
Global Clinical Development - General Medicine

LIK066

Clinical Trial Protocol CLIK066B2204 / NCT03152552

**A multi-center, randomized, double-blind, parallel-group
dose-finding study to assess the effect of 3 doses of
LIK066 compared to placebo or empagliflozin in type 2
diabetes mellitus patients with heart failure**

Document type: Clinical Trial Protocol Amendment
EUDRACT number: 2016-003084-19
Version number: v02 (clean)
Clinical trial phase: IIa
Release date: 04-Feb-2018

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Table of contents

Table of contents	2
List of tables	5
List of figures	6
List of abbreviations	7
Glossary of terms.....	9
Amendment 2	10
Amendment 1	12
Protocol summary.....	14
1 Introduction	19
1.1 Background.....	19
1.2 Purpose	20
2 Study objectives and endpoints	20
2.1 Primary objective.....	20
2.2 Secondary objectives	20
[REDACTED]	21
3 Investigational plan	21
3.1 Study design.....	21
3.1.1 Epoch 1 (screening).....	21
3.1.2 Epoch 2 (placebo run-in).....	22
3.1.3 Epoch 3 (treatment).....	22
3.1.4 Epoch 4 (treatment).....	23
3.2 Rationale for study design	23
3.3 Rationale for dose/regimen, route of administration and duration of treatment....	24
3.4 Rationale for choice of comparator	24
3.5 Purpose and timing of interim analysis	25
3.6 Risks and benefits	25
4 Population.....	27
4.1 Inclusion criteria	27
4.2 Exclusion criteria	27
5 Treatment.....	30
5.1 Study treatment.....	30
5.1.1 Investigational and control drugs	30
5.1.2 Additional treatment.....	31
5.2 Treatment arms	31
5.3 Treatment assignment and randomization	31

5.4	Treatment blinding.....	32
5.5	Treating the patient	33
5.5.1	Patient numbering	33
5.5.2	Dispensing the study drug.....	33
5.5.3	Handling of study and additional treatment	33
5.5.4	Instructions for prescribing and taking study treatment.....	34
5.5.5	Permitted dose adjustments and interruptions of study treatment	34
5.5.6	Rescue medication	34
5.5.7	Concomitant medication	35
5.5.8	Prohibited medication	35
5.5.9	Emergency breaking of assigned treatment code.....	36
5.6	Study completion and discontinuation.....	37
5.6.1	Study completion and post-study treatment.....	37
5.6.2	Discontinuation of study treatment	37
5.6.3	Withdrawal of informed consent.....	38
5.6.4	Lost to follow-up.....	38
5.6.5	Early study termination by the sponsor.....	39
6	Visit schedule and assessments	39
6.1	Information to be collected on pre-screening failures or screening failures	44
6.2	Patient demographics/other BL characteristics	44
6.3	Treatment exposure and compliance	44
6.4	Efficacy.....	45
6.4.1	Weight and height	45
6.4.2	NT-proBNP	45
6.4.3	Body composition	45
	46
6.4.5	Echocardiography	46
6.4.6	HbA1c	46
6.4.7	FPG	46
6.4.8	Blood pressure (BP)	47
6.4.9	Fasting lipid profile	47
6.4.10	24h urine collection.....	48
6.4.11	Appropriateness of efficacy assessments	48
6.5	Safety	48
6.5.1	Physical examination	48
6.5.2	Vital signs.....	49

9.4.4	Supportive analyses.....	67
9.5	Analysis of secondary variables	68
9.5.1	Efficacy variables.....	68
9.5.2	Safety variables	71
		71
9.5.4	DNA	71
		71
		72
		72
		72
9.7	Interim analyses	74
9.8	Sample size calculation.....	74
10	Ethical considerations.....	75
10.1	Regulatory and ethical compliance.....	75
10.2	Informed consent procedures.....	75
10.3	Responsibilities of the investigator and IRB/IEC.....	76
10.4	Publication of study protocol and results.....	76
10.5	Quality Control and Quality Assurance.....	76
11	Protocol adherence	77
11.1	Protocol amendments.....	77
12	References	78
13	Appendix 1: Clinically notable laboratory values and vital signs	80
14	Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements	81
15	Appendix 3: Specific Renal Alert Criteria and Actions	83

List of tables

Table 5-1	Rescue criteria for FPG or HbA1c	35
Table 5-2	Prohibited medication	36
Table 6-1	Assessment schedule.....	40
Table 6-2	Fasting lipid profile & TG, hs-CRP	48
Table 6-3	Hematology evaluations.....	49
Table 6-4	Clinical chemistry	49
Table 6-5	Urinalysis	50
Table 6-6	Biomarkers	50

Table 7-1	Guidance for capturing the study treatment errors including misuse/abuse	59
Table 9-1	Power for detecting a significant dose response signal*	74
Table 9-2	Comparison of LIK versus placebo (at 2-sided alpha of 0.05)	75
Table 9-3	Comparison of LIK versus empagliflozin.....	75
Table 13-1	Vital signs notable range deviations	80
Table 14-1	Liver Event and Laboratory Trigger Definitions	81
Table 14-2	Follow Up Requirements for Liver Events and Laboratory Triggers ...	81
Table 15-1	Specific Renal Alert Criteria and Actions.....	83

List of figures

Figure 3-1	Study design	22
Figure 9-1	Dose-response curve of candidate models	66

List of abbreviations

ACE(i)	Angiotensin converting enzyme (inhibitor)
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin II receptor blocker
ARNi	Angiotensin receptor/neprilysin inhibitor
AST	Aspartate aminotransferase
AV	Atrioventricular
BL	Baseline
BMI	Body-mass index
BMD	Bone mineral density
BP	Blood pressure
CFR	US Code of Federal Regulations
CHF	Chronic heart failure
CRF	Case report/record form (paper or electronic)
CPO	Country pharma organization
CRO	Contract research organization
CV	Cardiovascular
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
FAS	Full analysis set
FDA	Food & Drug Administration
FPG	Fasting plasma glucose
GCP	Good clinical practice
(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
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
IEC	Independent ethics committee
IN	Investigator notification

IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
██████	██
(V)LDL	(Very) low-density lipoprotein
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MACE	Major cardiovascular events
MAR	Missing at random
MI	Myocardial infarction
MMRM	Model of repeated measures
MRA	Mineralcorticoid receptor antagonist
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
OAD	Anti-diabetic drug
OC/RDC	Oracle Clinical/Remote Data Capture
PCI	Percutaneous coronary intervention
██████	██
██████	████████████████████
PPD	Premature patient discontinuation
PPS	Per protocol set
(e)PRO	(Electronic) patient reported outcomes
██████	██
RAN	Randomized set
RBC	Red blood cell (count)
RR	Relative reduction
SAE	Serious adverse event
SAF	Safety set
SBP	Systolic blood pressure
SCR	Screened set
SD	Standard deviation
SGLT(i)	Sodium-glucose co-transporter (inhibitor)
SU	Sulfonylurea
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
ULN	Upper limit of normal
UTI	Urinary tract infection
WBC	White blood cell (count)
WHO	World Health Organization

Glossary of 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 study 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

Amendment 2

Amendment rationale

The protocol is being amended to provide the option for patients to be pre-screened for certain laboratory parameters (NT-proBNP, HbA1c, eGFR, serum potassium) assessed by the central laboratory before patients enter the study at screening (Visit 1). This measure is expected to significantly decrease the number of screen failure patients which will reduce the burden on many patients, who otherwise have to undergo the full range of screening assessments but do not qualify for the study.

