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(54) Title: USE OF LIK066 IN HEART FAILURE PATIENTS

(57) Abstract: The invention concerns the use of LIK066 in heart failure patients and those patients with heart failure in conjunction with Type II diabetes.



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USE OF LIK066 IN HEART FAILURE PATIENTS**Field of the invention**

The present invention relates to pharmaceutical uses of LIK066, their pharmaceutically acceptable salts, and prodrugs thereof specifically for the treatment of heart failure.

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Background of the invention

Type 2 diabetes (T2D) is a serious condition associated with high risk of cardio-vascular disease (CVD), and its complications, such as heart failure (HF). In patients with T2DM, both the incidence rate of HF and hospitalizations/mortality are higher than in patients without diabetes (Nichols et al, 2004; Kazsnicki et al, 2014). The poor prognosis in patients with T2DM and HF has been attributed to increased myocardial hypertrophy, myocardial fibrosis and abnormal cardiac metabolism (Kazsnicki et al, 2014), which may contribute to the development of myocardial ischemia, worsening of ventricular dysfunction, and arrhythmias (Taegtmeyer et al, 2002). HF is associated with recurrent hospitalizations and increased mortality rates (Chun et al, 2012). The risk of hospitalization and mortality associated with heart failure was significantly reduced with standard treatments, such as mineralocorticoid receptor antagonists (MRAs), β -blockers, angiotensin converting enzyme-inhibitors (ACEi) and angiotensin II receptor blockers (ARBs), as well as the recently studied sacubitril/valsartan treatment (Yancy et al, 2013; Solomon et al, 2016).

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Sodium-glucose co-transporter (SGLT) 2 inhibitors are approved for the treatment of type 2 diabetes. In addition, long-term treatment with the SGLT2 inhibitor empagliflozin in the EMPA REG Outcome study resulted in 14% relative reduction (RR) in major adverse cardiovascular events (MACE) vs placebo driven by a statistically significant 38% RR in cardiovascular (CV) death. The risk of hospitalizations for HF was also reduced (Zinman et al, 2015). In this study, patients with eGFR down to 30 ml/min/1.73m² were included. In a subgroup analysis by renal function categories, the risk of CV death or HF hospitalization was significantly reduced in the groups with mild and moderate renal impairment. This composite endpoint was also significantly reduced in patients without previously diagnosed HF, and was numerically lower in patients with HF at baseline, who comprised approximately 10% of the study population (Fitchett et al, 2016). It is hypothesized that the observed benefit may have derived from the specific effects of SGLT2 inhibition on renal sodium and glucose handling, leading to both diuresis and improvements in diabetes-related maladaptive renal arteriolar responses (Sattar et al, 2016), from the switch of free fatty acids oxidation in the heart to the more efficient beta - hydroxybutyrate oxidation, as

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well as from the enhanced oxygen supply due to hemoconcentration (Ferrannini et al, 2016).

Therefore there is a need to provide treatments for heart failure in a subject in need of such treatment that can address the different aspects of this complex condition, in any patient in need of such treatment while demonstrating an acceptable safety and/or tolerability profile. The inhibition of both SGLT1 and SGLT2 might provide additional benefits for improving treatment efficacy and response rates.

Summary of the invention

LIK066 is an inhibitor of SGLT1 and SGLT2. Via inhibition of both SGLT1 and SGLT2 in the proximal renal tubule, the drug may further enhance the effects on renal sodium and glucose handling compared with the selective SGLT2 inhibitors. In addition, SGLT1 is expressed in the small intestine where it is required for glucose and galactose absorption. Inhibition of enteric SGLT1 results in glucose and galactose malabsorption (Turk et al, 1991) which leads to calorie wasting and other potential endocrine-based weight loss mechanisms. Considering its dual mode of action (renal and intestinal) on re-absorption/absorption of glucose, LIK066 is planned for investigation in obese and overweight patients as a weight loss drug (calorie-loss enhancer). In a phase I study with normal- and dysglycemic adults with body-mass index (BMI) $\geq 35\text{kg/m}^2$, treatment with LIK066 150mg qd resulted in a mean 5.7% placebo subtracted weight loss at 12 weeks.

SGLT1 receptors are expressed in the heart, and it is believed that administration of LIK066 may ameliorate, treat or improve the symptoms associated with those individuals which exhibit comprised cardiac function.

In accordance with a first aspect of the invention, there is provided a method for the treatment or prevention of heart failure in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of an inhibitor of SGLT1 and SGLT2, e.g. LIK066, or a pharmaceutically acceptable salt thereof.

In another aspect, the invention is the compound LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.

In yet another embodiment, the invention is a pharmaceutical composition comprising LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.

- 5 In another embodiment the invention is the use of LIK066, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in the treatment or prevention of heart failure.

10 In accordance with another aspect of the invention, there is provided a method for the treatment or prevention of heart failure in a subject with Type 2 Diabetes, which comprises administering to said subject a therapeutically effective amount of LIK066, or a pharmaceutically acceptable salt thereof.

15 In another aspect, the invention is the compound LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure in a patient with Type 2 diabetes.

20 In yet another embodiment, the invention is a pharmaceutical composition comprising LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure in a patient with Type 2 diabetes.

In another embodiment the invention is the use of LIK066, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in the treatment or prevention of heart failure in a patient with Type 2 Diabetes.

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Brief Description of the Drawings

FIG. 1 depicts the study design.

FIG. 2 depicts the assessment schedule.

30 **FIG. 3** depicts the assessment schedule.

FIG. 4 depicts the assessment schedule.

FIG. 5 depicts the assessment schedule.

Detailed description of the invention

In a first embodiment, the invention is a method for the treatment or prevention of heart failure, including heart failure with preserved ejection fraction and heart failure with reduced ejection fraction in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of LIK066, or a pharmaceutically acceptable salt thereof.

In a second embodiment, the invention is the method according to the first embodiment, wherein about 2.5 mg of LIK066 is administered.

In a third embodiment, the invention is the method according to the first embodiment, wherein 10 mg of LIK066 is administered.

In a fourth embodiment, the invention is the method according to the first embodiment, wherein 50 mg of LIK066 is administered.

In a fifth embodiment, the invention is the method according to any one of the first through fourth embodiments, wherein LIK066 is administered once a day.

In a sixth embodiment, the invention is the method according to any one of the first through fifth embodiments, wherein LIK066 is administered at bedtime.

In a seventh embodiment, the invention is the method according to any one of the first through sixth embodiments, wherein the subject is at least 18 years old.

In an eighth embodiment, the invention is the method according to any one of the first through seventh embodiments, wherein the subject has a BMI $\geq 22\text{kg/m}^2$.

In a ninth embodiment, the invention is the method according to any of first through eighth embodiments, wherein the subject has Type 2 diabetes with HbA1c between 7.0% and 10.0%.

In a tenth embodiment, the invention is the method according to any of the first through ninth embodiments, wherein the subject has documented symptomatic chronic heart failure (NYHA II-IV) with at least one of following symptoms selected from, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea and Peripheral edema.

In an eleventh embodiment, the invention is the method according to any one of the first through tenth embodiments, wherein the subject has plasma NT-proBNP > 400 pg/ml.

5 In a twelfth embodiment, the invention is the method according to any one of the first through eleventh embodiments, wherein the subject is concurrently receiving a medication selected from, ACEi, ARBs, MRAs, ARNi and/or β -blockers and is on a stable dose of said medication.

10 In a thirteenth embodiment, the invention is the method according to any one of the first through twelfth embodiments, wherein the subject is on diuretic therapy.

In a fourteenth embodiment, the invention is the method according to any one of the first through thirteenth embodiments, wherein the subject has controlled systolic BP of less than
15 140mmHG.

In fifteenth embodiment, the invention is the method according to any one of the first through fourteenth embodiments, wherein the subject has an eGFR $\geq 45\text{ml/min/1.73m}^2$.

20 In a sixteenth embodiment, the invention is the method according to any one of the first through fifteenth embodiments, wherein the subject has serum potassium $\leq 5.2\text{mM}$.

In a seventeenth embodiment, the invention is the compound LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.
25

In an eighteenth embodiment, the invention is a pharmaceutical composition comprising LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.

30 In a nineteenth embodiment, the invention is the pharmaceutical composition according to the eighteenth embodiment, wherein the compositions comprises 2.5 mg, 10mg, or 50 mg of LIK066.

In a twentieth embodiment, the invention is the pharmaceutical composition according to the eighteenth or nineteenth embodiment, wherein the pharmaceutical composition is administered once a day.

- 5 In a twenty-first embodiment, the invention is the pharmaceutical composition according to any one of the nineteenth or twentieth embodiments, wherein the subject has a BMI $\geq$ 22kg/m².

- 10 In a twenty-second embodiment, the invention is the pharmaceutical composition of any of eighteenth through twenty-first embodiments, wherein the subject has Type 2 diabetes, particularly to any individual with an HbA1c between 7.0% and 10.0%.

- 15 In a twenty-third embodiment, the invention is the pharmaceutical composition of any of the eighteenth through the twenty-second embodiments, wherein the subject has documented symptomatic chronic heart failure (NYHA II-IV) with at least one of following symptoms selected from, Dyspnea on exertion, Orthopnea, Paroxysmal nocturnal dyspnea and Peripheral edema.

- 20 In a twenty-fourth embodiment, the invention is the pharmaceutical composition of any one of the eighteenth through twenty-third embodiments, wherein the subject is concurrently receiving a medication selected from, ACEi, ARBs, MRAs, diuretics, ARNi and/or β -blockers, or combinations thereof and is on a stable dose of said medication.

- 25 In a twenty-fifth embodiment, the invention is the pharmaceutical composition of any one of the eighteenth through twenty-fourth embodiments, wherein the subject has controlled systolic BP of less than 140mmHG.

- 30 In twenty-sixth embodiment, the invention is the pharmaceutical composition of any one of the eighteenth through twenty-fifth embodiments, wherein the subject has an eGFR $\geq$ 45ml/min/1.73m².

