence of AEs leading to discontinuation of empagliflozin
- Absolute change from baseline in potassium over time (central laboratory)
- Occurrence of acute renal failure (based on narrow standardized Medical Dictionary for Regulatory Activities [MedDRA] standardized MedDRA query [SMQ] 'Acute Renal Failure')
- Time to first acute kidney injury (based on preferred term)

Pharmacokinetics

Through plasma concentrations of Compound **1** (10 mg) and empagliflozin (10 mg) at steady state at Week 12, Week 32 and Week 52 will be collected from all participants in selected countries and thus limited to a subset of approximately 2000 participants. Based on the recruitment trends, the collection will be stopped in all or some of these countries once a sufficient number of samples has been secured, or for logistical reasons if the shipment and the assessment of further samples (i.e., those collected late in the trial) would delay the timely completion of the trial. Samples for the analysis of the metabolite of Compound **1** will be taken in approximately 200 participants out of the 2000 participants mentioned above. Plasma samples from participants receiving placebo matching Compound **1** and empagliflozin (10 mg) will not be analyzed.

Biomarkers

- Relative change from baseline in N-terminal pro-brain natriuretic peptide (NT proBNP) to Week 32
- Relative change from baseline in hsTnT to Week 32
- Change from baseline in aldosterone, cortisol and precursors over time
- Change from baseline in other disease activity biomarkers (e.g., GDF-15, erythropoietin) to Weeks 12 and 32

Table 2. NYHA classifications:

Classification	Characteristics
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnoea (shortness of breath)
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea (shortness of breath)
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnoea

IV	Unable to carry on any physical activity without discomfort. Symptoms of HF at rest. If any physical activity is undertaken, discomfort increases.

Linkage to real world data:

For participants who consent, a token is stored in the clinical database, that later facilitates linking clinical data to real world databases in a privacy preserving manner.

3. TRIAL DESIGN

Aspects of the study design are summarized in Table 3 and further described below:

Table 3. Treatment groups and blinding:

Short label	Description
Compound **1** + empagliflozin	Compound **1** (10 mg) QD + empagliflozin (10 mg) QD
Placebo + empagliflozin	Placebo (matching Compound 1) + empagliflozin (10 mg) QD

Participants, investigators, and everyone involved in trial conduct or analysis, or with any other interest in this double-blind trial, will remain blinded with regard to the randomized treatment assignments until after database lock. Emergency unblinding will be available to the investigator via the interactive response technology (IRT).

Comparators/background medication:

The use of treatments for HF will be at the discretion of the investigator and should be consistent with best possible SOC in accordance with applicable HF local/international guidelines. MRAs are prohibited medication from 14 days prior to randomization until the follow-up visit (planned 7 days after permanent discontinuation of Compound **1** or placebo matching Compound **1**).

For participants who discontinue Compound **1** or placebo matching Compound **1** treatment early, MRA is prohibited until 7 days after permanent discontinuation of Compound 1 or placebo matching Compound **1** and the MRA should thereafter be dosed per investigator judgment.

Empagliflozin will be provided to all participants as part of the study medication. The use of any SGLT2i or combined SGLT1i/SGLT2i, in addition to the provided study medication, is prohibited from the day of randomization until their end of study visit (planned 7 days after EoT for treatment completers) or until empagliflozin is discontinued early.

Randomization requirement, stratification factors, block size, and ratio:

Participants will be randomized via IRT in a 1:1 ratio. Randomization is stratified by geographical region (North America, Latin America, Europe & Australia, Asia, Africa/South Asia/West Asia) and LVEF (<50, ≥50). The block size used for the randomization will be provided in the clinical trial report (CTR).

In order to ensure that the trial will recruit a sufficient number of participants, who most likely benefit from an ASi, there is a planned 30% cap for the number of enrolled trial participants with a BMI <30 kg/m².

In order to ensure that the trial will accrue sufficient events in a reasonable time frame, there is a planned 20% cap for the number of enrolled trial participants with an LVEF ≥60%.

The Executive Committee may recommend to the sponsor to increase, decrease, or omit the cap for the number of enrolled trial participants with BMI <30 kg/m². The Executive Committee may also recommend exempting certain countries from capping, e.g., countries where trial participants with a BMI of 30 kg/m² or higher are encountered less often. The sponsor will review the proposal and make a final decision.

Sample Size:

Overall sample size: approx. 6000*

Sample size for each group (n = 2 groups): approx. 3000 participants per group

* If the accumulated blinded data suggests a slower accrual of first key secondary outcome events over calendar time than was originally projected, then the number of participants randomized may be increased up to 8000. Such a decision would be made during recruitment and

before any unblinding. The number of outcome events required (912 events) is not affected by this consideration.

Overview of treatment course:

After randomization, participants are dosed with assigned treatment for approximately 19 to 45 months (event-driven trial).

Trial oversight and adaptation:

An independent Data Monitoring Committee (DMC) will monitor the safety on an ongoing basis in order to ensure participant safety and make benefit-risk assessments.