In addition, sites are allowed to use their own weight scales in case where patients exceed the weight limits of the bio-impedance/weight scales provided by the sponsor.

It was clarified that if an echocardiography LVEF result from Visit 101 (placebo run-in) assessed by central reading is not available in time for randomization and stratification at V201, the echocardiography from Visit 101 can also be read locally by a cardiologist so the most recent LVEF result can be used for stratification.

It was also clarified that, as different calibrated models of the bio-impedance scales are being provided by the sponsor (according to availability in different countries), not all body composition parameters can be assessed by all bio-impedance scale models.

Changes to the protocol

In [Section 3.1](#) the option for pre-screening was added and the process explained.

[Figure 3-1](#) was updated to include the optional pre-screening into the study design.

In [Section 3.1.3](#) local reading of the V101 echocardiography by a local cardiologist was allowed to obtain LVEF result for stratification.

In [Section 4](#) the expected number of participating centers was updated.

In [Section 4.2](#) it was clarified that the time point for excluding atrial fibrillation is Visit 1.

[Section 5.5.1](#) , [Table 6-1](#) and [Section 6.1](#) were updated to reflect optional pre-screening.

In [Section 6.4.1](#) it was clarified that in exceptional cases sites can use their own scales for weight measurements.

In [Section 6.4.2](#) it was clarified that NT-proBNP measurements do not require fasting blood samples.

In [Section 6.4.3](#) it was clarified that not all body composition parameters can be assessed by all models of bio-impedance scales used in this study.

In [Section 6.4.8](#) it was clarified that the mean of the three sitting BP readings at V201 will be used to assess eligibility for the study.

[Section 7.1](#) and [Section 7.2.2](#) were updated to clarify that from patients attending the pre-screening, certain SAEs will be collected after the patients have signed the pre-screening informed consent form.

Throughout the protocol amendment it was clarified whether the term “informed consent/ICF” refers to the pre-screening informed consent, to the study informed consent or to both.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

Changes described in this amended protocol are substantial and require IRB/IEC approval prior to implementation.

Amendment 1

Amendment rationale

The protocol was amended to provide information related to a new risk identified from data of the SGLT-2 inhibitor canagliflozin where more cases of lower limb amputations (mainly of the toe) have been observed in the canagliflozin group compared to the placebo group. No lower limb amputations have been seen in LIK066 studies, but this risk could constitute a possible class-effect. Patients with a history of lower limb amputation or with diabetic foot ulcer are excluded from enrollment into the study.

In addition, the inclusion criterion for NT-proBNP has been lowered from >400 to >300 pg/mL. When designing initially the study protocol, a NT-proBNP value of >400 pg/mL was selected to make a patient eligible for the study. This was based on the experience and results from the PARAMOUNT study, which included patients with chronic HF and preserved left ventricular ejection fraction (LVEF) (Solomon et al, 2012). Based on more recent guidelines defining patients with preserved LVEF by NT-proBNP >125 pg/mL, (Ponikowski et al, 2016), the NT-proBNP value to qualify patients for this study was changed to >300 pg/mL, as this cut-off has a robust predictive value to identify chronic HF patients with preserved LVEF (Bay et al, 2003).

The inclusion criterion for serum potassium has been changed from ≤ 5.2 mM to ≤ 5.3 mM in order to be in line with the reference range used by the Central laboratory in this study.

The HbA1c inclusion criterion has been modified from 7.0% - 10.0% to 6.5% - 10.0% in order to allow for exploration of LIK066 effects in the group of patients with HbA1c 6.5% - 7.0%.

For safety reasons, patients with any history of ketoacidosis, lactic acidosis, or hyperosmolar coma are excluded from enrollment into the study.

Furthermore, some minor changes and corrections of inconsistencies and typographical errors have been done.

Changes to the protocol

Section 3.1 has been amended regarding the duration of Epoch 1 and Epoch 2, as these epochs are now approximately 2 weeks. Also clarification with regards to missing LVEF results at randomization has been added, to also allow previous LVEF results for stratification; this was also updated in several other sections of the protocol. In addition, examples have been provided under which circumstances laboratory re-tests can be done.

Section 3.6 has been updated to add a newly identified risk (lower limb amputation) observed with the SGLT-2 inhibitor canagliflozin and preventive measures are provided; this was also updated in other sections of the protocol (e.g. Section 6.5.1).

In Section 4 the number of expected study centers was updated.

In Section 4.1 the inclusion criterion for NT-proBNP was changed from 400 to 300 pg/mL, for serum potassium from ≤ 5.2 mM to ≤ 5.3 mM and for HbA1c from 7.0% - 10.0% to 6.5% - 10.0%.

Section 4.2 was changed to also exclude any history of ketoacidosis, lactic acidosis or hyperosmolar coma. Furthermore, a typo was corrected with regards to the units for

hemoglobin, and in addition history of lower limb amputation and diabetic foot ulcer were added to the exclusion criteria.

[Section 5.5.4](#) was updated to clarify the time point when patients should take their medication on study visit days.

In [Section 5.6.2](#) diabetic foot ulcer and lower limb amputation were added as conditions when study treatment has to be discontinued. It was also clarified, that patients who discontinue study medication during Epoch 3 should be followed-up until they discontinue the study at the end of Epoch 3.

[Table 6-1](#) was revised to clarify the time when the first glycemia diary has to be dispensed to the patients and also to clarify when the diaries will be reviewed.

In [Section 6.4.1](#) it is explained, that indoor clothing is also acceptable for weight measurements.

[Section 6.4.2](#) was corrected to state that NT-proBNP results will be blinded after randomization.

In [Section 6.4.7](#) the definition of overnight fast was updated.

[Section 6.4.8](#) has been amended to clarify that also BP devices can be used, which are not automated electronic BP devices and also to clarify the order of assessments.

[Sections 6.4.10](#) and [Table 6-6](#) have been amended to update the renal biomarker parameters measured by the central laboratory.

In [Section 6.5.3.3](#) it was explained that urine dipstick for hematuria can be re-tested.

In [Section 6.5.5](#) it was clarified that 3 DXA scans are needed for BMD.

In [Section 7.8.2](#) some corrections and explanations for the use and the dispensation of the glycemia study diary were provided.

In [Section 9](#) some minor clarifications and corrections were done with regards to the data analysis.