- In a twenty-seventh embodiment, the invention is the pharmaceutical composition of any one of the eighteenth through twenty-sixth embodiments, wherein the subject has serum potassium $\leq$ 5.2mM.

In a twenty-eighth embodiment, the invention is the use of LIK066, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in the treatment or prevention of heart failure.

- 5 In a twenty-ninth embodiment, the invention is the medicament according to the twenty-eighth embodiment, wherein the compositions comprises 2.5 mg, 10mg, or 50 mg of LIK066.

In a thirtieth embodiment, the invention is the medicament is for use in the treatment of heart failure in a subject with Type 2 diabetes, particularly to any individual with an HbA1c
10 between 7.0% and 10.0%.

In a thirty-first embodiment, the invention comprises LIK066 for use in the treatment of heart failure.

- 15 In a thirty-second embodiment, the invention comprises LIK066 for use in the treatment of heart failure with preserved ejection fraction (HFpEF).

In a thirty-third embodiment, the invention comprises LIK066 for use in the treatment of heart failure with reduced ejection fraction (HFrEF).
20

In a thirty-fourth embodiment, the invention comprises LIK066 for use in the treatment of heart failure in a subject with T2D, particularly to any individual with an HbA1c between 7.0% and 10.0%.

- 25 In a thirty-fifth embodiment, the invention comprises LIK066 for use in the treatment of heart failure with preserved ejection fraction (HFpEF) in a subject with T2D, particularly to any individual with an HbA1c between 7.0% and 10.0%.

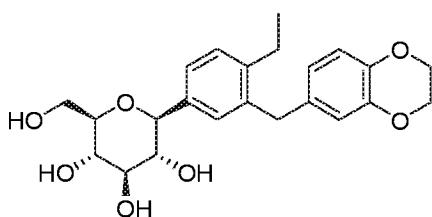
In a thirty-sixth embodiment, the invention comprises LIK066 for use in the treatment of heart failure with reduced ejection fraction (HFrEF) in a subject with T2D, particularly to any
30 individual with an HbA1c between 7.0% and 10.0%.

- In a thirty-seventh embodiment, the invention is the use according to any of the thirty-first through thirty-sixth embodiments, wherein the compositions comprises 2.5 mg, 10mg, or 50
35 mg of LIK066.

In another embodiment, the invention is a pharmaceutical unit dose comprising 2.5 mg, 10mg, or 50 mg of LIK066.

- 5 A "pharmaceutically acceptable salt" is intended to mean a salt of a free base/free acid of a compound represented by formula (I) that is not toxic, biologically intolerable, or otherwise biologically undesirable. Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. Such salts are known in the field (e.g. S.M. Berge, et al, "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19; and "Handbook of Pharmaceutical Salts, Properties, Selection, and Use", Stahl, R.H., Wermuth, C.G., Eds.; Wiley-VCH and VCH: Zurich, 2002).

- 15 LIK066 is an inhibitor of the sodium-glucose co-transporter-1 (SGLT1) and sodium-glucose co-transporter-2 (SGLT2). LIK066 has the following chemical structure:



- 20 LIK066 has the following IUPAC name: (2S,3R,4R,5S,6R)-2-(3-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-4-ethylphenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

- LIK066 for use in the present invention is either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

- 25 Furthermore, LIK066 including its salts, can also be obtained in the form of its hydrates, or include other solvents used for its crystallization. LIK066 may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are 30 those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like.

The term "hydrate" refers to the complex where the solvent molecule is water. LIK066, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

- 5 The higher oral bioavailability of LIK066 may give rise to the following beneficial effects relating to less bioavailable compounds: (i) an enhanced biological effect may be achieved after oral administration; (ii) an earlier onset of action may be observed following oral administration; (iii) a lower dose may be needed to achieve the same effect; (iv) a higher effect may be achieved by the same dose or (v) a prolonged action may be observed at the
10 same dose.

The term "subject" as used herein typically refers to a human, especially to a human patient diagnosed with heart failure or to a human patient suffering from heart failure associated with Type 2 diabetes.

15

The term "treatment" as used herein refers to any type of treatment that imparts a benefit to a subject affected with heart failure.

Heart failure (HF) often referred to as congestive heart failure (CHF), occurs when
20 the heart is unable to pump sufficiently to maintain blood flow to meet the body's needs. Signs and symptoms commonly include shortness of breath, excessive tiredness, and leg swelling. The shortness of breath is usually worse with exercise, while lying down, and may wake the person at night. A limited ability to exercise is also a common feature. Chest pain, including angina, does not typically occur due to heart failure.

25 Common causes of heart failure include coronary artery disease including a previous myocardial infarction (heart attack), high blood pressure, atrial fibrillation, valvular heart disease, excess alcohol use, infection, and cardiomyopathy of an unknown cause. These cause heart failure by changing either the structure or the functioning of the heart.

30 There are two main types of heart failure: *heart failure due to left ventricular dysfunction* and *heart failure with normal ejection fraction* depending on whether the ability of the left ventricle to contract is affected, or the heart's ability to relax. The severity of disease is usually graded by the degree of problems with exercise. Heart failure is not the same as myocardial infarction (in which part of the heart muscle dies) or cardiac arrest (in which

blood flow stops altogether). Other diseases that may have symptoms similar to heart failure include obesity, kidney failure, liver problems, anemia, and thyroid disease.

The condition is diagnosed based on the history of the symptoms and a physical examination with confirmation by echocardiography, Blood tests, electrocardiography,
5 and chest radiography may be useful to determine the underlying cause.

For the above-mentioned indications (the conditions and disorders) the appropriate dosage will vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in are
10 indicated to be obtained at a daily dosage of from about 0.01 to about 100 mg/kg body weight, preferably from about 1 to about 30 mg/kg body weight, e.g. 10 mg/kg. An indicated daily dosage is in the range from about 0.1 to about 1000 mg, preferably from about 1 to about 100 mg, most preferably from about 1 to about 75 mg of LIK066 conveniently administered, for example, in a single dose once a day. In one embodiment, about 2.5mg of
15 LIK066 is administered once a day. In another embodiment, about 10mg of LIK066 is administered once a day. In yet another embodiment, about 50mg of LIK066 is administered once a day.

For use according to the invention, LIK066 may be administered in any usual manner, e.g.
20 orally, for example in the form of tablets, capsules or drinking solutions; rectally, for example in the form of suppositories; intravenously, for example in the form of injection solutions or suspensions; or transdermal, for example in the form of a patch.

In one embodiment, the manner of administration is oral administration, for example in the
25 form of a tablet, capsule or drinking solution. In one embodiment, the manner of administration is rectal administration, for example in the form of a suppository. In one embodiment, the manner of administration is transdermal administration, for example in the form of a patch. In one preferred embodiment, the manner of administration is oral administration.

30 Preferred pharmaceutical compositions comprise LIK066 in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms may contain LIK066 in an amount greater than or equal to 2.5mg, for example greater than or equal to 10mg, such as for example greater than or equal to

50mg. Unit dosage forms may also contain LIK066 in an amount of greater than or equal to 2.5mg, 10mg, 40mg, 50mg, 75mg or 100mg or greater than or equal to 150mg or 200mg.

Unit dosage forms may contain LIK066 in an amount less than or equal to 100mg, for example less than or equal to 100mg, such as for example less than or equal to 50 mg or for example less than or equal to 10mg or for example less than or equal to 2.5mg. Unit dosage forms may also contain LIK066 in an amount in the range from 1-100mg, e.g. 1-75mg or 1-60mg such as 2-55mg.

10 The pharmaceutical compositions according to the invention are compositions for enteral administration, such as oral or rectal administration; or parenteral administration, such as intramuscular, intravenous, and nasal or transdermal administration, to warm-blooded animals (human beings and animals) that comprise an effective dose of the pharmacological active ingredient alone or together with a significant amount of a pharmaceutically acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, body weight, age and individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

The pharmaceutical compositions comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

Compositions for transdermal administration are described in Remington's Pharmaceutical Sciences 16th Edition Mack; Sucker, Fuchs and Spieser, Pharmazeutische Technologie, 1st Edition, Springer.

Examples

List of Abbreviations

ACE(i) Angiotensin converting enzyme (inhibitor)

30 AE Adverse event

ALT Alanine aminotransferase

ARB Angiotensin II receptor blocker

AST Aspartate aminotransferase

AV Atrioventricular

35 BL Baseline

	BMI	Body-mass index	BMD	Bone mineral density
	BP	Blood pressure		
	CFR	US Code of Federal Regulations		
	CHF	Chronic heart failure		
5	CRF	Case report/record form (paper or electronic)		
	CPO	Country pharma organization		
	CRO	Contract research organization		
	CV	Cardiovascular		
	CVD	Cardiovascular disease		
10	DBP	Diastolic blood pressure		
	DXA	Dual-energy x-ray absorptiometry		
	ECG	Electrocardiogram		
	EDC	Electronic data capture		
	EOS	End of study		
15	EQ-5D-5L	EuroQoL 5 dimensions 5 level version		
	FAS	Full analysis set		
	FDA	Food & Drug Administration		
	FPG	Fasting plasma glucose		
	GCP	Good clinical practice		
20	(e)GFR	(Estimated) glomerular filtration rate		
	GI	Gastrointestinal	HbA1c	Glycated hemoglobin
	HDL	High-density lipoprotein	HF	Heart failure
	HFpEF	Heart failure with preserved ejection fraction		
	HFrfEF	Heart failure with reduced ejection fraction		
25	IB	Investigator brochure		
	ICD	Implantable cardioverter defibrillator		
	ICF	Informed consent form		
	ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use		
30	IEC	Independent ethics committee		
	IN	Investigator notification		
	IRB	Institutional review board		
	IRT	Interactive response technology		
	ITT	Intent-to-treat		
35	KCCQ	Kansas City Cardiomyopathy Questionnaire		