Following unblinded data review, the DMC will provide written recommendations that will be transferred to Boehringer Ingelheim and the Executive Committee (EC) Chair.

An EC consisting of external experts involved in the trial and sponsor representatives will be established. The composition of the EC will be documented in the Trial Master File (TMF). The tasks and responsibilities, including scientific input and operational oversight, will be agreed in contracts between the EC members and the sponsor and also summarized in an EC Charter.

Study periods and duration of treatment:

- Screening period = up to 3 weeks
- Treatment period = planned treatment continues for each participant until the individual EoT visit. The EoT Visit should be planned in the close-out period of the trial.
  Follow-up period = 1 week after EOT for participants who complete the treatment period with vicadrostat/placebo matching vicadrostat.

Completion of treatment

Participants who prematurely discontinue study drug are expected to remain engaged during the post-treatment follow-up period, adhering to all protocol-specified study visits. They should be

actively encouraged to continue with their regular study visits and to complete all scheduled assessments.

Definition of the end of study

The end of the study is defined as last participant, last End of Study/Follow-up Visit completed, 1 week (+ 7 days) after end of treatment.

End of study visit

The trial includes an end of study visit, which is planned 1-week after the planned end of treatment. The study is event-driven, and close-out will start as soon as the required number of events are expected to be reached. Follow up for an individual participant ends with a post-treatment follow-up visit 1 week after the end of treatment visit in the close-out period. For participants who discontinue treatment early, an end of study visit is planned in the close-out period (see also follow-up options for participants with early treatment discontinuation above). A 7-day follow-up visit (EoS Visit) after Compound **1** (or Compound **1** matching placebo) discontinuation is not planned for these participants, since they will remain in the study follow-up.

Main diagnosis for trial entry

The main diagnosis for trial entry is HF (NYHA classes II to IV) and LVEF ≥40%.

Inclusion criteria

Eligible participants will have a diagnosis of HF with LVEF ≥40% and meet eligibility criteria below.

1. At least 18 years old and at least of the legal age of consent in countries where it is greater than 18 years
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
3. Male or female participants. Women of childbearing potential (WOCBP) must be ready and able to use highly effective methods of birth control per International Conference on

Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly.

4. Chronic HF diagnosed at least 3 months before Visit 1, and in NYHA class II-IV at Visit 1, with LVEF ≥40% per local reading (obtained by echocardiography, radionuclide ventriculography, invasive angiography, MRI, or CT). A historical LVEF may be used if it was measured within 12 months prior to Visit 1, or the LVEF may be measured after study consent has been obtained and before randomization at Visit 2 (if several values are available, the most recent one should be considered)

5. Presence of structural heart abnormality (confirmed by any imaging modality; i.e., echocardiography at Visit 1, as defined by left ventricular hypertrophy or left atrial enlargement). (See Table 4). Historical imaging may be used if performed within 12 months prior to Visit 1, or imaging may be completed after study consent has been obtained and before Visit 2. If several values are available, the most recent one should be considered

6. Elevated NT-proBNP[#,##] at Visit 1, analyzed at the central laboratory at Visit 1:

a) in participants with BMI <27 kg/m2: ≥300 pg/mL for participants without Afib or Aflutter (at Visit 1 ECG) and ≥900 pg/mL for participants with Afib or Aflutter (at Visit 1 ECG)

b) in participants with BMI ≥27 kg/m2 to <35 kg/m2: ≥220 pg/mL for participants without Afib or Aflutter (at Visit 1 ECG) and ≥660 pg/mL for participants with Afib or Aflutter (at Visit 1 ECG)

c) in participants with BMI ≥35 kg/m2: ≥125 pg/mL for participants without Afib or Aflutter (at Visit ECG) and ≥375 pg/mL for participants with Afib or Aflutter (at Visit 1 ECG)

7. At least one of the following:

a) Currently treated with diuretic therapy e.g., loop diuretics or thiazides, and on a stable dose for at least 1 week prior to Visit 1

b) Documented hospitalisation for HF within 6 months prior to Visit 1

c) Elevated NT-proBNP at Visit 1, analyzed at the central laboratory at Visit 1

   a. in participants without Afib or Aflutter (at Visit 1 ECG): ≥900 pg/mL

   b. for participants with Afib or Aflutter (at Visit 1 ECG): ≥1800 pg/mL

d.) UACR ≥ 30 mg/g, analyzed at the central laboratory at Visit 1

8. Treated according to best possible SOC (disregarding SGLT2is and MRAs) in accordance with applicable HF local/international guidelines and judgment of the investigator

Additional inclusion criteria apply to the optional accelerometry substudy:

1. Willing and able to provide informed consent for substudy participation; and
2. Capable of ambulation, with or without a walking aid

Additional inclusion criteria apply to the optional corticosteroid surveillance substudy:

1. Willing and able to provide informed consent for substudy participation
2. Early morning serum cortisol of ≥ 83 nmol/L (≥3 µg/dL) at Visit 2

Table 4. Structural heart disease criteria in patients with LVEF ≥40%.