Protocol summary

Protocol number	CLIK066B2204
Title	A multi-center, randomized, double-blind, parallel-group dose-finding study to assess the effect of 3 doses of LIK066 compared to placebo or empagliflozin in type 2 diabetes mellitus patients with heart failure
Brief title	A dose finding study to assess the effect of LIK066 compared to placebo or empagliflozin in patients with type 2 diabetes mellitus and heart failure
Sponsor and Clinical Phase	Novartis, Phase 2a
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Evaluate the efficacy, safety and tolerability of LIK066 in T2DM patients with cardiac disease and HF to help inform decisions on further development of LIK066
Primary Objective(s)	To determine the dose-response signal and assess the dose-response relationship of three dose regimens of LIK066 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	<ol style="list-style-type: none"> To evaluate the effect of all LIK066 doses vs placebo at 12 weeks and 36 weeks on: <ul style="list-style-type: none"> Change from BL in glycated hemoglobin (HbA1c) Change from BL in fasting plasma glucose (FPG) Change from BL in weight Change from BL in body composition (bio-impedance in all patients where appropriate and dual-energy x-ray absorptiometry (DXA) in a subset of patients) Change from BL in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) Change from BL in the fasting lipid profile and hsCRP Change from BL in 24h urinary glucose and sodium excretion, in a subset of patients Change from BL in left atrial size and volume assessed by echocardiography Change from BL in NYHA class To evaluate the effect of all LIK066 doses vs empagliflozin at 12 weeks and 36 weeks on: <ul style="list-style-type: none"> Change from BL in HbA1c

	<ul style="list-style-type: none"> • Change from BL in FPG • Change from BL in weight • Change from BL in body composition (bio-impedance in all patients where appropriate and DXA in a subset of patients) • Change from BL in sitting SBP and DBP • Change from BL in the fasting lipid profile and hsCRP • Change from BL in 24h urinary glucose and sodium excretion, in a subset of patients <p>3. To evaluate the change from BL to 36 weeks in all LIK066 doses vs placebo on NT-proBNP.</p> <p>4. To evaluate safety (adverse events (AEs) and lab parameters) and tolerability of LIK066 over 12 weeks and over 36 weeks for all patients</p> <p>5. To evaluate 24h urinary calcium and phosphate excretion after 12 weeks and after 36 weeks in a subset of patients</p> <p>6. To evaluate bone mineral density in a subset of patients</p>
Study design	Multi-center, randomized, double-blind, double-dummy, parallel-group dose-finding study to assess efficacy, tolerability and safety of LIK066 versus placebo or empagliflozin. Patients can be pre-screened for certain laboratory parameters. Following a screening visit, eligible subjects will enter the run-in. After the run-in period, eligible subjects will be randomized and treated for 36 weeks. The total duration of the study is up to 40 weeks
Population	Approximately 496 female and male patients ≥ 18 years old
Key Inclusion criteria	<ul style="list-style-type: none"> • Male or female outpatients, ≥ 18 years of age • BMI $\geq 22\text{kg/m}^2$ • Type 2 diabetes with HbA1c between 6.5% and 10.0% • Documented symptomatic chronic heart failure (NYHA II-IV) • Plasma NT-proBNP $> 300\text{pg/ml}$ • Patients receiving ACEi, ARBs, MRAs, ARNi and/or β-blockers must be on a stable dose of these medications • eGFR $\geq 45\text{ml/min/1.73m}^2$ (calculated by MDRD)
Key Exclusion criteria	<ul style="list-style-type: none"> • Type 1 diabetes, monogenic diabetes, diabetes resulting from pancreatic injury, or secondary forms of diabetes

	<ul style="list-style-type: none"> • History of ketoacidosis, lactic acidosis, or hyperosmolar coma , or if occurring prior to randomization • Symptomatic genital infection or UTI within 4 weeks of screening • Myocardial infarction, stroke, surgery for heart disease, percutaneous coronary intervention within 3 months of randomization • Unstable angina within 3 months of screening • Isolated right HF due to pulmonary disease • Patients with a mean sitting systolic blood pressure \leq 100mmHg, at randomization • History of lower limb amputation (including toe amputation), or if occurring prior to randomization • Diabetic foot ulcer at screening, or before randomization
Study treatment	<ul style="list-style-type: none"> • LIK066 • Placebo • Empagliflozin
Efficacy assessments	<ul style="list-style-type: none"> • NT-proBNP • glycated hemoglobin (HbA1c) • fasting plasma glucose (FPG) • body weight • body composition (bio-impedance/dual-energy x-ray absorptiometry) • systolic blood pressure and diastolic blood pressure • fasting lipid profile and hsCRP • 24h urinary glucose and sodium excretion • left atrial size and volume assessed by echocardiography • NYHA class
Key safety assessments	<ul style="list-style-type: none"> • Physical examinations • Vital signs • Monitoring of laboratory markers in blood and urine • Electrocardiogram • Bone mineral density • AE monitoring • Liver & renal safety monitoring
Other assessments	<div style="background-color: black; width: 100%; height: 1.2em;"></div>

	<div style="background-color: black; width: 100%; height: 40px; margin-bottom: 10px;"></div> <ul style="list-style-type: none"> • AEs of special interest (hypoglycemia & ketoacidosis) <div style="background-color: black; width: 100%; height: 20px; margin-top: 10px;"></div>
Data analysis	<p>The primary efficacy variable is the 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). It will be analyzed using the Multiple Comparison Procedure-Modeling (MCP-MOD) method (Pinheiro et al, 2006 & Pinheiro et al, 2014).</p> <p>In the MCP step, the following hypotheses will be used to test the dose response signal:</p> <ul style="list-style-type: none"> • H_{01}: There is no dose-response relationship or there is 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). • H_{11}: There is a dose-response relationship in the right direction for LIK066 after 12 weeks of treatment (i.e. as dose increases, there is more reduction in NT-proBNP from baseline). <p>A set of the dose-response candidate models will be defined. In order to preserve the family-wise error rate at one-sided significance level of 2.5 %, the optimal contrasts derived from the model candidate set will be individually compared to the critical value derived using a multiplicity adjustment accounts for all tests of comparing LIK066 doses to placebo with the candidate models simultaneously. The rejection of the null hypothesis will be achieved using the maximum test statistic from each estimated contrast test in the candidate set.</p> <p>The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) 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%) as factors, and the baseline in log-transformed NT-proBNP as a covariate.</p> <p>In the MOD step, model averaging will be used to obtain the dose response estimates.</p> <p>Missing Week 12 values will be imputed using a multiple imputation approach under the assumption of missing at random.</p> <p>As a secondary endpoint, the dose-response of LIK doses versus placebo in the log-transformed ratio of NT-proBNP (pg/mL) at</p>

	<p>Week 36 will be analyzed similarly using the method described above for the primary endpoint.</p> <p>Other secondary endpoints, including the changes from BL in HBA1c, FPG, weight, left atrial size and volume (assessed by echocardiography) etc. at both Weeks 12 and 36 will be analyzed using a mixed effect model of repeated measures (MMRM) as appropriate.</p>
Key words	T2DM, heart failure, dose-finding, interventional study

1 Introduction

1.1 Background

Type 2 diabetes (T2DM) 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).

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

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 normo- 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 [Data on file].

SGLT1 receptors are also expressed in the heart, however their role is not fully understood. The current study is planned to explore the effect of the dual SGLT1/2 inhibitor LIK066 on the HF biomarker NT-proBNP in a T2DM population with compromised cardiac function, along with exploration of its glucose-lowering potential.

1.2 Purpose

The purpose of the study is to evaluate the efficacy, safety and tolerability of LIK066 in T2DM patients with cardiac disease and HF to help inform decisions on further development of LIK066.

2 Study objectives and endpoints

2.1 Primary objective

To determine the dose-response signal and assess the dose-response relationship of 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.