- (V)LDL (Very) low-density lipoprotein
 LFT Liver function test
 LVEF Left ventricular ejection fraction
 MACE Major cardiovascular events
 5 MAR Missing at random
 MI Myocardial infarction
 MMRM Model of repeated measures
 MRA Mineralocorticoid receptor antagonist
 NOAEL No observed adverse effect level
 10 NYHA New York Heart Association
 OAD Anti-diabetic drug
 OC/RDC Oracle Clinical/Remote Data Capture
 PCI Percutaneous coronary intervention
 PGIS Patient Global Impression of Severity
 15 PK Pharmacokinetics
 PPD Premature patient discontinuation
 PPS Per protocol set
 (e)PRO (Electronic) patient reported outcomes
 PROMIS Patient-Reported Outcomes Measurement Information System
 20 RAN Randomized set
 RBC Red blood cell (count)
 RR Relative reduction
 SAE Serious adverse event
 SAF Safety set
 25 SBP Systolic blood pressure
 SCR Screened set
 SD Standard deviation
 SGLT(i) Sodium-glucose co-transporter (inhibitor)
 SU Sulfonylurea
 30 T2DM Type 2 diabetes mellitus
 TG Triglyceride
 TD Study treatment discontinuation
 TSH Thyroid-stimulating hormone
 UACR Urine albumin-to-creatinine ratio UGE Urinary glucose excretion
 35 ULN Upper limit of normal

UTI Urinary tract infection
WBC White blood cell (count)
WHO World Health Organization

5 Terms

- Control drug: Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
- Dosage: Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
- Enrollment: Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol).
- Epoch: A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up.
- Investigational drug: The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
- Medication pack number: A unique identifier on the label of each investigational drug package.
- Patient ID: A unique number assigned to each patient upon signing the informed consent
- Randomization number: A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
- Study drug/ treatment: Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy.
- Study Treatment Discontinuation (TD): When the patient permanently stops taking study treatment prior to the defined study treatment completion date.
- Variable: A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
- Withdrawal of consent: Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material.

Study objectives and endpoints

Primary objective

Determine the dose-response signal and assess the dose-response relationship of
5 LIK066 2.5mg, 10mg, and 50mg qd as measured by the change from baseline (BL) in
NT-proBNP relative to placebo after 12 weeks of treatment in T2DM patients with HF.

Secondary objectives

1. To evaluate the change from BL to 36 weeks in all LIK066 doses vs placebo on NT-
10 proBNP.

2. To evaluate safety (adverse events (AEs) and lab parameters) and tolerability of
LIK066 over 12 weeks and over 36 weeks for all patients.

15 Study design

This is a multi-center, randomized, double-blind, double-dummy, parallel-group study
evaluating the efficacy, safety and tolerability of 3 doses of LIK066 vs placebo and vs
empagliflozin.

20 Epoch 1 (screening)

Patients are screened at Visit 1 (see Figure 1). The screening period (Epoch1) takes up to 2
weeks. Patients meeting all eligibility criteria enter the run-in Epoch 2 at Visit 101. If
patients fail to meet one or more inclusion/exclusion criteria, they are re-screened once.

25 Epoch 2 (placebo run-in)

Patients meeting the eligibility criteria enter the placebo run-in (Epoch 2). During the 2
weeks duration of Epoch 2, patients receive single-blind placebo run-in medication. At Visit
101, the patients' volume status is assessed based on physical examination and laboratory
values and, if hypovolemic, corrected during the run-in.

30

Epoch 3 (treatment)

After the placebo run-in Epoch 2, eligible patients are randomized in a 1:1:2:2:2 ratio to one
of the following regimens at Visit 201 (randomization): LIK066 2.5mg qd at bedtime; LIK066
10mg qd at bedtime; LIK066 50mg qd at bedtime; Empagliflozin (up-titrated from 10mg qd

to 25mg qd after 2 weeks) in the morning; and Placebo LIK066 at bedtime/Placebo Empagliflozin in the morning.

At randomization, patients are stratified based on geographical region and the left ventricular ejection fraction (LVEF) measurement at Visit 101: < 45% versus $\geq$ 45%.

Following randomization, patients will attend study visits in Epoch 3 (12 weeks) for the evaluation of the short-term efficacy (change in NT-proBNP). During Epoch 3, patients take the study medication.

10 **Treatment of T2DM**

Patients continue their usual T2DM treatment. Patients taking sulfonylureas (SU) or insulin may be at an increased risk of hypoglycemia when LIK066 or empagliflozin is added, therefore reduction of the dose of the SU or insulin should be considered: A reduction by 50%, or as close to 50% as possible based on dose options available locally, of the dose of SUs for patients using such medication (either as monotherapy or in combination with other oral anti-diabetic drugs (OADs)) should be considered. In case of persistent deterioration in glycemic control, the concomitant background OAD should be initially escalated to the maximal approved dose, followed by addition of rescue medication when required. To limit the number of patients with early deterioration of glycemic control who would meet the FPG rescue criteria early after randomization an FPG randomization criterion.

For patients on insulin, initial dose reduction of the total daily insulin dose by 10% or more should be considered at the investigator's discretion based on patient's total daily dose and glycemic control. Due to the potential risk of ketoacidosis with SGLT2i, dose reduction in patients with HbA1c $\geq$ 8% may not be appropriate. In case of deterioration in glycemic control, insulin can be up-titrated.

Epoch 4 (treatment)

After completing the procedures required at the last study visit of Epoch 3 (Visit 301) patients continue in Epoch 4 the treatment they were allocated to in Epoch 3 for 24 weeks. Long-term efficacy (assessed by HbA1c, echocardiography and NT-proBNP), tolerability and safety parameters are evaluated.

Rationale for study design

The study is designed as a standard randomized, controlled, parallel-group study. A single-blind placebo run-in epoch (Epoch 2) is included to familiarize patients with the study drug intake schedule and correct hypovolemia (if diagnosed at Visit 101). The effect on NT-proBNP is evaluated after 12 weeks of treatment in Epoch 3, as well as after 36 weeks of the study (Epoch 4) to provide information about the longer-term effect of LIK066 on NT-proBNP, and on clinical and echocardiography parameters. Glycemic control is assessed after 12 and 36 weeks of treatment

Rationale for dose/regimen, route of administration and duration of treatment

LIK066 has been studied in multiple clinical trials with a variety of dosing regimens using either single or multiple daily doses at durations of up to 12 week in healthy subjects, patients with T2DM and obese patients. The pharmacokinetic half-life of LIK066 (approximately 16h) allows for once-daily LIK066 oral dosing, and significant pharmacodynamic effects such as 24 hour urinary glucose excretion (UGE24) and body weight have been observed in these populations. Pharmacodynamic data from phase I studies in patients with T2DM showed that the minimal tested dose, 2.5mg qd, resulted in 24 hour urinary glucose excretion (glucosuria) of approximately 37g, and is considered appropriate as the minimally effective dose in this study. Urinary glucose excretion over 24-hour plateaued at ~90g with doses $\geq$ 30mg qd. After 14 day once daily dosing at 15 mg in patients with T2DM, 24 hour UGE plateaued at ~100g. Since the objective is to find a dose with sub-optimal to optimal effect on SGLT1 and SGLT2 inhibition in the kidney, but with no or minimal gut effect to minimize the risk of diarrhea, LIK066 50mg qd is selected as the highest dose for this study. The 50mg dose represents a dose potentially at the maximal end of the UGE dose-response curve in patients with T2DM and would be suitable to be tested in this vulnerable population. Gastrointestinal (GI) tolerability was better with LIK066 30mg qd than with 150 mg qd. To minimize the risk of GI adverse effects of the SGLT1 inhibition in the gut such as diarrhea, the LIK066 dose will not be taken around mealtime; hence dose administration is recommended at bedtime. The 10mg dose is selected between the low and top dose in the study and to enable exploration of the shape of the dose-response curve.

Based on results from previous exploratory phase II studies in HF comparing sacubitril/valsartan with valsartan (e.g. LCZ696B2214; Solomon et al, 2012), treatment with LIK066 for a duration of 12 weeks would be expected to be sufficient in order to reveal a significant change in NT-proBNP. Twelve weeks after introducing an anti-diabetic treatment

is an accepted time point for initial evaluation of drugs' effect on glycemic control (HbA1c). The full duration of exposure of 36 weeks will provide data for parameters requiring longer follow-up to be evaluated (echocardiography) as well as safety data.

5 Rationale for choice of comparator

A placebo group is included to obtain efficacy, tolerability and safety data in an unbiased manner and to determine the dose-response characteristics of the investigational drug. An active comparator empagliflozin, which is approved in the treatment of T2DM to improve glycemic control, is included as a reference drug (Zinman et al, 2015). Empagliflozin has also shown CV benefit in T2DM patients in the EMPA-REG Outcome study. Considering that the mechanism leading to the CV benefit with empagliflozin currently remains unclear, the higher of the two approved doses in patients with T2DM, empagliflozin 25mg qd, was chosen as a comparator to potentially achieve a maximum effect on NT-proBNP. Choosing the higher of the two doses should not pose a safety concern, as no difference in the safety profile of empagliflozin 10 mg and 25 mg was reported in the EMPA REG Outcome study in patients with eGFR ≥ 30 ml/min/1.73m² (Fitchett et al, 2016), a cut-off value lower than the 45 ml/min/1.73m² in CLIK066B2204. In order to minimize potential adverse effects empagliflozin will be up-titrated from 10mg qd to 25mg qd after 2 weeks of treatment.

Benefits to participation in the study may include blood glucose reduction, weight reduction and, potentially, improvement in HF signs and symptoms, as well as in some cardio-metabolic markers such as NT-proBNP, blood pressure or lipids.

Population

The study population consists of male and female patients (≥ 18 years old) with type 2 diabetes and heart failure (heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF)). The goal is to randomize a total of approximately 496 patients in approximately 100 centers worldwide. Since a 25% screening failure rate and a 33% run-in failure rate is expected, approximately 1000 patients are screened.