Left atrial (LA) enlargement is defined by at least one of the following measurements	
LA width	≥4.0 cm
LA length	≥5.0 cm
LA area	≥20 cm^2
LA volume	≥55 mL
LA volume index	≥34 mL/m^2
Left ventricular (LV) hypertrophy is defined by at least one of the following measurements	
Septal thickness or posterior wall thickness	≥1.1 cm
LVMI	≥115 g/m2 for males and ≥95 g/m2 for females

Exclusion criteria

1. Treatment with an MRA (e.g., spironolactone, eplerenone, finerenone) within 14 days prior to Visit 1 or requiring such treatment before randomization or planned during the trial

based on the judgment of the investigator. Treatment with MRA should not be interrupted with the intention of enrollment into the study.

2. Treatment with amiloride, or other potassium-sparing diuretic within 14 days prior Visit 1 or requiring such treatment before randomization or planned during the trial that cannot be stopped prior to randomization and for the duration of the treatment period, based on the judgment of the investigator.

3. Receiving the following treatments:

a. a direct renin inhibitor (e.g., aliskiren) at Visit 2

b. more than one ACEI, ARB or ARNI, used simultaneously at Visit 2

c. in case of acute decompensated HF:

- i.v. inotrope, i.v. vasodilating drug (e.g., nitrate, nitroprusside), or i.v. natriuretic peptide (e.g., nesiritide, carperitide), or mechanical support (e.g., intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, any ventricular assist device) within 24 hours prior to randomization (Visit 2)
- i.v. diuretic with a dose that has been increased/intensified within 6 hours prior to randomization (a stable dose of an i.v. diuretic is not exclusionary)

d. systemic mineralocorticoid replacement therapy (e.g., fludrocortisone) at Visit 2

e. other aldosterone synthase inhibitors, e.g., baxdrostat at Visit 2 or planned during the trial

4. MI, TIA, stroke, coronary artery bypass graft surgery/CABG, heart valve surgery/intervention or any other major surgery (major according to the investigator's assessment) within 90 days prior to Visit 2, or scheduled for major elective surgery (e.g., hip replacement, coronary artery bypass graft surgery/CABG)

5. Percutaneous coronary intervention (PCI, scheduled or unscheduled) or any angiography using iodinated contrast agents in the 7 days prior to Visit 2

6. Heart transplant recipient, awaiting heart transplant, or currently implanted LVAD

7. Known cardiomyopathy based on infiltrative diseases (e.g., amyloidosis), accumulation diseases (e.g., haemochromatosis, Fabry disease), muscular dystrophies, hypertrophic obstructive cardiomyopathy or genetic hypertrophic cardiomyopathy, known pericardial constriction, or

cardiomyopathy with potentially reversible cause such as stress or peripartum cardiomyopathy or cardiomyopathy induced by chemotherapy within the 12 months prior to Visit 1 and until Visit 2

8. Acute inflammatory heart disease, such as acute myocarditis, within the 90 days preceding prior to Visit 1and until Visit 2

9. Known severe valvular heart disease (obstructive or regurgitant), as per investigator's judgment, or valvular heart disease scheduled for surgical or invasive procedures at Visit 1, or anticipated invasive treatment during the study

10. Atrial fibrillation or Atrial flutter with a resting heart rate >110 bpm documented by ECG at Visit 2

11. Untreated clinically relevant ventricular arrhythmia without an ICD at Visit 1 and/or Visit 2

12. Unless managed with an implanted pacemaker: symptomatic bradycardia, sick sinus syndrome, Mobitz Type II second degree AV-Block, or third degree heart block

13. Implantation of aCRT within 3 months prior to Visit 1 or until Visit 2 or scheduled for a CRT device implantation

14. Symptomatic hypotension and/or a SBP <100 mmHg at Visit 1 or Visit 2

15. SBP ≥180 mmHg at Visit 1 or Visit 2. If SBP >150 mmHg and <180 mmHg at Visit 1, the participant should be receiving at least 3 antihypertensive drugs

16. Severe chronic pulmonary disease according to investigator's judgment: e.g., with known FEV1 <50% or need for home oxygen for pulmonary disease, pulmonary arterial hypertension, Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or chronic obstructive pulmonary disease exacerbation requiring i.v. or chronic oral steroids within 3 months prior to Visit 1 or until Visit 2

17. Serum potassium >5.2 mmol/L measured by the central laboratory at Visit 1 (Note: one reassessment of serum potassium is allowed during screening)

19. ALT or AST >3x ULN at Visit 1 or known hepatic cirrhosis (Child Pugh C), or other liver disease causing severe impaired liver function, according to investigator's judgment

19. Impaired renal function, defined as eGFR <20 mL/min/1.73 m2 (CKD-EPI) as determined at Visit 1 by the central laboratory, or on renal replacement therapy. Note: one reassessment of eGFR is allowed during screening