2.2 Secondary objectives

1. To evaluate the effect of all LIK066 doses vs placebo at 12 weeks and 36 weeks on:
 - Change from BL in glycated hemoglobin (HbA1c), see [Section 6.4.6](#).
 - Change from BL in fasting plasma glucose (FPG), see [Section 6.4.7](#).
 - Change from BL in weight, see [Section 6.4.1](#).
 - Change from BL in body composition (bio-impedance in all patients where appropriate and dual-energy x-ray absorptiometry (DXA) in a subset of patients, see [Section 6.4.3](#))
 - Change from BL in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP), see [Section 6.4.8](#).
 - Change from BL in the fasting lipid profile and hsCRP, see [Section 6.4.9](#).
 - Change from BL in 24h urinary glucose and sodium excretion, in a subset of patients, see [Section 6.4.10](#).
 - Change from BL in left atrial size and volume assessed by echocardiography, see [Section 6.4.5](#).
 - Change from BL in NYHA class, see [Section 6.4.4](#).
2. To evaluate the effect of all LIK066 doses vs empagliflozin at 12 weeks and 36 weeks on:
 - Change from BL in HbA1c, see [Section 6.4.6](#).
 - Change from BL in FPG, see [Section 6.4.7](#).
 - Change from BL in weight, see [Section 6.4.1](#).
 - Change from BL in body composition (bio-impedance in all patients where appropriate and DXA in a subset of patients, see [Section 6.4.3](#))
 - Change from BL in sitting SBP and diastolic blood pressure (DBP), see [Section 6.4.8](#).
 - Change from BL in the fasting lipid profile and hsCRP, see [Section 6.4.9](#).

- Change from BL in 24h urinary glucose and sodium excretion, in a subset of patients (see [Section 6.4.10](#)).
3. To evaluate the change from BL to 36 weeks in all LIK066 doses vs placebo on NT-proBNP.
 4. To evaluate safety (adverse events (AEs) and lab parameters) and tolerability of LIK066 over 12 weeks and over 36 weeks for all patients (see [Section 6.5](#))
 5. To evaluate 24h urinary calcium and phosphate excretion after 12 weeks and after 36 weeks in a subset of patients (see [Section 6.4.10](#)).
 6. To evaluate bone mineral density in a subset of patients (see [Section 6.5.5](#))

3 Investigational plan

3.1 Study design

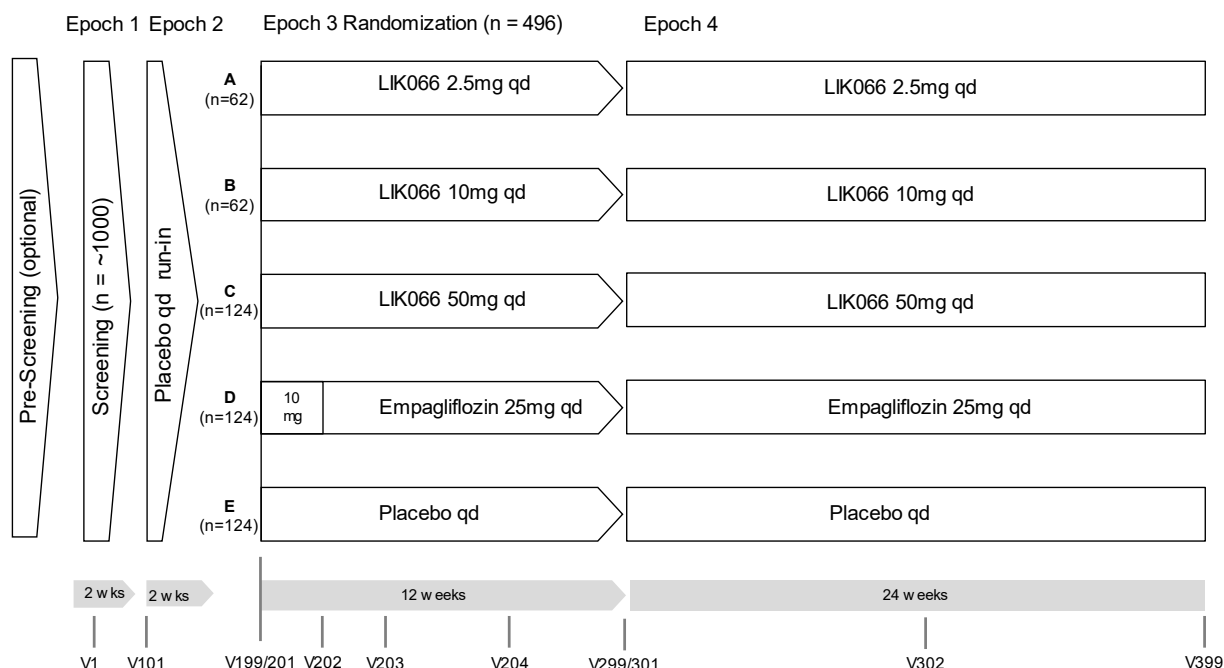
This is a multi-center, randomized, double-blind, double-dummy, parallel-group study evaluating the efficacy, safety and tolerability of 3 doses of LIK066 vs placebo and vs empagliflozin.

Pre-Screening: Pre-screening for some blood tests is possible (it is optional) and can be used to identify appropriate patients to be screened for this clinical study. The pre-screening visit includes blood tests for NT-proBNP, HbA1c, eGFR and serum potassium, which will be analyzed at the central laboratory. At Visit 1, these laboratory parameters will be assessed by the central laboratory, independently whether or not pre-screening was done for the patient.

3.1.1 Epoch 1 (screening)

Patients will be screened at Visit 1 (see [Figure 3-1](#)). The screening period (Epoch1) takes approximately 2 weeks. Patients meeting all eligibility criteria will enter the run-in Epoch 2 at Visit 101. If patients fail to meet one or more inclusion/exclusion criteria, they can be re-screened once. If for technical reasons (e.g. hemolyzed blood sample, broken or lost tube) laboratory results are not definable, such parameters can be re-tested.

Figure 3-1 Study design



3.1.2 Epoch 2 (placebo run-in)

Patients meeting the eligibility criteria defined in [Section 4](#) will enter the placebo run-in (Epoch 2). During the approximately 2 weeks duration of Epoch 2, patients will receive single-blind placebo run-in medication as described in [Section 5.2](#).

At Visit 101, the patients' volume status must be assessed based on physical examination and laboratory values and, if hypovolemic, corrected during the run-in.

3.1.3 Epoch 3 (treatment)

After the placebo run-in Epoch 2, eligible patients will be randomized in a 1:1:2:2:2 ratio to one of the following regimens at Visit 201 (randomization), see [Section 5.2](#):

- 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
- Placebo LIK066 at bedtime/Placebo Empagliflozin in the morning

At randomization, patients must be stratified based on geographical region and the left ventricular ejection fraction (LVEF) measurement at Visit 101: < 45% versus ≥ 45%. Only if the LVEF results from the central reading vendor are not available in time for randomization, the LVEF result from Visit 101 read locally by a cardiologist or from the last measurement (echocardiogram, nuclear study, or left ventricular angiography) done locally prior to enrollment into the study can be used for stratification.

Following randomization, patients will attend study visits in Epoch 3 (12 weeks) for the evaluation of the short-term efficacy (change in NT-proBNP), tolerability and safety parameters as defined in [Table 6-1](#). During Epoch 3, patients will take the study medication as described in [Section 5.5.4](#).

Treatment of T2DM

Patients will 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 (see [Section 5.5.3](#)) 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 (see [Section 5.5.6](#)). To limit the number of patients with early deterioration of glycemic control who would meet the FPG rescue criteria early after randomization (see [Section 5.5.6](#)) an FPG randomization criterion is included in [Section 4.2](#).
- 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 (see [Section 5.5.6](#)), insulin can be up-titrated.