Inclusion criteria

Patients eligible for inclusion in this study must fulfill all of the following criteria: 1. Written informed consent must be obtained before any assessment is performed; 2. Male or female outpatients, ≥ 18 years of age at Visit 1; 3. BMI ≥ 22 kg/m² at Visit 1; 4. Type 2 diabetes with

HbA1c between 7.0% and 10.0% at Visit 1; 5. Documented symptomatic chronic heart failure (NYHA II-IV) with at least one of the following symptoms at the time of Visit 1: (Dyspnea on exertion; Orthopnea; Paroxysmal nocturnal dyspnea; and Peripheral edema); 6. Plasma NT-proBNP > 400pg/ml at Visit 1; 7. Patients receiving ACEi, ARBs, MRAs, ARNi and/or β -blockers must be on a stable dose of these medications during the 1 month period prior to Visit 1; 8. Patients must be on diuretic therapy prior to Visit 1 (flexible dosing is permitted); 9. Controlled systolic BP defined as a target systolic BP less than 140mmHg; systolic BP up to and including 160mmHg if patient is on three or more medications to control BP, at randomization (Visit 201); 10. eGFR $\geq$ 45ml/min/1.73m² at Visit 1 (calculated by the Modification of Diet in Renal Disease formula (MDRD)); and 11. Serum potassium $\leq$ 5.2mM at Visit 1.

Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions are applied by the investigator, in order to ensure that the study population is representative of all eligible patients.

1. Use of other investigational drugs within 5 half-lives of Visit 1, or within 30 days, whichever is longer.
2. History of hypersensitivity to any of the study drugs or their excipients or to drugs of similar chemical classes.
3. History or current diagnosis of electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study such as: Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV -block without a pacemaker; History of familial long QT syndrome or known family history of torsades de pointes; and Atrial fibrillation with a resting heart rate >100 beats per minute (bpm).
4. Patients taking medications prohibited by the protocol.
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
6. Pregnant or nursing (lactating) women.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during

dosing of investigational drug. Basic contraception methods include: Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception; Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment; Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient; Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository; and Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If the above wording is not in line with specific country regulations, exclusion criteria for women of child-bearing potential is managed locally and in line with those regulations.

8. Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes (e.g. Cushing's syndrome or acromegaly-associated diabetes).
9. Use of SGLT2 inhibitors within 2 months of Visit 1, or between Visit 1 and Visit 201 (randomization).

10. Self-measured FPG > 12.2mM (220mg/dL) on two occasions in the week prior to randomization (Visit 201).
11. Ketoacidosis, lactic acidosis, or hyperosmolar coma within 6 months of Visit 1, or between Visit 1 and Visit 201 (randomization).
- 5 12. Symptomatic genital infection or UTI in the 4 weeks prior to Visit 1, or between Visit 1 and Visit 201 (randomization).
13. GI disorders associated with chronic diarrhea.
14. Myocardial infarction (MI), stroke, surgery for heart disease, percutaneous coronary intervention (PCI) in the 3 months prior to Visit 201 (randomization).
- 10 15. Unstable angina within 3 months of Visit 1, or between Visit 1 and Visit 201 (randomization).
16. Isolated right HF due to pulmonary disease.
17. Dyspnea and/or edema from non-cardiac causes, such as lung disease, anemia, or severe obesity.
- 15 18. Hemodynamically significant mitral and /or aortic valve disease.
19. Hemodynamically significant obstructive lesions of left ventricular outflow tract, including aortic stenosis.
20. Hypertrophic obstructive cardiomyopathy.
21. Secondary forms of cardiomyopathy such as restrictive cardiomyopathy or infiltrative cardiomyopathy (e.g., amyloid disease).
- 20 22. Patients with a history of any organ transplant or who were on a transplant list (life expectancy < 6 months at time of entry into the study).
23. Patients with a mean sitting systolic blood pressure $\leq$ 100mmHg, at randomization (Visit 201).
- 25 24. Patients with an implantable medical device (e.g. cardioverter defibrillator (ICD) that has discharged in the month prior to Visit 1).
25. Episode(s) of malignant ventricular tachycardia or any other types of severe arrhythmia producing significant hemodynamic consequences or considered life - threatening within 3 months of Visit 1.
- 30 26. Acute or chronic liver disease (except liver steatosis), such as hepatitis, cirrhosis or portal hypertension at Visit 1 or Visit 201 (randomization).
27. History of hepatitis B or C, or Hepatitis A or B vaccination in the last 3 months prior to Visit 1, or between Visit 1 and Visit 201 (randomization).
28. Active substance abuse, alcohol abuse (as defined by consumption of more than 24 alcohol units per week) and alcohol related history of disease within the past 2 years.
- 35

29. Chronic treatment with medication which has a hepatotoxic potential.
30. Chronic use of anti-retroviral therapies.
31. Chronic use of strong CYP3A4 inhibitors (e.g. clarithromycin, telithromycin, itraconazole, ketoconazole, voriconazole or posaconazole) or chronic use of strong uridine -5'- diphosphoglucuronosyltransferase (UGT) inhibitors (e.g. probenecid, valproic acid or mefenamic acid).
32. Concurrent medical condition that may interfere with the interpretation of efficacy and safety data.
33. Clinically significant thyroid stimulation hormone (TSH) level outside of the normal range at Visit 1.
34. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) more than three-fold above upper limit of normal ($>3 \times \text{ULN}$), or total bilirubin/direct bilirubin $> 1.5 \times \text{ULN}$ at Visit 1, confirmed by repeat measurement within 5 working days of the respective visit.
35. Hemoglobin $< 11\text{g/L}$ in men, $< 10\text{g/L}$ in women at Visit 1 (screening).
36. Platelet count $< 100,000/\mu\text{L}$ and/or white blood cell (WBC) count $< 4000/\mu\text{L}$ at Visit 1 (screening).
37. Hematuria determined by dipstick measurement at Visit 1 (screening).
38. Elevated fasting triglycerides (TG) $> 5.6\text{mM}$ (500mg/dL), at Visit 1 (screening), confirmed by repeat measurement within 3 working days of the respective visit.
39. Clinically significant laboratory abnormalities which, in the opinion of the investigator, cause the patient to be considered inappropriate for inclusion in the study.

Treatment arms

- 25 All patients entering Epoch 2 (run-in) receive single-blind placebo. At visit 201 (randomization), patients eligible for randomization are assigned to one of the following 5 treatment arms in Epoch 3 (treatment) in a ratio of 1:1:2:2:2: 2.5mg qd LIK066; 10mg qd LIK066; 50mg qd LIK066; 10mg qd empagliflozin up-titrated to 25mg qd after 2 weeks; and Placebo qd.

30

In Epoch 4 (Epoch 4 (treatment)), patients continue to receive the treatment they were assigned to in Epoch 3.

Treatment assignment and randomization

At Visit 201 (randomization) all eligible patients are randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate contacts the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT assigns a randomization number to the patient, which is used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number is not communicated to the user of the IRT system.

The randomization numbers are generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list is produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list is produced by or under the responsibility of Novartis drug supply management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s). The randomization scheme for patients is reviewed and approved by a member of the Novartis randomization group. Randomization is stratified according to geographical region and LVEF (< 45% versus $\geq$ 45% at Visit 101)).

Treatment blinding

Patients, investigator staff, Novartis study team, persons performing the assessments, and data analysts remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: 1. Randomization data are kept strictly confidential until the time of unblinding, and are not accessible by anyone else involved in the study with the following exceptions: the randomization codes associated with patients from whom PK samples are taken will be disclosed to PK analysts who will keep the PK results confidential until database lock and 2. The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. A double dummy design will be used as the identity of the study drugs cannot be disguised due to their different forms.

Unmasking will only occur in the case of patient emergencies, at the time of the Week 12 analysis and at the conclusion of the study.

The analysis group (statisticians/programmers), who are unmasked to perform the Week 12 analysis, are not involved in any study conduct activities related to the study Week 12 to Week 36 period (Epoch 4) after the unmasking. A separate analysis group, who does not have access to the analysis results and the identity of treatments at Week 12 analysis, performs the pre-planned final analysis at the end of the study.

The core study team (including the study leader(s), study physician and data manager), who are directly involved in study conduct activities during the study Week 12 to Week 36 period (Epoch 4), do not have access to the patient level data with identity of treatments such as patient listings at Week 12 analysis.

The Week 12 analysis results and the identity of treatments are not shared with the study site personnel until after the final database lock at the end of study.

15 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site, the first patient is assigned patient number 1, and subsequent patients/subjects are assigned consecutive numbers (e.g. the second patient is assigned patient number 2; the third patient is assigned patient number 3). The investigator or his/her staff contacts the IRT and provide the requested identifying information for the patient to register them into the IRT. For studies using eCRFs, only the assigned patient number must be entered in the field labeled "Patient ID" on the EDC data entry screen (e.g. enter '1', '2', etc.). Once assigned to a patient, the patient number is not reused. If the patient fails to be randomized for any reason, the IRT must be notified within 2 days that the patient was not randomized. The reason for not being randomized will be entered on the Screening Log, and the Demography eCRF is completed.

30 Dispensing the study drug

Each study site is supplied with study drug in packaging of identical appearance. The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the treatment arms. Investigator staff identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient,

investigator staff detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Handling of study treatment

- 5 Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are dispensed only in accordance with the protocol. Technical complaints are reported to the respective Novartis CPO Quality Assurance. Medication labels are in the local language and comply with the legal requirements of each country. They include storage conditions for the study treatment but no information about the patient except for the medication number. The investigator maintains an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability is performed by monitors during site visits or remotely and at the completion of the trial. Patients are asked to return all unused study treatment and packaging at each study visit and where applicable, at the time of discontinuation of study treatment.

- At the conclusion of the study, and as appropriate during the course of the study, the investigator returns all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

Instructions for prescribing and taking study treatment

- 25 The patients have to take study medication, 1 capsule in the morning, with or without food, and 1 tablet at bedtime. All prescribed dosages and all dose changes during the study are recorded on the appropriate study drug Dosage Administration Record eCRF. All kits of study treatment assigned by the IRT are recorded/databased in the IRT. During each study visit, the investigator should encourage compliance with study medication by instructing the patient to take the study drug exactly as prescribed to maintain the validity of the study and to optimize any potential effect of the study drug regimen. The patient is instructed to contact the investigator if he/she is unable for any reason to take the study drug regimen as prescribed.