20. Haemoglobin (Hb) <9 g/dL as determined at Visit 1 by the central laboratory
21. Known adrenal insufficiency (e.g., Addison disease) or Cushing's syndrome at Visit 1
22. History of ketoacidosis within 5 years prior to Visit 1 or until Visit 2
23. Gastrointestinal surgery or gastrointestinal disorder that could interfere with trial medication absorption in the investigator's opinion
24. Type 1 diabetes mellitus, or history of other autoimmune causes of diabetes mellitus (e.g., LADA)
25. Any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of uterine cervix or low risk prostate cancer (participants with pre-treatment PSA <10 ng/mL and biopsy Gleason score of ≤6 and clinical stage T1c or T2a)
26. Presence of any other disease than heart failure with a life expectancy of <1 year in the investigator's opinion
27. Participants who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial
28. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s) or within 5x half-lives since the last dose of the relevant unlicensed investigational medicinal product (whichever is longer) or receiving other investigational treatment(s). Those participating in a purely observational trial will not be excluded
29. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable trial participant or unlikely to complete the trial
30. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
31. Intolerance or known allergy or hypersensitivity to Compound **1** or empagliflozin or other SGLT2 inhibitors and/or any of the excipients (including lactose)
32. Any condition not covered by any of the other exclusion criteria, including abnormal laboratory values, which in the investigator's opinion, might jeopardize the participant's safety or compliance with the protocol

An additional exclusion criterion applies to the optional accelerometry substudy:

1. Self-reported allergy or sensitivity to metals or medical adhesives used in dermatology

An additional exclusion criterion applies to the optional corticosteroid surveillance substudy:

1. Treatment with any glucocorticoids within 14 days prior to Visit 1 or requiring such treatment before randomization or planned during the trial based on the judgment of the investigator

Table 5. Restricted medications

Medication	**During screening (until randomization)**	**During treatment period (including REP)[1]**
Inhibitors of aldosterone-mediated effects like MRA (including non-steroidal MRA)[2] like finerenone, eplerenone, spironolactone, canrenone, esaxerenone), any renin inhibitor	Not permitted from 14 days prior to Visit 1	Not permitted
Potassium-sparing diuretics like amiloride	Not permitted from 14 days prior to Visit 1	Not permitted
SGLT2 or SGLT1/2 inhibitors[3]	Permitted	Not permitted
OAT3 substrates	Methotrexate should be used with caution by doing the standard drug monitoring	Methotrexate should be used with caution by doing the standard drug monitoring
UGT inhibitors (Probenecid, Valproic acid, Fluconazole, Clomipramine, Amitriptyline)	Should be used with caution because vicadrostat concentration may be increased	Should be used with caution because vicadrostat concentration may be increased

Medication	**During screening (until randomization)**	**During treatment period (including REP)[1]**
UGT inducers (Rifampicin, Phenytoin)	Should be used with caution because vicadrostat concentration may be decreased	Should be used with caution because vicadrostat concentration may be decreased

[1] For participants who do not discontinue prematurely: up to end of study visit planned 7 days after treatment stop. No medications are restricted afterwards.
[2] For participants who discontinue trial treatment early, MRA is prohibited until 7 days after permanent discontinuation of Compound **1**, and the MRA should thereafter be adjusted per investigator judgment.
[3] Participants should be instructed to lastly take their prescribed SGLT2 or SGLT1/2 inhibitor on the day before randomization.

4. TREATMENTS

Table 6 summarizes the investigation product, placebo and empagliflozin used in the clinical trial.

Table 6.

Substance: Compound **1**	
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	10 mg
Posology:	1 tablet once daily
Mode of administration:	p.o.
Substance: Placebo matching Compound **1**	
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	Matching
Posology:	1 tablet once daily
Mode of administration:	p.o.

Substance: Empagliflozin	
Pharmaceutical formulation:	Film-coated tablet
Unit strength:	10 mg
Posology:	1 tablet once daily
Mode of administration:	p.o.

Selection of doses in the trial and dose modifications:

During the treatment period, participants will receive either Compound **1** (10 mg) or matching placebo and empagliflozin (10 mg).

Method of assigning trial participants to treatment groups:
Randomization codes will be generated through a validated software and kept blinded to the trial team, sites, and trial participants. Access to the codes will be controlled and documented. An Interactive Response Technology (IRT) system will be used to screen participants, create a participant number, perform treatment assignment, manage initial/re-supply ordering of IMP supplies, and handle emergency unblinding.

After the assessment of all inclusion and exclusion criteria, each eligible trial participant will be randomized to a treatment group according to a randomization plan in a 1:1 ratio at visit 2 via IRT.

Note that the medication number is different from the participant number (the latter is generated during screening via the IRT system).

Drug assignment and administration of doses for each trial participant

At Visit 2 (start of treatment period), participants will be randomly assigned to receive the 10 mg dose of Compound **1** or matching placebo.

In addition, all participants will receive a study medication kit containing empagliflozin.

During the treatment period, all trial medication will be dispensed at each on-site visit and medication will be administered from the kit dispensed at the current visit.

Compound **1** or matching placebo will be dispensed in bottles of 112 tablets to cover 16 weeks including reserve. Empagliflozin will be dispensed in wallets of 112 tablets to cover 16 weeks including reserve.