3.1.4 Epoch 4 (treatment)

After completing the procedures required at the last study visit of Epoch 3 (Visit 301) patients will 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 as defined in [Table 6-1](#) will be evaluated.

3.2 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 will be 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 will also be assessed after 12 and 36 weeks of treatment.

The patient population is described in more detail in [Section 4](#) below.

3.3 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.

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.

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.

3.4 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.

3.5 Purpose and timing of interim analysis

No interim analysis is planned.

3.6 Risks and benefits

The risk to patients in this study will be minimized by compliance with the eligibility criteria and study procedures, and close clinical monitoring.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Further information is provided in the Investigator Brochure (IB).

Publications on SGLT2 inhibition in subjects with T2DM treated with selective SGLT2 inhibitors reported higher incidences of urinary tract infections (UTIs) and genital mycotic infections compared with placebo (Bailey et al, 2010; Nauck et al, 2011; Nyirjesy et al, 2012) and some genital infections have been seen in healthy volunteers and patients treated with LIK066. SGLT2 inhibition may result in hypotension in elderly subjects, in subjects with low blood systolic pressure, or if on diuretics, ACE inhibitors, or ARBs. Patients with T2DM treated with antidiabetic agents, especially with sulphonylurea or insulin, may be at an increased risk of hypoglycemia. In rare cases treatment with SGLT2 inhibitors may be complicated by ketoacidosis (Rosenstock et al, 2015). However, this has not been seen to date in clinical studies with LIK066. In long-term clinical studies in patients with T2DM with CVD or at high risk for CVD, an increase in cases of lower limb amputation (primarily of the toe) has been observed with the SGLT-2 inhibitor canagliflozin (Neal et al, 2017). No lower limb amputations have been seen in LIK066 studies to date, but since this risk may constitute a possible class effect, patients with a higher risk for amputation events should be instructed on routine preventative foot care and maintaining adequate hydration. The only preclinical/class safety issues which have been seen in clinical studies with LIK066 are the GI side effects and vulvovaginal infections. A detailed description of safety in humans with LIK066 is found in the LIK066 IB.

Hematology and biochemistry tests will be monitored at each study visit after randomization and study drug can be discontinued for clinically significant laboratory change or abnormality as per investigator's judgment. Detailed criteria for follow-up in case of a liver event are defined in Appendix 2. To prevent UTIs and genital infections, patients will be instructed to pay attention to genital hygiene and have appropriate hydration. If UTI and/or genital infections occur, treatment will be initiated as appropriate at the investigator's discretion.

Strict criteria for deterioration of glycemic control and initiation of rescue anti-diabetic medication are provided (Section 5.5.6). To minimize the risk of hypoglycemia when study drug is added to patients treated with SUs or insulin, guidance is provided in Section 3.1.3. Considering the potential benefit patients with T2DM and mild and moderate renal impairment may have on their risk of CV death and HF hospitalization (Section 1.1) patients with eGFR down to 45 ml/min/1.73m² are included in this study. No safety concern in addition to the known adverse effects of SGLT2i has been reported in the EMPA REG Outcome study which included patients with T2DM with eGFR down to 30 ml/min/1.73m² (Zinmann et al, 2015).

This clinical study involves exposure to radiation from DXA total body and bone scans in a subset of patients. The total amount of radiation exposure per patient from these scans will be equivalent to less than 30 days of exposure to natural background radiation. For effective radiation doses at this level the risk for the patient is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired (Stabin, 2016).

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.

4 Population

The study population will consist 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 140 centers worldwide. Since a 25% screening failure rate and a 33% run-in failure rate is expected, approximately 1000 patients will be screened.

4.1 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 $\geq 22\text{kg/m}^2$ at Visit 1.
4. Type 2 diabetes with HbA1c between 6.5% 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
 - Peripheral edema
6. Plasma NT-proBNP $> 300\text{pg/ml}$ 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 $\geq 45\text{ml/min/1.73m}^2$ at Visit 1 (calculated by the Modification of Diet in Renal Disease formula (MDRD)).
11. Serum potassium $\leq 5.3\text{mM}$ at Visit 1.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be 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. 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.
 - Atrial fibrillation with a resting heart rate >100 beats per minute (bpm) at Visit 1.
4. Patients taking medications prohibited by the protocol (see [Section 5.5.8](#))
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.
 - 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 will be 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. History of ketoacidosis, lactic acidosis, or hyperosmolar coma, or any of these occurring between Visit 1 and Visit 201 (randomization).
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).
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.
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).
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 Visit 201 (randomization).
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.

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.
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'-diphosphoglucoronosyltransferase (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 $< 11 \text{ g/dL}$ in men, $< 10 \text{ g/dL}$ 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) $> 5.6 \text{ mM}$ (500 mg/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.
40. History of lower limb amputation (including toe amputation), or if occurring between Visit 1 and Visit 201 (randomization).
41. Diabetic foot ulcer at Visit 1, or between Visit 1 and Visit 201 (randomization).

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

The sponsor will provide single-blind study medication for Epoch 2:

- LIK066-matching placebo tablets

- Empagliflozin-matching placebo capsules (tablets over-encapsulated)

The sponsor will provide double-blind study medication for Epoch 3 and Epoch 4:

- LIK066 2.5mg film-coated tablets
- LIK066 10mg film-coated tablets
- LIK066 50mg film-coated tablets
- LIK066-matching placebo tablets
- Empagliflozin 10mg film-coated tablets (over-encapsulated)
- Empagliflozin 25mg film-coated tablets (over-encapsulated)
- Empagliflozin-matching placebo capsules (tablets over-encapsulated)

For each treatment arm (see [Section 5.2](#)), patients will receive a combination of one tablet and one capsule as described above. All patients will take the study medication as explained in [Section 5.5.4](#), and the dose regimens will be prepared for each treatment arm in medication wallets.

No other drugs will be supplied. Sufficient medication will be supplied for treatment according to the study protocol.

5.1.2 Additional treatment

No additional treatment beyond investigational drug and control drug are included in this study.

5.2 Treatment arms

All patients entering Epoch 2 (run-in) will receive single-blind placebo (see [Section 3.1.2](#) & [Section 5.5.4](#)).

At visit 201 (randomization), patients eligible for randomization will be assigned to one of the following 5 treatment arms in Epoch 3 (see [3.1.3 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
- Placebo qd

In Epoch 4 (see [3.1.4 Epoch 4 \(treatment\)](#)), patients will continue to receive the treatment they were assigned to in Epoch 3.

5.3 Treatment assignment and randomization

At Visit 201 (randomization) all eligible patients will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT

will assign a randomization number to the patient, which will be 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 will not be communicated to the user of the IRT system.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be 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 will be 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 will be reviewed and approved by a member of the Novartis randomization group.

Randomization will be stratified according to geographical region and LVEF (< 45% versus \geq 45%), see [Section 3.1.3](#).

5.4 Treatment blinding

Patients, investigator staff, Novartis study team, persons performing the assessments, and data analysts will 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 will not be 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.
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 (see [Section 5.5.9](#)), at the time of the Week 12 analysis and at the conclusion of the study.