- 35 **Permitted dose adjustments and interruptions of study treatment**

Investigational dose adjustments and/or interruptions are not permitted, unless done for safety reasons.

Rescue medication

- 5 During Epoch 3 and Epoch 4, rescue medication may be used in addition to ongoing study medication for those patients whose glycemic control is deteriorating. The patient must come in for an unscheduled visit to have a sample drawn for FPG & HbA1c measurement performed by the central laboratory if: Self-measured FPG on three consecutive occasions exceeds the limits in Table 5-1; and The FPG result from a blood sample analyzed at the
- 10 central laboratory exceeds the limits described in Table 1.

Table 1 Rescue criteria for FPG or HbA1c

Timeframe	Parameter	Value	Action
Between V201 (Randomization) and V204 (Week 8)	FPG	>240mg/dL (13.3mM)	Unscheduled visit for central lab parameter measurement.
Between V204 (Week 8) and V201 (Week 12)	FPG	>220mg/dL (12.2mM)	If elevation confirmed by central lab: background OAD to escalate to the maximum approved dose, followed by addition of insulin as per the investigator's discretion.
Between V301 (Week 12) and V309 (Week 36)	FPG	>200mg/dL (11.1mM)	
Between V201 (Week 12) and V309 (Week 36)	HbA1c	>8%	

- If the results confirm the exceeded limits, the background OAD should be initially escalated
- 15 to the maximal approved dose, followed by addition of rescue medication. Rescue medication, preferably insulin, should be used according to the local label and must be provided locally. Rescued patients will continue to participate in the study to allow for assessment of exposure and safety of LIK066. Use of rescue medication must be recorded on the Rescue Medication eCRF.

20

Concomitant medication

- The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions)
- 25 administered after the patient was enrolled into the study must be recorded in the Concomitant Medications/Surgical and Medical Procedures eCRF. Every effort should be made by the Investigator to keep the dose level of each patient's allowed background heart failure medications stable throughout the entire study duration. However; if the clinical condition of the patient warrants a change in any of these medications, it is allowed at the

discretion of the study Investigator. Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

5

Prohibited medication

Use of the treatments displayed in Table 2 is not allowed after patients have become eligible for participation into the study. At the latest, patients should stop using the medications listed in Table 2 at the start of Epoch 2.

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Table 2 Prohibited medication

Medication/product	Prohibition period	Action taken
St. John's wort (strong CYP3A inducer)	Entire study (from V1 until end-of-study)	Discontinue treatment during the screening period once patient is eligible for participation in the study.
SGLT inhibitors other than study medication	Entire study (and up to 2 months before Visit 1)	SGLTi has to be stopped immediately, otherwise the patients has to be discontinued from study medication

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Some medications or products must be used with caution: Use of grapefruit juice (strong inhibitor of CYP3A4) should be discouraged and its consumption must not happen within 2h of study medication intake; Use of antibiotic or antifungal medications that are strong inhibitors of CYP3A4 should be limited to 10 days during the study and must not be used at the time of randomization. Examples of such medications are clarithromycin, telithromycin, itraconazole, ketoconazole, voriconazole or posaconazole; and Use of UGT inhibitors such as probenecid, valproic acid or mefenamic acid should be limited to 10 days during the study and must not be used at the time of randomization.

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Emergency breaking of assigned treatment code

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Emergency code breaks are only undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator then receives details of the

investigational drug treatment for the specified patient and communication confirming this information. The system automatically informs the Novartis monitor for the site and the Study Team that the code has been broken.

- 5 It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT system at any time in case of emergency. The investigator provides the protocol number, the study drug name (if available) and the patient number.

10 In addition, oral and written information to the patient is provided on how to contact the investigator's backup in cases of emergency, or when the investigator is unavailable, to ensure that un-blinding can be performed at any time. Patients whose treatment has been unmasked must be discontinued from study treatment.

Study completion and post-study treatment

- 15 A patient is considered to have completed the study when the patient has completed the last planned visit (see Figures 2-5). The study as a whole is considered completed when all randomized subjects have completed the last visit planned in the protocol or have discontinued the study prematurely. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for
20 appropriate ongoing care.

Visit schedule and assessments

- Figures 2-5 list all of the study visits and assessments and indicates with an "X" when the assessments are performed. Patients must be seen for all visits on the designated day, or as
25 close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the eCRF.
30 Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Patient demographics/other BL characteristics

- Demographic and BL characteristics data collected on all randomized patients include: year
35 of birth, age, sex, race, ethnicity, relevant medical history/current medical conditions present

before signing informed consent including smoking and alcohol history. Where possible, diagnoses and notable symptoms are recorded. Investigators have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent form (ICF) signature.

5

Treatment exposure and compliance

Compliance is assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information is captured in the source documents at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. The site is also required to complete the appropriate Dosage Administration Record eCRF to record any study drug regimen changes or interruptions.

10

Efficacy**Weight and height**

Body weight is measured to the nearest 0.1kg at visits indicated in Figures 2-5 on a calibrated scale. The measurement is performed with the study patient in underwear and without shoes. Voiding before weight measurement is required. Height is measured at Visit 1 and is used to automatically calculate BMI.

15

NT-proBNP

NT-proBNP is measured from a blood sample obtained after an overnight fast (at least 8 hours after last evening food intake) at visits indicated in Figures 2-5 and analyzed at a central laboratory. NT-proBNP measured at Visit 1 is used for assessing an inclusion criterion and will not be masked. The results of all other NT-proBNP measurements remain masked until final database lock, except that they are extracted to a restricted area for the statistical/programming team to perform the analysis at the Week 12 database lock.

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Body composition

Body composition is measured in all patients using bio-impedance, except in patients where it is contra-indicated, e.g. those using an implantable cardioverter-defibrillator, at visits indicated in Figure 2. In about 25% of patients at participating sites, a DXA scan is performed at visits indicated in Figures 2-5. A whole body DXA scan is acquired to assess body composition (lean body mass, fat mass, visceral fat mass, body water (calculated); in addition bone mineral density (BMD) is assessed. The exam takes approximately 10-15 minutes and is non-invasive. In order to assure quality throughout the study, the DXA

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instrument manufacturer and model should remain consistent at a site and its calibration should be monitored. Use of a standardized scan acquisition protocol and appropriate and unchanging scan acquisition and analysis software is essential to achieve consistent results. In order to reduce variability in interpretation of the scans, centralized scan analysis are
5 done by experienced staff. DXA is performed according to the procedures described in the Imaging Manual. Prior to the examination, the patient is checked for absence of removable metal objects on his/her body, such as snaps, belts, underwire bras, jewelry, and so on. The patient is then positioned so that his/her body is straight on the mat and the site personnel must ensure that the positioning is consistent from scan to scan. A whole body array scan is
10 then initiated on the patient. Immediately after the whole body scan, a DXA scan is acquired to measure lumbar spine, hip and/or distal forearm bone mineral density. DXA data is transferred to a central reading vendor for independent review and analysis.

HF signs and symptoms

15 HF signs and symptoms are reviewed at visits indicated in Figures 2-5. The signs and symptoms evaluation may include paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit, and the results are entered in the appropriate eCRF.

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Echocardiography

Echocardiography is performed at visits indicated in Figures 2-5. A subset of a standard echocardiographic two-dimensional and Doppler examination are performed. The images are sent to a central reading vendor for independent review and analysis. An
25 Echocardiography Manual with detailed instructions and data transfer procedures is provided to the study sites. The following echocardiographic assessments are performed: Left ventricular ejection fraction (LVEF); Left ventricular end systolic volume (LESV); Left ventricular end diastolic volume (LEDV); Left atrial size and volume; Tricuspid regurgitation (TR) velocity; Left ventricular mass (LVM); Mitral inflow pulsed wave Doppler (E wave, A
30 wave); and Isovolumetric relaxation time (IVRT).

HbA1c

HbA1c is measured from a blood sample obtained at visits indicated in Figures 2-5 and analyzed using a National Glycohemoglobin Standardization Program (NGSP) certified
35 method at a central laboratory.

FPG

FPG is measured from a blood sample obtained after an overnight fast (at least 8h after last evening food intake) at visits indicated in Figures 2-5 and analyzed at a central laboratory.

5

Blood pressure (BP)

Arterial BP, pulse rate readings and signs and symptoms of orthostasis are assessed with an automated electronic BP device available at the study site. Three sitting BP measurements and one standing BP measurement are performed at visits indicated in

10 Figures 2-5. Every effort should be made to have the same staff member obtain BP measurements for a given patient, at the same time of day, using the same equipment, at each visit. Sitting BP and standing measurements must be performed prior to any procedure (e.g. blood draw) or medication intake. At Visit 1 (screening) BP must be measured at both arms. The arm with the higher SBP reading must be used for the BP measurements at Visit

15 1 and the same arm must be used at all subsequent visits. The arm used at each visit must be documented in the source documentation. The patient should be in a relaxed setting and measurements should not be taken immediately after exertion or the consumption of coffee. At each study visit, after the patient has been sitting for 5 minutes with the back supported and both feet placed on the floor, SBP and DBP are measured three times using the

20 automatic BP monitor and an appropriate size cuff. The bladder of the cuff should be large enough to encircle 80% of the arm. The cuff should be placed so its bottom is 1 to 2cm above the elbow and the arm should be supported so that the bottom of the cuff is at the level of the heart. The tube should run down the center of the arm, approximately in line with the middle finger. The patient is asked to relax his/her arm and turn the palm upward. The

25 patient should not speak or move their arm during the measurement deflation of the cuff. Three separate sitting BP should be obtained with a full two-minute interval between measurements and with the cuff fully deflated between measurements. The patient then stands, and after standing for two minutes, one BP measurement is taken. All 3 sitting BP measurements and the single standing measurement are recorded and documented in the

30 eCRF and in the patient's source documents. All 3 sitting BP readings are used for evaluation of sitting BP.