In exceptional situations where it is not possible to distribute the IMP to the participant during an on-site visit and where permitted by local law and regulations, IMP may be shipped directly to the participant's home from the site to reduce participant burden.

Interruption or discontinuation of trial treatment based on serum potassium levels
Serum potassium will be closely monitored, and interruption or discontinuation of Compound **1** or placebo may be required due to serum potassium elevations as follows:

- If patients experience clinically significant hyperkalaemia or serum potassium ≥6.0 mmol/L, temporary discontinuation should be considered.
- Treatment may be restarted when serum potassium levels have fallen below 5.2 mmol/L.
- The aim is to maintain serum potassium levels at ≤6.0 mmol/L, and ideally ≤5.5 mmol/L.
- For any episode of increased serum potassium >5.5 mmol/L, a clinical evaluation should be performed to make individual treatment decisions if a prompt intervention is required or not.

Management of serum potassium elevation
A rise in serum potassium under treatment with Compound **1** cannot be excluded and, therefore, regular measurements of potassium levels are an integral part of the visit schedule.
The following safety measurements will be put in place: Site training materials to include details of management of hyperkalemia and recommendations for potassium level control and restart of Compound **1** (or placebo) in case of temporary discontinuation

Management of serum cortisol decrease

After randomization, serum cortisol testing will be performed at Visits 3 and 4 (i.e., 4 and 12 weeks after randomization) as an early morning test (i.e., before 9:00 AM and within 4 hours of waking) using local lab cortisol assessment as these results are available locally in almost real-time, and can be rapidly repeated, if necessary. A cortisol <83 nmol/L (<3 μg/dL) is consistent with biochemical cortisol insufficiency and requires confirmation with a second early morning test within 2 weeks (whilst on study treatment, if possible). The investigator may decide on additional local blood tests to confirm or investigate any identified abnormalities.

If symptoms or signs suggestive of a cortisol insufficiency are reported whilst on study treatment, an unscheduled visit with early morning sample for local measurement cortisol should be performed.

In addition, the following safety measurements will be put in place:

Site training materials to include details of cortisol deficiency including presenting signs and symptoms

Written information for participants describing symptoms of adrenal crisis & required actions

Restrictions

Pre-clinical and in vitro data suggest Compound **1** is mainly cleared through glucuronidation via UGT2B7 and UGT2B4. Therefore, uridine 5' diphospho-glucuronosyltransferase (UGT) inhibitors and inducers should in general be considered with caution. However, strong UGT inhibitors will be listed in the Investigator Site File (ISF) and should not be used to avoid potentially significant increase of exposure to Compound **1**. Investigators will be asked to refer to the list of relevant drugs in the ISF. Concomitant medication restrictions are described in Table 5.

Due to potential interference with laboratory results, participants taking biotin will be asked to discontinue, and to schedule laboratory testing to occur ≥72 hours after the last biotin intake. This includes biotin (Vitamin B7, Vitamin H, or coenzyme R) ≥5 mg/day (including food supplements) and is applicable to laboratory testing at screening visits or any other trial visit.

The following should be used with caution, at the discretion of the investigator on a case by case basis: potassium supplementation, non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim and trimethoprim/sulfamethoxazole, any other medication known to raise potassium levels and/or cause deterioration in renal function.

Restrictions on diet and lifestyle
There are no restrictions on diet and lifestyle.

Contraception requirements
A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Throughout the trial and for a period of at least 7 days after the last dose of IMP, women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the participant information.

5. ASSESSMENT OF EFFICACY

The investigator is responsible for reviewing the endpoints. Investigators are blinded to trial treatment and will receive dedicated training on event review prior to trial initiation. Investigators assigned to the trial after initiation will also undergo event review training for subsequent qualification. Heart failure events will be reviewed by the Investigators based on clinical judgment and objective criteria assessed in relevant source documents and documented in a structured eCRF.

For the mortality component of the primary endpoint, the date of death and cause of death will be required. Investigators will further be requested to categorize deaths as CV or non-CV mortality based on available information, clinical judgment, and guidance in the eCRF. Investigators will

also be requested to categorize hospitalisations into elective and nonelective hospitalisations. MI, stroke and TIA events will be collected in the eCRF as reported by the Investigator.

Detailed information with event criteria and instructions how to report the endpoint events is available in the event review charter which may be accessed through the ISF.

Urine albumin creatinine ratio
Urinary albumin and creatinine measurements are the basis for the calculation of UACR.

UACR will be collected at the time required points.
Urinary albumin and creatinine will be analyzed at a central laboratory using routine validated methods.

Heart failure events and cardiovascular death
Death and HHFs as well as urgent care visits for HF will be categorized by the Investigator according to pre-specified criteria as defined herein.

New York Heart Association Functional Classification
The NYHA Functional Classification will be used to classify HF severity (Dolgin M, New York Heart Association. Criteria Committee. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. 1994. p. 253-256.; Table 4). The Investigator should place the participants in one of the four NYHA categories based on the participant's physical activity limitations.