The analysis group (statisticians/programmers), who will be unmasked to perform the Week 12 analysis, will not be 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, will perform 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), will 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 will not be shared with the study site personnel until after the final database lock at the end of study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 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 pre-screening or study 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). At screening (Visit 1) the investigator or his/her staff will contact 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 will not be 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 should also be completed.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the treatment arms. Investigator staff will 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 will 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.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

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 to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients will be 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 will return 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.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

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 must be recorded on the appropriate study drug Dosage Administration Record eCRF. All kits of study treatment assigned by the IRT will be 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 should be instructed to contact the investigator if he/she is unable for any reason to take the study drug regimen as prescribed.

On study visit days, the patients must take their study medication or their anti-diabetic treatment only after blood draws have been done.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted, unless done for safety reasons (see [Section 7.1](#)).

5.5.6 Rescue medication

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 and HbA1c measurement performed by the central laboratory if:

- Self-measured FPG on three consecutive occasions exceeds the limits in [Table 5-1](#).
- The FPG result from a blood sample analyzed at the central laboratory exceeds the limits described in [Table 5-1](#).

Table 5-1 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 V301 (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 V399 (Week 36)	FPG	>200mg/dL (11.1mM)	
Between V301 (Week 12) and V399 (Week 36)	HbA1c	>8%	

If the results confirm the exceeded limits, the background OAD should be initially escalated 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.

5.5.7 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) 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.

5.5.8 Prohibited medication

Use of the treatments displayed in [Table 5-2](#) 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 5-2](#) at the start of Epoch 2.

Table 5-2 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

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.
- 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.

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be 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 will then receive details of the investigational drug treatment for the specified patient and communication confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

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 will provide the protocol number, the study drug name (if available) and the patient number.

In addition, oral and written information to the patient must be 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 (see [Section 5.6.2](#)).

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last planned visit (see [Table 6-1](#)). The study as a whole will be considered completed when all randomized subjects have completed the last visit planned in the protocol or have discontinued the study prematurely.

For subjects who are lost to follow-up, see [Section 5.6.4](#).

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see [Section 6.5.6](#) and [Section 7.6](#))
- Use of prohibited treatment see [Table 5-2](#)
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse event: Ketoacidosis, diabetic foot ulcer or lower limb amputation (including toe amputation)
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
- Patients whose study treatment has been unmasked (see [Section 5.5.9](#))
- Withdrawal of consent (see [Section 5.6.3](#))

If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit (see [Table 6-1](#)). Treatment discontinuation visit assessments detailed in [Table 6-1](#) should be completed and recorded in the eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate eCRF.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should to be collected at clinic visits or via telephone visits:

- new / concomitant treatments
- adverse events/Serious Adverse Events

If the patient cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the patient, or with a person pre-designated by the patient. This telephone contact should preferably be done according to the study visit schedule.

Patients who discontinue study medication during Epoch 3 should be followed-up until they discontinue the study at the end of Epoch 3 (V299).

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If study drug discontinuation occurs because treatment code has been broken, please refer to [Section 5.5.9](#)

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when all of the following applies:

- A patient does not want to participate in the study anymore

and

- does not want any further visits or assessments

and

- does not want any further study related contacts

and

- does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal.

A final evaluation at the time of the patient's study withdrawal should be made as detailed in [Table 6-1](#).

5.6.4 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.


6 Visit schedule and assessments

[Table 6-1](#) lists 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 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.

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

Table 6-1 Assessment schedule

Epoch		1	2	3						4		
Visit	Pre-screen	1 Screen	101 Run-in	199 TD/PPD	201 RND/ BL	202	203	204	299 TD ^A / PPD	301	302	399 TD ^A / PPD/ EOS
Week		-4	-2	0	2	4	8	12	24	36		
Screening assessments												
Pre-screening informed consent	S ^P											
Study informed consent		X										
Inclusion/exclusion (Section 4)		X		X*	X*							
Patient demographics (Section 6.2)		X										
Medical history		X										
Medical history: protocol solicited & Heart Failure/Diabetes		X										
Smoking & alcohol history (Section 6.2)		X										
Efficacy												
Height (Section 6.4.1)		X										
Weight / BMI (Section 6.4.1)		X ^C	X		X	X	X	X	X	X	X	X
Blood pressure (Section 6.4.8)		X	X		X	X	X	X	X	X	X	X
 NYHA classification (see Section 6.4.4)		X	X		X	X	X	X	X	X	X	X
Body composition: bio-impedance (see Section 6.4.3)					X				X	X		X
Echocardiography (see Section 6.4.5)			X							X ^D		X ^D
NT-ProBNP (Section 6.4.2)	S ^P	X			X		X ^B		X ^B	X ^B		X ^B

[illegible]

Epoch		1	2	3						4		
Visit	Pre-screen	1 Screen	101 Run-in	199 TD/ PPD	201 RND/ BL	202	203	204	299 TD ^A / PPD	301	302	399 TD ^A / PPD/ EOS
Week		-4	-2	0		2	4	8	12		24	36
Urinalysis (Section 6.5.3)					X				X ^G	X ^G		X ^G
Urine albumin to creatinine ratio (spot UACR, Section 6.5.3)					X		X		X	X		X
AEs (Section 7.1)		S	X	X	X	X	X	X	X	X	X	X
SAEs (Section 7.2)		(X ^P)	X	X	X	X	X	X	X	X	X	X
Ketoacidosis AEs (Section 7.8.1)			X	X	X	X	X	X	X	X	X	X
Hypoglycemia AEs (Section 7.8.2)			X	X	X	X	X	X	X	X	X	X
Medication records & procedures												
Prior & concomitant medications, rescue medication		X	X	X	X	X	X	X	X	X	X	X
Surgical and medical procedures			X	X	X	X	X	X	X	X	X	X
Dose administration record			X	X	X	X	X	X	X	X	X	X
Administrative procedures												
Contact IRT system		X	X	X	X	X	X	X	X	X	X	X
Dispense glucometer and first glycemia study diary			S									
Patient returns glycemia study diary for review				S	S	S	S	S	S	S	S	S
Drug dispensing			X		X	X	X	X		X	X	
Study drug accountability				S	S	S	S	S	S	S	S	S
Screening phase disposition		X										
Run-in phase disposition				X								

Epoch		1	2		3					4		
Visit	Pre-screen	1 Screen	101 Run-in	199 TD/ PPD	201 RND/ BL	202	203	204	299 TD ^A / PPD	301	302	399 TD ^A / PPD/ EOS
Week		-4	-2	0		2	4	8	12		24	36
Epoch 3 phase disposition									X			
Study completion												X
Sub-studies (subset of patients)												
Sub-study 1: DXA (Section 6.4.3 & Section 6.5.5): Body composition/BMD					X					X ^D		X ^D
Sub-study 2: 24h urine collection (Section 6.4.10) Bone biomarkers (Section 6.5.3.4) Renal biomarkers (Section 6.5.3.4)					X				X ^G	X ^G		X ^G

RND = Randomization visit;

EOS = End of Study;

TD = study treatment discontinuation;

PPD = premature patient discontinuation;

X = assessment to be recorded on clinical data base;

S = assessment to be recorded on source documentation only;

* = reassessed prior to randomization;

A = patients only discontinuing study medication need to have such assessments done per unplanned assessment eCRF;

B = laboratory values will be blinded;

C = BMI will be calculated at Visit 1;

D = no echocardiography/DXA assessment for patients <12 weeks after Visit 201 with PPD/TD. If week 12 echocardiography/DXA done before PPD/TD, no repeat echocardiography/DXA needed for patients < 24 weeks after Visit 201;

G = urinary glucose values will be blinded;

T = only triglycerides

P = pre-screening for NT-proBNP, HbA1c, eGFR and serum potassium is optional (the pre-screening data will be handled as source documentation only). These laboratory parameters will be assessed from all patients by the central laboratory at Visit 1, independently whether or not pre-screening was done. At Visit 1, SAEs are to be collected from pre-screened patients only if the SAE is reported to be causally related with study procedures (i.e. blood sampling).