Fasting lipid profile

Fasting lipid profile and TGs as described in Table 3 is measured on blood samples obtained

35 after an overnight fast at visits indicated in Figures 2-5 and analyzed at a central laboratory.

Table 3 Fasting lipid profile & TG, hs-CRP

Category	Parameter(s)
Fasting lipid profile & TGs	TG, total cholesterol, HDL cholesterol, LDL cholesterol, calculated VLDL cholesterol and non-HDL cholesterol, lipoproteins (apolipoprotein A-I, apolipoprotein B) LDL cholesterol will be calculated if TG $\leq$ 400 mg/dL, if TG > 400 mg/dL then direct LDL cholesterol measurement will be done.
Inflammation biomarker	hs-CRP

24h urine collection

- 5 UGE, albumin, creatinine and sodium excretion are measured from a 24h urinary collection from about 25% of randomized patients at visits indicated in Figures 2-5 and analyzed at a central laboratory. UGE results after the baseline assessment are kept blinded until the final analysis, except that they are extracted to a restricted area for the statistical/programming team to perform the analysis at the Week 12 database lock. Bone biomarkers (urinary
- 10 calcium and phosphate excretion) and renal biomarkers (cystatin C/creatinine ratio) are measured from the same urine collection. Detailed instructions for urine collection is provided to patients, and handling of the urine sample is described in the laboratory manual. 24h urine collection is done by the patients at home; therefore no overnight stay at the site is required.

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Appropriateness of efficacy assessments

- N-terminal pro-brain natriuretic peptide (NT-proBNP) is a stable, biologically inert fragment cleaved from proBNP along with BNP. NT-proBNP is a marker of left ventricular wall stress. Elevated NT-proBNP levels are associated with adverse outcomes and reductions in NT-
- 20 proBNP levels have been associated with better outcomes in patients with HF (Masson et al 2006; Komajda et al 2011).

- Echocardiography, weight and body composition, BP and fasting lipids are standard measures to assess the efficacy of a drug used in HF patients. HbA1c and FPG inform about
- 25 the glucose lowering effect of the drug. UGE measurement allows for evaluation of LIK066's primary mode of action's contribution to potential improvement in glycemic control and HF parameters.

Data collection

- The trial is conducted in a fully validated Data Capture system which conforms to US CRF 21 Part 11 requirements. Investigator site staff are not given access to the system until they have been trained. Designated investigator staff enter the data required by the protocol into the Data Capture system. Automatic validation programs within the system check for data discrepancies in the eCRFs and by generating appropriate error messages, allow the data to be confirmed or corrected by the investigator staff. The investigator staff must certify that the data entered are complete and accurate. After database lock, the investigator receives copies of the patient data for archiving at the investigational site.
- Designated investigator staff enter the data required by the protocol into the OC/RDC system. Designated investigator site staff are not given access to the system until they have been trained. Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff.
- The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator receives copies of the patient data for archiving at the investigational site.

Database management and quality control

- Novartis staff (or CRO working on behalf of Novartis) review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

- Concomitant medications entered into the database are coded using the World Health organization WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical (ATC) classification system. Concomitant procedures, non-drug therapies and adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples are processed centrally and the results will be sent electronically to Novartis (or a designated CRO). ECG, echocardiography and DXA assessments are processed centrally and the results are sent electronically to Novartis (or a designated CRO).

5

Patients using electronic PROs fill in their PRO data in a site based tablet. The system is supplied by a vendor, who also manages the database. The database is sent electronically to Novartis personnel (or designated CRO). Where no electronic PROs are available, patients complete paper PROs.

10

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes are tracked using an Interactive Response Technology (IRT). The system is supplied by a vendor, who also manages the database. The database is sent electronically to Novartis (or a designated CRO).

15

Each occurrence of a code break via IRT is reported to the clinical team and monitor. The code break functionality remains available until study shut down or upon request of Novartis. The occurrence of relevant protocol deviations is determined. After these actions have been completed and the database has been declared to be complete and accurate, it is locked and the treatment codes are unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

20

Data analysis

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The main analysis is performed at the end of Epoch 3 when all patients complete their treatment and assessments for Epoch 3, and data collected up to and including week 12 (Visit 301) are cleaned (referred as "*Week 12 analysis*" in sections below). The study remains blinded. Data collected during Epoch 4 is analyzed based on the secondary objectives requiring data collection beyond Week 12 and complements the results from the Week 12 analysis. The analysis performed after study end is referred as "*End of study analysis*" in sections below. For both *Week 12 analysis* and *End of study analysis*, treatment group refers to LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd unless specified otherwise.

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Analysis sets

The following analysis populations is defined for statistical analysis. These analysis sets are subsets of the patients who signed the informed consent at Visit 1.

Screened set (SCR) – All patients who signed the informed consent. The SCR includes only unique screened patients, i.e., in the case of re-screened subjects only the chronologically last screening data is counted.

Randomized set (RAN) – All patients who received a randomization number, regardless of receiving trial medication.

Safety set (SAF) (double-blind phase) – All patients who received at least one dose of double-blind study drug. Patients are analyzed according to treatment received. Treatment received is considered identical to the randomized treatment if the patient has received at least one dose of the randomized treatment.

Full analysis set (FAS) – All patients in RAN who were not mis-randomized*. Following the intent-to-treat (ITT) principle, patients are analyzed according to the treatment they have been assigned to at the randomization. * Mis-randomized patients are those who have not been qualified for randomization and who have been inadvertently randomized into the study, but have not received double-blind study drug. Mis-randomized patients are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the patient's final randomization eligibility and double-blind medication was not administered to the patient. These patients were subsequently discontinued from the study.

Per protocol set (PPS) – All patients in FAS who took at least one dose of study medication and had no major protocol deviations.

Major protocol deviations are those ones affecting the primary endpoint analyses, and are pre-specified prior to un-blinding treatment codes for analyses. A list is provided in the Clinical Study Report Statistical Analysis Plan.

Patient demographics and other baseline characteristics

Summary statistics are provided by treatment group for demographics and baseline characteristics, including sex, age, race, weight, height, body mass index (BMI), systolic

blood pressure, diastolic blood pressure, eGFR, LVEF, LVEF group (< 45% versus $\geq$ 45%), geographical region, NYHA class and medical history. These summaries are performed for the FAS. Continuous variables are summarized using n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables are summarized using frequency and percentage.

Week 12 analysis

The duration of double-blind treatment exposure in Epoch 3 is summarized descriptively by treatment group (using n, mean, standard deviation, median, Q1, Q3, minimum and maximum) for the SAF. In addition, the number and percentage of patients is summarized by treatment group for duration category. Concomitant medications and prior significant non-drug therapies are summarized in separate tables by therapeutic class, preferred term and treatment group for the safety population. The number and percentage of patients meeting rescue criteria and taking rescue medication, and duration of exposure to rescue medication during Epoch 3 are summarized by treatment group for the SAF. The use of prohibited medication, if any, is also summarized.

End of study analysis

The analyses for *End of study analysis* is similar to the analyses performed for *Week 12 analysis* as described above, except that the summaries of treatments are provided for the overall study treatment duration: Epoch 3+Epoch 4.

Analysis of the primary variable(s)

In general, NT-proBNP data follows a log-normal distribution. Therefore a log-transformation on the NT-proBNP data is performed before all statistical analyses are carried out. The analysis results are then be back-transformed and displayed as percentages for ease of data interpretation.

Variable(s)

The primary efficacy variable is log-transformed ratio of NT-proBNP (pg/mL) collected at Week 12 to BL (i.e., change from BL in log-transformed NT-proBNP at Week 12). Missing Week 12 values are imputed using a multiple imputation approach.

Statistical model, hypothesis, and method of analysis

The objective of determination of a dose-response signal and dose-response relationship in LIK066 doses compared to placebo are evaluated using the Multiple Comparison Procedure-Modeling (MCP-MOD) method described in Pinheiro et al, 2006 & Pinheiro et al, 2014.

Test of the dose response signal

- 5 The null hypothesis of a flat dose-response relationship for the reduction in NT-proBNP compared to placebo is tested at a one-sided significance level of 2.5% against the alternative hypothesis of a dose-response relationship leading to a significant decrease in NT- proBNP after 12 weeks of treatment.
- 10 Hence, the following null and alternative hypotheses are tested: H01: there is no dose-response relationship or a dose response in the wrong direction for LIK066 after 12 weeks of treatment (i.e. the dose response relationship is flat, or as dose increases, there is less reduction in NT-proBNP from baseline); and H11: there is a dose-response relationship in the right direction for LIK066 after 12 weeks of treatment (i.e. as dose increases, there is
- 15 more reduction in NT-proBNP from baseline).

- There are six candidate models to capture the shape of the dose response relationship for LIK066 at Week 12 endpoint. The candidate models generate a set of six contrasts which are evaluated using the data to test the above dose-response hypothesis: Model 1:
- 20 Emax with ED50 at 3mg; Model 2: Emax with ED50 at 10mg; Model 3: Emax with ED50 at 25mg; Model 4: linear; Model 5: sigmoid Emax with ED50 at 15mg and hill parameter h=2; and Model 6: sigmoid Emax with ED50 at 25mg and hill parameter h=3.

- The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA)
- 25 model with the log-transformed ratio of NT-proBNP (pg/mL) at Week 12 to baseline as a response variable, treatment (placebo and all LIK066 doses), stratification variables geographical region and LVEF (< 45% versus $\geq$ 45% at Visit 101) as factors, and the baseline in log-transformed NT-proBNP as a covariate. As needed, centers are pooled according to country and region for the purpose of analysis.

- 30 The response variable of log-transformed ratio of NT-proBNP (pg/mL) at Week 12 to baseline used in the above ANCOVA is from an imputed dataset, where the missing Week 12 NT- proBNP is imputed using the multiple imputation method. In order to account for the imputation uncertainty, this ANCOVA model is repeated for each imputed dataset, which
- 35 results in a set of least squares (LS) mean estimates for all dose groups and the related

covariance matrices. Rubin's rule will be used to combine the multiple sets of LS mean estimates and the related covariance matrices to a single set of LS mean estimates of log-transformed ratio of NT-proBNP (pg/mL) at Week 12 to baseline for all dose groups and the related covariance matrix.