Candidates for screening are required to have a NYHA Functional Class of II to III (see Table 2).

The classification of participant's physical activity according to NYHA will be performed at on-site visits as displayed in the SoA. If a visit is designated as an on-site visit but is conducted by phone, the NYHA Functional Classification must still be performed.

CLINICAL OUTCOME ASSESSMENTS

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-item self-administered questionnaire designed to evaluate physical limitations, symptoms (frequency, severity, and changes over time), social limitations, self-efficacy, and quality of life in patients with HF. (See Green CP, Porter CB, Bresnahan DR, et al. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35(5):1245-1255.) Electronic version in the required native language of the participant will be used. If the required language is not available, the participant is not required to complete the questionnaire.

The questionnaire takes about 5 to 8 minutes to complete and will be distributed according to the SoA.

The Investigator (or designated site personnel) should ensure that the participant has access to a quiet area at the site where he/she can be left alone to record his/her response in the questionnaire. In instances where a participant cannot give or decide upon a response, no response should be recorded. The Investigator (or designated site-personnel) should check that all items have been completed by the participant, but the response to each item should not be scrutinized. Instructions to participants are included in the questionnaire.

Patient global Impression of Severity (PGI-S)
PGI-S of Heart Failure Symptoms is a 1-item questionnaire to assess the participant's impression of symptoms severity, including shortness of breath, fatigue and swelling over the past two weeks over the last two weeks.

The PGI-S asks the participant to choose one response that best describes how his/her Heart Failure Symptoms, specifically: shortness of breath, fatigue and swelling are now on a 5-point scale:

- Not at all (1)
- Mild (2)
- Moderate (3)
- Severe (4)
- Very severe (5)

eCOA handling

Administration of eCOAs will be handled according to guidance documents from regulatory authorities and international societies (e.g., ISPOR). Participants are to complete ePRO assessments on his/her own in a quiet area at the frequency specified in the SoA, without being influenced by the investigator or other members of the trial team. ePRO assessments are to be completed by the participant in the same language the participant provided written consent for the trial and without any help from or interpretation/translation by other people.

Adequately trained and qualified site staff are to be available at any time for general questions and to support the participant, as well as to ensure PRO completion compliance.

Whether the participant was able to complete the PRO assessment himself/herself and the mode of administration will be documented.

ePRO data will be electronically transferred to the ePRO vendor database. In case of technical malfunctioning capture via paper should be done. ASSESSMENT OF SAFETY

Physical examination

A complete physical examination will be performed at the time points specified in the SoA. This examination includes, at a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight will be performed at the time points specified in the SoA.

ASSESSMENT OF BIOMARKER(S)

Exploratory and probable valid biomarkers

Probable valid biomarker analyses of established biomarkers of disease activity may include, but not be limited to:

- Mechanism of action related pharmacodynamic biomarker aldosterone and related corticosteroids such as 11-deoxycorticosterone, cortisol, 11-deoxycortisol and corticosterone to confirm selectivity of enzyme inhibition and to evaluate prognostic relevance of aldosterone suppression.

- Pharmacodynamics modulation of efficacy-related, disease activity biomarkers NT-proBNP and hsTnT indicative of heart wall remodeling and myocardial injury, respectively.

These analyses will be conducted in all participants in selected countries with sampling timepoints indicated in the SoA.

Sampling for additional exploratory disease activity biomarkers (e.g., GDF-15, erythropoietin) will be conducted in selected countries (as defined below) and, thus, limited to a subset of participants approx. 2000). In this subset, a pre-defined genetic analysis (enzyme variants and other relevant SNPs in pathway) will be conducted.

- Growth differentiation factor-15 (GDF-15) is a marker of worse heart failure severity, is an independent predictor of major heart failure outcomes and may be associated with more pronounced benefits of empagliflozin.
- Elevated endogenous erythropoietin (EPO) levels are associated with worse clinical outcomes in participants with heart failure (HF)
- Genetic analyses will include variants in aldosterone synthesis pathway and may be extended to other candidate gene variants.
- The analysis of biomarkers will be compared with the genetic ancestry of trial participants, specifically focusing on certain gene variants.

Assessment of the above-mentioned biomarkers is mandatory for all participants in US, Japan, Brazil and Taiwan. Other countries may be added, if deemed necessary to obtain a sufficient number of biosamples.

All biomarker samples can be analyzed in a staggered approach, and decisions for further analysis may depend on the results of prior analyses. This may also imply that not all collected samples will be analyzed, especially in case of termination of the project/trial or when baseline sample was not collected.

Should other biomarkers become relevant in the context of the trial and/or based on new information in the scientific literature or early trial analysis, these may also be explored from the available specimens.

The study samples will be discarded after completion of any investigations, but not later than 2 years after the CTR has been signed. Any leftover samples or derived material from prespecified analyses (e.g., RNA, DNA, and blood) may be used for method development/validation but will be destroyed no later than 2 years after the final trial report has been signed.

Exploratory and probable valid biomarker analyses will be performed by Boehringer Ingelheim or by a laboratory authorized by Boehringer Ingelheim.