6.1 Information to be collected on pre-screening failures or screening failures

For all patients who have signed the pre-screening informed consent but fail the pre-screening, only SAE data will be collected if the SAE is reported to be causally related with study procedures (i.e. blood sampling). Adverse events that are not meeting this criterion will be followed by the investigator and collected only in the source data.

All patients who have signed the study informed consent but fail the screening will have the Screening Phase Disposition eCRF for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not serious will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other BL characteristics

Demographic and BL characteristics data to be collected on all randomized patients include: year of birth, age, sex, race, ethnicity, relevant medical history/current medical conditions present before signing the study informed consent including smoking and alcohol history. Where possible, diagnoses and notable symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the study informed consent form (ICF) signature.

6.3 Treatment exposure and compliance

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

On-treatment medication

For all medications (other than the study drug regimen) initiated after the start of study, the reason for prescribing the medication, and the start and, where applicable, end dates will be recorded on the Concomitant Medications eCRF.

Rescue medication

Information regarding the administration of rescue medication as per [Section 5.5.6](#) will be recorded on the appropriate Rescue Medication eCRF.

6.4 Efficacy

6.4.1 Weight and height

Body weight will be measured to the nearest 0.1kg at visits indicated in [Table 6-1](#) on a calibrated scale (weight and bio-impedance measurements, [Section 6.4.3](#)), provided by the sponsor. Exceptionally (e.g. if the body weight exceeds the limits of the provided scale) sites can use another scale for weight measurement as available, but during the study the same scale should be used for the same patient. The measurement will be performed with the study patient in underwear and without shoes. Indoor clothing is also acceptable, but measurements should be done consistently (either with underwear or with indoor clothing) throughout the study. Voiding before weight measurement is required.

Height will be measured at Visit 1 and will be used to automatically calculate BMI.

6.4.2 NT-proBNP

NT-proBNP will be measured from a blood sample at visits indicated in [Table 6-1](#) and analyzed at a central laboratory. NT-proBNP measured at Visit 1 will be used for assessing an inclusion criterion (see [Section 4.1](#)) and will not be masked. The results of all NT-proBNP measurements after randomization (V201) will remain masked until final database lock, except that they will be extracted to a restricted area for the statistical/programming team to perform the analysis for the Week 12 analysis.

6.4.3 Body composition

Body composition will be 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 [Table 6-1](#). Body composition parameters will be assessed as available for the different models of calibrated bio-impedance scales.

In about 25% of patients at participating sites, a DXA scan will be performed at visits indicated in [Table 6-1](#). A whole body DXA scan will be acquired to assess body composition (lean body mass, fat mass, visceral fat mass, body water (calculated); in addition bone mineral density (BMD) will be assessed ([Section 6.5.5](#)). The exam takes approximately 10-15 minutes and is non-invasive.

In order to assure quality throughout the study, the DXA 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 will be done by experienced staff.

DXA will be performed according to the procedures described in the Imaging Manual. Prior to the examination, the patient will be checked for absence of removable metal objects on his/her body, such as snaps, belts, underwire bras, jewelry, and so on. The patient will then be 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 will then be initiated on the patient.

Immediately after the whole body scan, a DXA scan will be acquired to measure lumbar spine, hip and distal forearm bone mineral density. More details can be found in [Section 6.5.5](#).

DXA data will be transferred to a central reading vendor for independent review and analysis.

[REDACTED]

[REDACTED]

[REDACTED] NYHA classification will be assessed and scored at each visit, and the results will be entered in the appropriate eCRF.

6.4.5 Echocardiography

Echocardiography will be performed at visits indicated in [Table 6-1](#). A subset of a standard echocardiographic two-dimensional and doppler examination will be performed. The images will be sent to a central reading vendor for independent review and analysis. An Echocardiography Manual with detailed instructions and data transfer procedures will be provided to the study sites.

The following echocardiographic assessments will be performed:

- [REDACTED]
- [REDACTED]
- [REDACTED]

- Left atrial size and volume

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

6.4.6 HbA1c

HbA1c will be measured from a blood sample obtained at visits indicated in [Table 6-1](#) and analyzed using a National Glycohemoglobin Standardization Program (NGSP) certified method at a central laboratory.

6.4.7 FPG

FPG will be measured from a blood sample obtained after an overnight fast (patients should not eat or drink anything (except water) at least for 8h before each study visit.) at visits indicated in [Table 6-1](#) and analyzed at a central laboratory.

6.4.8 Blood pressure (BP)

Arterial BP, pulse rate readings and signs and symptoms of orthostasis will be assessed with an automated electronic BP device (if available at the study site). Alternatively, another BP device will be used.

Three sitting BP measurements and one standing BP measurement will be performed at visits indicated in [Table 6-1](#). 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 after completing the ePRO questionnaires (as applicable) and the ECG, and prior to blood draws and study medication and anti-diabetic 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 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 will be measured three times using the BP device 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 should be asked to relax his/her arm and turn the palm upward. The 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 will then stand, and after standing for two minutes, one BP measurement will be taken (see also [Section 6.5.2](#)).

All 3 sitting BP measurements and the single standing measurement will be recorded and documented in the eCRF and in the patient's source documents. All 3 sitting BP readings will be used for evaluation of sitting BP. The mean of the three sitting BP readings at randomization (Visit 201) will be used to assess eligibility for the study (see Inclusion/Exclusion Criteria in [Section 4](#)).

6.4.9 Fasting lipid profile

Fasting lipid profile and TGs as described in [Table 6-2](#) will be measured on blood samples obtained after an overnight fast at visits indicated in [Table 6-1](#) and analyzed at a central laboratory.

Table 6-2 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 ≤400 mg/dL, if TG >400 mg/dL then direct LDL cholesterol measurement will be done.
Inflammation biomarker	hs-CRP

6.4.10 24h urine collection

UGE, albumin, creatinine and sodium excretion will be measured from a 24h urine collection from about 25% of randomized patients at visits indicated in [Table 6-1](#) and analyzed at a central laboratory. UGE results after the baseline assessment will be kept blinded until the final analysis, except that they will be extracted to a restricted area for the statistical/programming team to perform the Week 12 analysis.

Bone biomarkers (urinary calcium and phosphate excretion) and renal biomarkers (cystatin C, albumin and creatinine) will be measured from the same urine collection (see [Section 6.5.3.4](#)).

Detailed instructions for urine collection will be provided to patients, and handling of the urine sample will be described in the laboratory manual. 24h urine collection will be done by the patients at home, therefore no overnight stay at the site is required.

6.4.11 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-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 will inform about 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.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will be performed at visits indicated in [Table 6-1](#) and includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities (including feet), vascular status, volume status (see [Section 3.1.2](#)) and neurological status. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed.