5

The optimal contrasts derived from the candidate model sets are applied to the combined estimated dose means and covariance matrix to obtain the t statistics for each candidate model and the common critical value C0.025. C0.025 is the common critical value derived from the reference multivariate t-distribution with the 6x6 correlation matrix induced by testing the candidate dose response models with respect to comparing all LIK doses to placebo group. The H01 will be rejected and the statistical significance of dose-response in NT-proBNP reduction is established if the $\max(t_1, t_2, t_3 \dots t_6) \geq C0.025$.

10

Model averaging to obtain the dose response

The response data in each imputed data set, including relevant covariates, is used to fit the models in the candidate set. The estimated dose-response is derived by using model averaging methods on a subset of candidate models, for which the associated contrast tests are statistically significant. If there are more than three candidate models that are statistically significant, the top three models with largest t-statistics as calculated above are selected as basis for the model averaging.

20

Model averaging is carried out for each imputed data set, and the resulting mean efficacy estimates and confidence intervals are derived using the combination variance that accounts for the uncertainty of the imputed data using Rubin's combination rules. Comparisons between LIK066 doses and placebo are simultaneously derived for the model averaged estimates together with confidence intervals reflecting the imputation procedure applied. The model- averaging-based estimates of mean changes in log-transformed NT-proBNP within each dose group mean differences between LIK066 and placebo and their confidence intervals are then back-transformed and displayed as ratios of NT-proBNP geometric mean at Week 12 to baseline within dose group, and relative rate of these ratios between LIK066 and placebo. Target dose selection is based on the model averaged dose response estimates of mean NT-proBNP reduction efficacy of LIK066 over the dose range studied in the study.

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35 Handling of missing values/censoring/discontinuations

Missing data for the primary endpoint is imputed using a multiple imputation approach assuming that the missingness mechanism is retrieved from observed data (missing at random (MAR)). The imputation model includes the longitudinal sequence of NT-proBNP data collected at baseline, Week 4 and Week 12 visits, stratification factors geographical region and LVEF at Visit 101 ($< 45\%$ versus $\geq 45\%$), and other baseline covariates (e.g. NYHA class, age, gender, race).

Supportive analyses

As a sensitivity analysis, the dose-response modeling is conducted for the PPS. Results based on the single best dose response model fit are also reported. Summary statistics for NT-proBNP are presented by visit (up to and including week 12 visit) and treatment for observed and imputed values. The summary statistics (n, mean, standard deviation (SD), and median, Q1, Q3, minimum and maximum) are presented by visit and treatment for NT-proBNP and change from BL in NT-proBNP. Figures are produced to visually show the raw and the imputed mean changes by visit over 12 weeks of Epoch 3 for each treatment group, for all patients and by LVEF group ($< 45\%$ vs. $\geq 45\%$ at V101).

In addition, summary statistics for the NT-proBNP are presented by visit (up to and including week 12 visit) and treatment for observed and imputed values, by the following subgroups: LVEF at Visit 101 $< 45\%$ vs. $\geq 45\%$; NYHA class at baseline: II vs. III&IV; HbA1c at baseline: $< 8\%$ vs. $\geq 8\%$; and NT-proBNP at baseline: $< \text{median}$ vs. $\geq \text{median}$.

Efficacy variables

For the comparison of LIK066 doses vs. placebo *and* LIK066 doses vs. empagliflozin (EMPA) at Week 12 and Week 36: Change from BL in HbA1c; Change from BL in FPG; Change from BL in SBP and DBP; Change from BL in weight; Change from BL in body composition (assessed by bio-impedance); Change from BL in body composition (assessed by DXA in a subset of patients); Percentage change from BL in fasting lipid profile (TG, total cholesterol, HDL cholesterol, LDL cholesterol, calculated VLDL cholesterol and non-HDL cholesterol, lipoproteins (apolipoprotein A-I, apolipoprotein B)); Change from BL in log-transformed hs-CRP; Change from BL in 24h urinary glucose and sodium excretion (in a subset of patients); For the comparison of LIK066 doses vs. placebo at Week 12 and Week 36; Change from BL in left atrial size and volume assessed by echocardiography; and Change from BL in NYHA class. For the comparison of LIK066 doses vs. placebo at Week 36: Change from BL in log-transformed NT-proBNP

Analysis of change from BL in log-transformed NT-proBNP at Week 36

The same dose-response modeling approach using MCP-Mod on the primary endpoint of change from BL in NT-proBNP at week 12 is used to evaluate the dose response in NT-proBNP change at BL to Week 36 for the LIK066 doses as compared to placebo. Summary statistics for NT-proBNP are presented by visit and treatment for observed and imputed values throughout the overall trial period. The summary statistics (n, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum) are presented by visit and treatment for the BL values, post-BL values and changes from BL in NT-proBNP. Figures are reproduced to visually show the raw and the imputed mean changes by visit for each treatment group, for all patients and by LVEF group (< 45% vs. ≥ 45% at V101).

Analysis of other continuous outcome variables

The following continuous variables are analyzed using the methods described in this section:

Change from BL in HbA1c at Week 12 and Week 36; Change from BL in FPG at Week 12 and Week 36; Change from BL in SBP and DBP at Week 12 and Week 36; Change from BL in weight at Week 12 and Week 36; Change from BL in body composition (assessed by bio-impedance) at Week 12 and Week 36; Percentage change from BL in fasting lipid profile (TG, total cholesterol, HDL cholesterol, LDL cholesterol, calculated VLDL cholesterol and non-HDL cholesterol, lipoproteins (apolipoprotein A-I, apolipoprotein B)) at Week 12 and Week 36; Change from BL in log-transformed hs-CRP at Week 12 and Week 36; and Change from BL in left atrial size and volume assessed by echocardiography at Week 12 and Week 36.

The change from baseline in a continuous outcome at Week 12 (or Week 36) is analyzed using a mixed effect model of repeated measures (MMRM) in which the stratification variables (geographical region and LVEF < 45% vs. ≥ 45% at V101), treatment group, visit, and treatment group-by-visit interaction are included as fixed-effect factors and baseline outcome variable will be included as a covariate, with a common unstructured covariance matrix for all treatment groups. The analysis is performed based on change from baseline in the outcome variable at all post-baseline scheduled visits up to Week 12 (or Week 36) and based on likelihood method with an assumption of MAR for missing data. Based on the MMRM model, the estimates and the 95% confidence intervals are provided for the adjusted means of the change from baseline in the outcome variable at Week 12 (or Week 36) for each treatment group, and for the adjusted mean difference at Week 12 (or Week 36).

For an outcome variable, the treatment effect (mean difference) of LIK066 doses vs. Placebo or LIK066 doses vs. empagliflozin are analyzed using the MMRM model as described above including all treatment groups: LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd. For the comparison of LIK066 doses vs. Placebo, the treatment effects of LIK066 2.5mg qd vs. Placebo qd, LIK066 10mg qd vs. Placebo qd and LIK066 50mg qd vs. Placebo qd will be presented; For the comparison of LIK066 doses vs. EMPA, the treatment effects of LIK066 2.5mg qd vs. Empagliflozin 25mg qd, LIK066 10gm qd vs. Empagliflozin 25mg qd and LIK066 50mg qd vs. Empagliflozin 25mg qd are presented. In addition, summary statistics (n, mean, SD, median, Q1, Q3, minimum and maximum, and geometric mean for log-transformed variables) for these variables are presented by visit and treatment.

Analysis of ordinal outcome variable

The change from BL in NYHA class at a given visit is a three-category ordinal variable (improved/unchanged/worsened) with the following definition: 1. Improved, if NYHA class decreases at least one level from BL; 2. Unchanged, if NYHA class is unchanged from BL; 3. Worsened, if NYHA class increases at least one level from BL. The NYHA class change from BL at Week 12 (or Week 36) is analyzed using a repeated measures proportional odds cumulative logit model in which the stratification factors (geographical region and LVEF < 45% vs. ≥ 45% at V101), treatment group, visit, and treatment group-by-visit interaction are included as fixed-effect factors, baseline NYHA class is included as a covariate, and patient is included as random effects. The analysis is performed based on change from baseline in NYHA class at all post-baseline scheduled visits up to Week 12 (or Week 36) and based on likelihood method with an assumption of MAR for missing data. The estimate and the 95% confidence interval is provided for the adjusted odds ratio at Week 12 (or Week 36) based on the longitudinal proportional odds cumulative logit model.

The treatment effect (odds ratio) of LIK066 doses vs. placebo is analyzed using the repeated measures proportional odds cumulative logit model as described above including all treatment groups: LIK066 2.5mg qd, LIK066 10mg qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd. For the comparison of LIK066 doses vs. Placebo, the treatment effects of LIK066 2.5mg qd vs. Placebo qd, LIK066 10gm qd vs. Placebo qd and LIK066 50mg qd vs. Placebo qd are presented. In addition, NYHA class will be summarized by visit and treatment group using frequency and percentage. A shift table is provided to summarize the

NYHA class shifting from BL to Week 12 (or Week 36) for *Week 12 Analysis* (or *End of Study Analysis*).

Pharmacokinetics

- 5 A listing of the PK concentrations is provided. Summary statistics of the PK concentrations are provided if feasible. Concentrations below lower limit of quantification (LLOQ) are treated as zero in summary statistics of concentration data.

PK/PD

- 10 Feasibility of PK/PD analyses is explored separately from the study.

Analysis of exploratory variables

- The exploratory variables are analyzed in the FAS. Statistical testing of hypotheses on the exploratory endpoints are performed at the two-sided 0.05 significance level without
15 adjustment for multiplicity.