Detailed instructions on sampling, preparation, processing, and shipment of the samples are provided in the laboratory manual. Sampling timepoints and periods may be adapted during the trial based on information obtained during trial conduct (e.g., as a result of preliminary PK/PD data), including addition or reduction of samples and visits.

Analytical results for the biomarker analyses will be described in an analytical report.

6. STATISTICAL DESIGN

NULL AND ALTERNATIVE HYPOTHESES

The primary and key secondary endpoints will be tested with a hierarchical testing procedure at the two-sided type I error level α=5% in the following order:

1. $H_0^{(1)}$: Time to first event of CV death , HHF, or urgent HF visit (primary endpoint).
2. $H_0^{(2)}$: Time to first event of CV death, or HHF (first key secondary endpoint).
3. Benjamini-Hochberg procedure for the following two endpoints:
    a. $H_0^{(3)}$: Occurrences (first and recurrent) of HHF (second key secondary endpoint)
    b. $H_0^{(4)}$: Absolute change from baseline in KCCQ-TSS at Week 32 (third key secondary endpoint)

If the null hypothesis ($H_0^{(1)}$) of step 1 is rejected, a benefit is concluded in the primary endpoint, then the first key secondary endpoint will also be tested in step 2. If the null hypothesis of step 2 ($H_0^{(2)}$) is subsequently rejected, then both the null hypotheses of the second key secondary ($H_0^{(3)}$) endpoint and of the third key secondary endpoint ($H_0^{(4)}$) will be tested simultaneously (following a Benjamini-Hochberg procedure) as part of step 3.

At any stage, when the corresponding null hypothesis is not rejected then all subsequent testing will be considered as exploratory.

The primary null hypothesis ($H_0^{(1)}$) to be tested is as follows:

- Null hypothesis ($H_0^{(1)}$): The hazard ratio (of time to first event of CV death, HHF, or urgent HF visit) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD equals 1.
- Alternative hypothesis ($H_1^{(1)}$): The hazard ratio (of time to first event of CV death, HHF or urgent HF visit) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is not equal 1.

The primary endpoint will be tested for superiority, and superiority will be declared if the hazard ratio between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is significantly less than 1 at the two-sided type I error level α=5%.

The first key secondary hypothesis ($H_0^{(2)}$) to be tested is as follows:

- Null hypothesis ($H_0^{(2)}$): The hazard ratio (of time to first event of CV death, or HHF) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD equals 1.
- Alternative hypothesis ($H_1^{(2)}$): The hazard ratio (of time to first event of CV death, or HHF) between BI 690517 10 mg+ empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is not equal 1.

The first key secondary endpoint will be tested for superiority, and superiority will be declared if the hazard ratio between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is significantly less than 1 at the two-sided Type I error level α=5%.

The second key secondary hypothesis ($H_0^{(3)}$) to be tested is as follows:

- Null hypothesis ($H_0^{(3)}$): The hazard ratio for the comparison (of first and recurrent HHF) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is equal 1.
- Alternative hypothesis ($H_1^{(3)}$): The hazard ratio for the comparison (of first and recurrent HHF) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is not equal 1.

The third key secondary hypothesis ($H_0^{(4)}$) to be tested is as follows:

- Null hypothesis ($H_0^{(4)}$): The unstratified win-ratio (considering death and change from baseline in KCCQ-TSS at week 32) between BI 690517 10 mg+ empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is equal 1.
- Alternative hypothesis ($H_1^{(4)}$): The unstratified win-ratio (considering death and change from baseline in KCCQ-TSS at week 32) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is not equal 1.

The second and third key secondary endpoint will be tested for superiority if $H_0^{(2)}$ can be rejected. $H_0^{(3)}$ and $H_0^{(4)}$ will be rejected if both p-values are <0.05. If one p-value is ≥ 0.05, then the other null hypothesis will be rejected if $p<0.025$, following the Benjamini-Hochberg procedure. Superiority will be declared if the null hypothesis can be rejected in favour of the alternative hypothesis and if the difference in the effect favors the active treatment group (that is, for $H_0^{(3)}$ a hazard ratio less than 1, and for $H_0^{(4)}$,) a mean difference greater than 0).

The fourth key secondary null hypothesis (*H*0 (5)) to be tested is as follows:

- Null hypothesis (*H*0 (5)): The hazard ratio (of time to CV death) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD equals 1.

- Alternative hypothesis (*H*1(5)): The hazard ratio (of time to CV death) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin10 mg QD is not equal 1.

The fourth key secondary endpoint will be tested for superiority, and superiority will be declared if the hazard ratio between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is significantly less than 1, at the two-sided type I error level α =5%.

The fifth key secondary null hypothesis (*H*0(6)) to be tested is as follows:

- Null hypothesis (*H*0(6)): The hazard ratio (of time to all-cause mortality) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD equals 1.

- Alternative hypothesis (*H*1(6)): The hazard ratio (of time to all-cause mortality) between BI 690517 10 mg + empagliflozin 10 mg QD and placebo +empagliflozin 10 mg QD is not equal 1.

The fifth key secondary endpoint will be tested for superiority, and superiority will be declared if the hazard ratio between BI 690517 10 mg + empagliflozin 10 mg QD and placebo + empagliflozin 10 mg QD is significantly less than 1, at the two-sided type I error level α =5%.

PLANNED ANALYSES

General considerations

Participants will be analysed according to their randomised treatment including all participants randomised (intention-to-treat principle, ITT). For time to event and count endpoints, participants who do not have an event will be censored at the last day the participant was known to be free of the event, except other intercurrent events occur which may result in earlier censoring as specified below.

Analysis sets:

- Randomized Set (RS): the RS includes all randomized patients. The primary efficacy analysis will be based on the RS.
- Treated Set (TS): the TS includes all randomized patients who received at least one dose of trial treatment. If not stated otherwise, safety analyses will be based on this analysis set.
- Pharmacokinetic Set (PKS) is defined as all patients in the TS who provided at least one Compound **1** or empagliflozin concentration which was not excluded due to non-evaluability or an important protocol deviation relevant for PK.

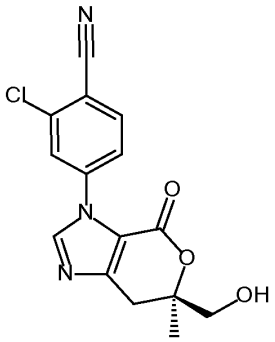
Definition of baseline in general, unless otherwise specified in the TSAP, the last non-missing measurement on or prior to the date of first dose of study treatment will be used as baseline for efficacy and safety variables.

Definition of on-treatment for the purposes of on-treatment safety analyses, an assessment (or AE start date) will be considered "on-treatment" if the assessment date (or AE start date) is between the date of first dose and 7 days after the date of last trial medication intake.

Claims

What is claimed is:

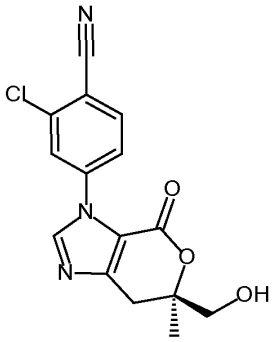
1. A method for reducing the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure in patients with heart failure and left ventricular ejection fraction ≥40%, the method comprising administering to a patient in need thereof a pharmaceutically effective amount of Compound **1**:



(**1**),

optionally in combination with a SGLT2 inhibitor.

2. Use of Compound **1**:

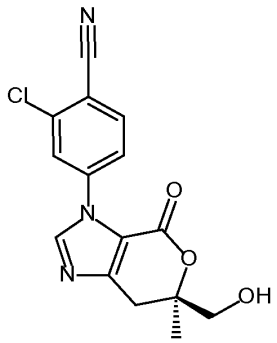


(**1**),

optionally in combination with a SGLT2 inhibitor, for treatment of heart failure with a left ventricular ejection fraction ≥40%.

3. Use according to claim 2, for reducing the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure visit.

4. Use of Compound **1**:



(**1**),

optionally in combination with a SGLT2 inhibitor, for the preparation of a medicament for treating a patient with heart failure and a left ventricular ejection fraction ≥40%.

5. Use according to claim 4, for reducing the risk of cardiovascular death, hospitalization for heart failure, and/or urgent heart failure visit.

6. The method or use according to any one of the preceding claims, wherein the heart failure is chronic heart failure, symptomatic heart failure or urgent heart failure.

7. The method or use according to any one of the preceding claims, wherein the patient is an adult patient.

8. The method or use according to any one of the preceding claims, wherein the patient is ineligible for treatment with mineralocorticoid receptor antagonists (MRAs).

9. The method or use according to any of claims 1 to 5, wherein:

the patient has chronic heart failure, symptomatic heart failure, or urgent heart failure,

the patient is diagnosed with chronic heart failure at least 3 months prior to the start of treatment, and/or

the patient is diagnosed with chronic heart failure at least 3 months prior to the start of treatment and is classified in NYHA class II to IV at the start of treatment.

10. The method or use according to any one of the preceding claims, wherein in the patent is a type 2 diabetes mellitus patient.

11. The method or use according to any one of the preceding claims, wherein Compound **1** is used in combination with an SGLT2 inhibitor, wherein the SLGT2 inhibitor is selected from the group consisting of empagliflozin, dapagliflozin, sotagliflozin and canagliflozin.

12. The method or use according to claim 11, wherein the SGLT2 inhibitor is empagliflozin.

13. The method or use according to claim 12, wherein Compound **1** is administered in an amount of 3 mg, or 6 mg, or 10 mg, or 20 mg; and empagliflozin is administered in an amount of 10 mg or 25 mg.

14. The method or use according to claim 13, wherein Compound **1** is administered in an amount of 10 mg; and empagliflozin is administered in an amount of 10 mg.

15. The method of use according to any one of claims 12 to 14, wherein Compound **1** is administered once daily and empagliflozin is once daily.