Variables

- For the comparison of LIK066 doses vs. placebo *and* LIK066 doses vs. EMPA at Week 12 and Week 36: Change from BL in echocardiographic parameters other than left atrial size
20 and volume; Change from BL in quality of life (assessed by the Clinical Summary Score, Total Symptom Score and Overall Summary Score from the KCCQ; descriptive system and VAS from the EQ-5D-5L; SF-36 total score; and PROMIS for physical function and PGIS State). For the comparison of LIK066 doses vs. EMPA at Week 12 and Week 36: Change from BL in log-transformed NT-proBNP; Change from BL in left atrial size and volume
25 assessed by echocardiography; and Change from BL in NYHA class.

Analysis method

- The exploratory variables are analyzed according to the methods described in the Analysis method. The MMRM model is used for the continuous outcome variables, and the repeated
30 measures proportional odds cumulative logit model is used for the ordinal outcomes.

Analysis of change from BL in log-transformed NT-proBNP at Week 12 and Week 36

- The change from BL in log-transformed NT-proBNP at Week 12 and Week 36 is analyzed
35 using the MMRM method. The MMRM model will include the stratification variables

(geographical region and LVEF < 45% vs. $\geq$ 45% at V101), treatment group, visit, and treatment group-by-visit interaction as fixed-effect factors and baseline log-transformed NT-proBNP as a covariate, with a common unstructured covariance matrix for all treatment groups. The analysis is performed based on change from baseline in log-transformed NT-proBNP at all post-baseline scheduled visits up to Week 12 (or Week 26) and based on likelihood method with an assumption of MAR for missing data. Based on the MMRM model, the estimates and the 95% confidence intervals are provided for the adjusted means of the change from baseline in log-transformed NT-proBNP at Week 12 (or Week 36) for each treatment group, and for the adjusted mean difference at Week 12 (or Week 36).

The treatment effect (mean difference) of LIK066 doses vs. EMPA is analyzed using the MMRM model as described above including all treatment groups: LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd. For the comparison of LIK066 doses vs. EMPA, the treatment effects of LIK066 2.5mg qd vs. Empagliflozin 25mg qd, LIK066 10gm qd vs. Empagliflozin 25mg qd and LIK066 50mg qd vs. Empagliflozin 25mg qd are presented. The analysis results are back-transformed and displayed as percentages for ease of data interpretation.

Analysis of change from BL in echocardiographic parameters at Week 12 and Week 36

The change from BL in echocardiographic parameters at Week 12 and Week 36 are analyzed using the MMRM method. The treatment effect (mean difference) of LIK066 doses vs. EMPA or LIK066 vs. placebo is analyzed using the MMRM model as described above including all treatment groups: LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd. For the comparison of LIK066 doses vs. placebo, the treatment effects of LIK066 2.5mg qd vs. Placebo qd, LIK066 10gm qd vs. Placebo qd and LIK066 50mg qd vs. Placebo qd are presented; For the comparison of LIK066 doses vs. EMPA, the treatment effects of LIK066 2.5mg qd vs. Empagliflozin 25mg qd, LIK066 10gm qd vs. Empagliflozin 25mg qd and LIK066 50mg qd vs. Empagliflozin 25mg qd are presented.

Analysis of change from BL in NYHA class at Week 12 and Week 36

The treatment effect (odds ratio) of LIK066 doses vs. EMPA is analyzed using the same repeated measures proportional odds cumulative logit model, including all treatment groups: LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo

qd. For the comparison of LIK066 doses vs. EMPA, the treatment effects of LIK066 2.5mg qd vs. Empagliflozin 25mg qd, LIK066 10gm qd vs. Empagliflozin 25mg qd and LIK066 50mg qd vs. Empagliflozin 25mg qd are presented.

5 **Analysis of change from BL in quality of life at Week 12 and Week 36**

The following quality of life assessments are continuous variables: Clinical Summary Score, Total Symptom Score and Overall Summary Score from the KCCQ, EQ VAS (from EQ-5D-5L), PROMIS for physical function and SF-36 total score. Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) are provided by visit and
10 treatment group for the measurement at each visit and change from baseline values (up to Week 12 or Week 36) for these continuous variables. The following quality of life assessments are ordinal variables: PGIS state and EQ-5D-5L descriptive system. These variables are summarized by visit and treatment group using frequency and percentage. Shift tables are also provided to summarize the endpoint shifting from BL to Week 12 (or
15 Week 36) for Week 12 Analysis (or End of Study Analysis).

Regulatory and ethical compliance

This clinical study is designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with
20 applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

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Listing of Claims:

1. A method for the treatment or prevention of heart failure in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of LIK066, or a pharmaceutically acceptable salt thereof.
- 5 2. The method of claim 1, wherein 2.5 mg of LIK066 is administered.
3. The method of claim 1, wherein 10 mg of LIK066 is administered.
- 10 4. The method of claim 1, wherein 50 mg of LIK066 is administered.
5. The method according to any one of claims 1-4, wherein LIK066 is administered once a day.
- 15 6. The method according to any one of claims 1-5, wherein LIK066 is administered at bedtime.
7. The compound LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.
- 20 8. A pharmaceutical composition comprising LIK066, or a pharmaceutically acceptable salt or prodrug thereof, for use in the treatment or prevention of heart failure.
9. Use of LIK066, or a pharmaceutically acceptable salt or prodrug thereof, the
- 25 treatment or prevention of heart failure.
10. Use of LIK066, or a pharmaceutically acceptable salt or prodrug thereof, in the manufacture of a medicament for use in the treatment or prevention of heart failure.

Figure 1. STUDY DESIGN

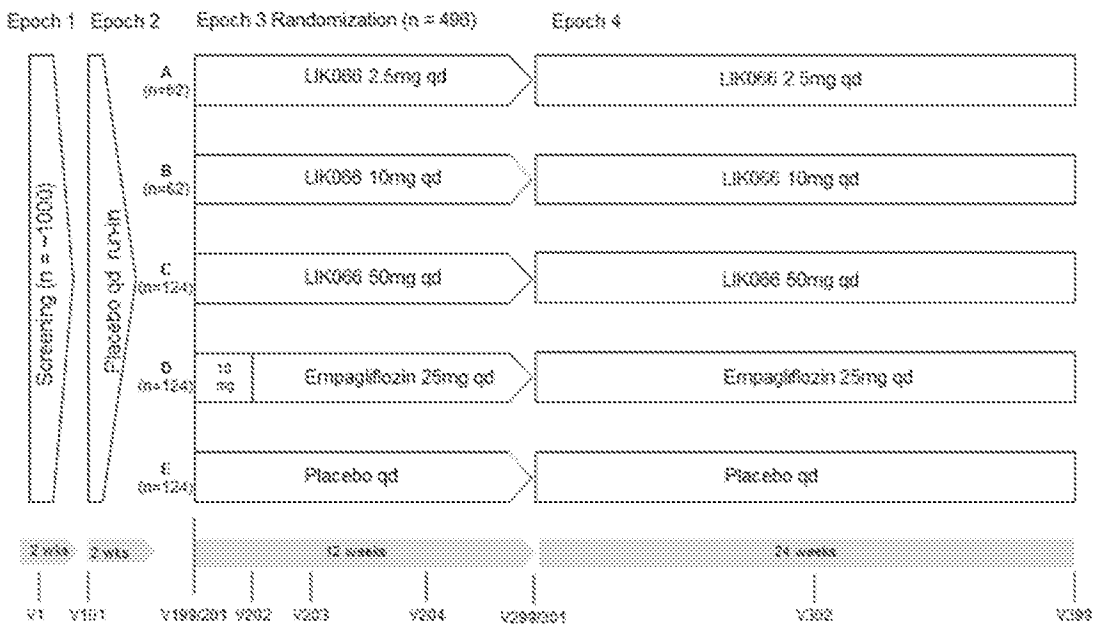


Figure 2. Assessment schedule

Epoch	1			2			3				4		
Visit	1 Screen	191 Run-in	198 1D/ PPD	201 RND/ BL	202	203	204	206 1D/ PPD	201	202	203 1D/ PPD	204	205
Week	-4	-2	0	2	4	6	8	12	14	16	18	20	22
Screening assessments													
Informed consent	X												
Inclusion/exclusion (Section 4)	X		X*	X*									
Patient demographics (Section 5.2)	X												
Medical history	X												
Medical history: protocol related S, Heart Failure/Diabetes	X			X*									
Smoking & alcohol history (Section 6.2)	X												
Efficacy													
Height (Section 6.4.1)	X												
Weight / BMI (Section 6.4.1)	X ^a	X		X	X	X	X	X	X	X	X	X	X
NT-proBNP (Section 6.4.2)	X			X ^b		X ^b		X ^b	X ^b	X ^b	X ^b	X ^b	X ^b
Body composition: bio-impedance (see Section 6.4.3)				X				X	X	X	X	X	X
HFr signs and symptoms with HFrA classification (see Section 6.4.4)	X	X		X	X	X	X	X	X	X	X	X	X
Echocardiography (see Section 6.4.5)		X							X ^c	X ^c	X ^c	X ^c	X ^c
HRa1n (Section 6.4.6)	X			X				X	X	X	X	X	X
PPD (Section 6.4.7)	X			X				X	X	X	X	X	X
Blood pressure (Section 6.4.8)	X	X		X	X	X	X	X	X	X	X	X	X
Fasting lipid profile, hsCRP (Section 6.4.9)				X				X	X				X

Figure 3. Assessment schedule

[illegible]

Figure 4. Assessment schedule

[illegible]

Figure 5. Assessment schedule

Serum Event	
Serum creatinine increase 25 -- 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase $\geq$ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria $\geq$ 1+ Albumin- or Protein-creatinine ratio increase $\geq$ 2-fold Albumin-creatinine ratio (ACR) $\geq$ 30 mg/g or $\geq$ 3 mg/mmol; Protein-creatinine ratio (PCR) $\geq$ 150 mg/g or $>$ 15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick hematuria $\geq$ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
<u>Document contributing factors in the CRF:</u> co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with $\pm$ 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm$ 50% variability over last 6 months.	

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/052497

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/7048 A61P9/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

6 July 2018

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/052497

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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International application No

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