A short physical exam will be performed at all scheduled visits indicated in [Table 6-1](#) and at unscheduled study visits. This exam will include the examination of general appearance, feet,

vital signs (SBP and DBP, see [Section 6.4.8](#)), pulse rate, respiratory rate and assessment of heart failure signs and symptoms.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing IC must be included in the medical history part of the eCRF. Significant findings made after first administration of investigational drug which meet the definition of an AE must be recorded on the AE section of the eCRF.

6.5.2 Vital signs

BP will be measured as described in [Section 6.4.8](#). The pulse rate from the last sitting BP measurement will be recorded. Respiratory rate will also be measured. Clinically notable vital signs are defined in [Appendix 1](#).

6.5.3 Laboratory evaluations

Laboratory evaluations for safety will be performed at visits indicated in [Table 6-1](#) and all specimens collected will be analyzed at a central laboratory. Details on the collection, shipment of samples, reporting of results by the central laboratory as well as laboratory notable range deviations are provided in the laboratory manual.

6.5.3.1 Hematology

Samples for analysis of hematology (see [Table 6-3](#)) will be collected at visits indicated in [Table 6-1](#).

Table 6-3 Hematology evaluations

Category	Parameter(s)
Hematology	RBC (total), WBC (total), platelet count (direct), hemoglobin, hematocrit, basophils (absolute, %), eosinophils (absolute, %), lymphocytes (absolute, %), monocytes (absolute, %), neutrophils (absolute, %)

6.5.3.2 Clinical chemistry

Samples for analysis of clinical chemistry (see [Table 6-4](#)) will be collected at visits indicated in [Table 6-1](#).

Table 6-4 Clinical chemistry

Category	Parameter(s)
Biochemistry	ALT, albumin, alkaline phosphatase (ALP), AST, bicarbonates, bilirubin (direct, total), blood urea nitrogen (BUN), calcium (total), chloride (Cl ⁻), creatinine, cystatin C, eGFR (MDRD), magnesium (Mg ²⁺), phosphates, potassium (K ⁺), protein (total), sodium (Na ⁺), uric acid, γ-GT, amylase, lipase, serum ketones and beta hydroxybutyrate
Chemistry (TSH)	TSH (only at screening visit (Visit 1))
Chemistry (pregnancy)	Serum β-HCG (only at screening visit (Visit 1))

6.5.3.3 Urinalysis

Urine samples will be collected for analysis of parameters listed in [Table 6-5](#) at visits indicated in [Table 6-1](#). Urine will be used to assess pregnancy and hematuria (dipstick) at visits indicated in [Table 6-1](#) as well. Urine dipstick for hematuria can be re-tested in pre-menopausal women having their period (documented) at the time of the previous hematuria test. Urinary glucose results after the baseline assessment will be kept blinded until the final analysis, except that they will be extracted to a restricted area for the statistical/programming team to perform the Week 12 analysis.

Table 6-5 Urinalysis

Category	Parameter(s)
Urinalysis	pH, specific gravity, protein, glucose, ketones, nitrites, blood, leucocytes
Urinalysis	UACR Urine albumin to creatinine ratio (spot urine), cystatin C/creatinine ratio (spot urine)
Urine (dipstick)	Hematuria, only at screening visit (Visit 1)
Urine (dipstick)	Pregnancy test (β -hCG)

6.5.3.4 Bone and renal biomarkers

Serum samples for bone and renal biomarkers (see [Table 6-6](#)) will be collected from the patients participating in sub-study 2 at visits indicated in [Table 6-1](#).

Urine samples for bone and renal biomarkers from the patients participating in the sub-study will be assessed from 24h urine collection ([Section 6.4.10](#)).

Table 6-6 Biomarkers

Category	Parameter(s)
Bone biomarkers	β -c-terminal telopeptide (β -CTX1), serum procollagen type 1 N-propeptide (sP1NP), intact parathyroid hormone (iPTH), 25-hydroxy vitamin D, 1,25 dihydroxy vitamin D, osteocalcin, oestradiol, Ca^{2+} , Mg^{2+} , phosphates (see also Table 6-4)
Renal biomarkers	Serum cystatin C, urinary cystatin C (24h urine sample), urinary creatinine (24h urine sample), urinary albumin (24h urine sample),

6.5.4 ECG

Twelve-lead ECGs must be performed at visits described in [Table 6-1](#). ECG equipment will be provided to the sites to ensure standardized output allowing for interpretation of the ECGs at a central reading facility.

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable ECG baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

Each ECG tracing must be labeled with study number, patient initials, patient number, date and time, and filed in the study site source documents. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety.

Clinically significant abnormalities must be recorded on the relevant section of the Medical History/Current Medical Conditions/AE eCRF(s) as appropriate.

6.5.5 Bone mineral density (BMD)

In about 25% of patients at participating sites, DXA scans will be performed at visits indicated in [Table 6-1](#).

Immediately after DXA whole body scan to measure body composition (see [Section 6.4.3](#)), lumbar spine, hip and distal forearm DXA scans will be acquired to measure BMD. Optimum patient positioning will be described in the Imaging Manual.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing (see [Section 6.5.3.2](#) & [Section 6.5.3.3](#)). Additional pregnancy testing may be performed if requested by local requirements.

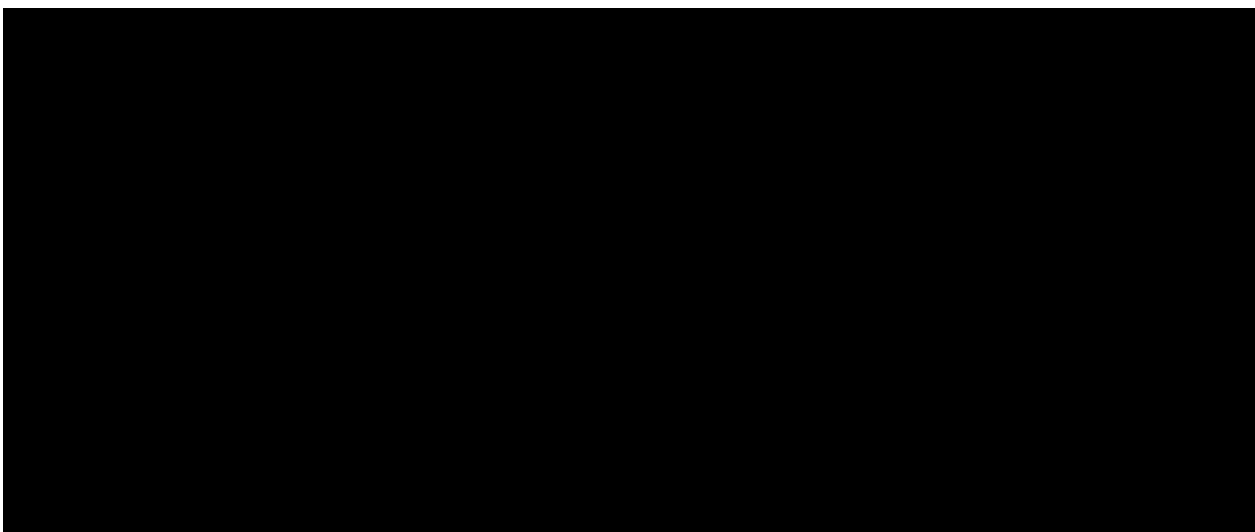
A positive urine pregnancy test requires immediate interruption of study drug until serum β -human chorionic gonadotropin (β -hCG) is performed and found to be negative. If positive, the patient must be discontinued from the study treatment (see [Section 5.6.2](#)).

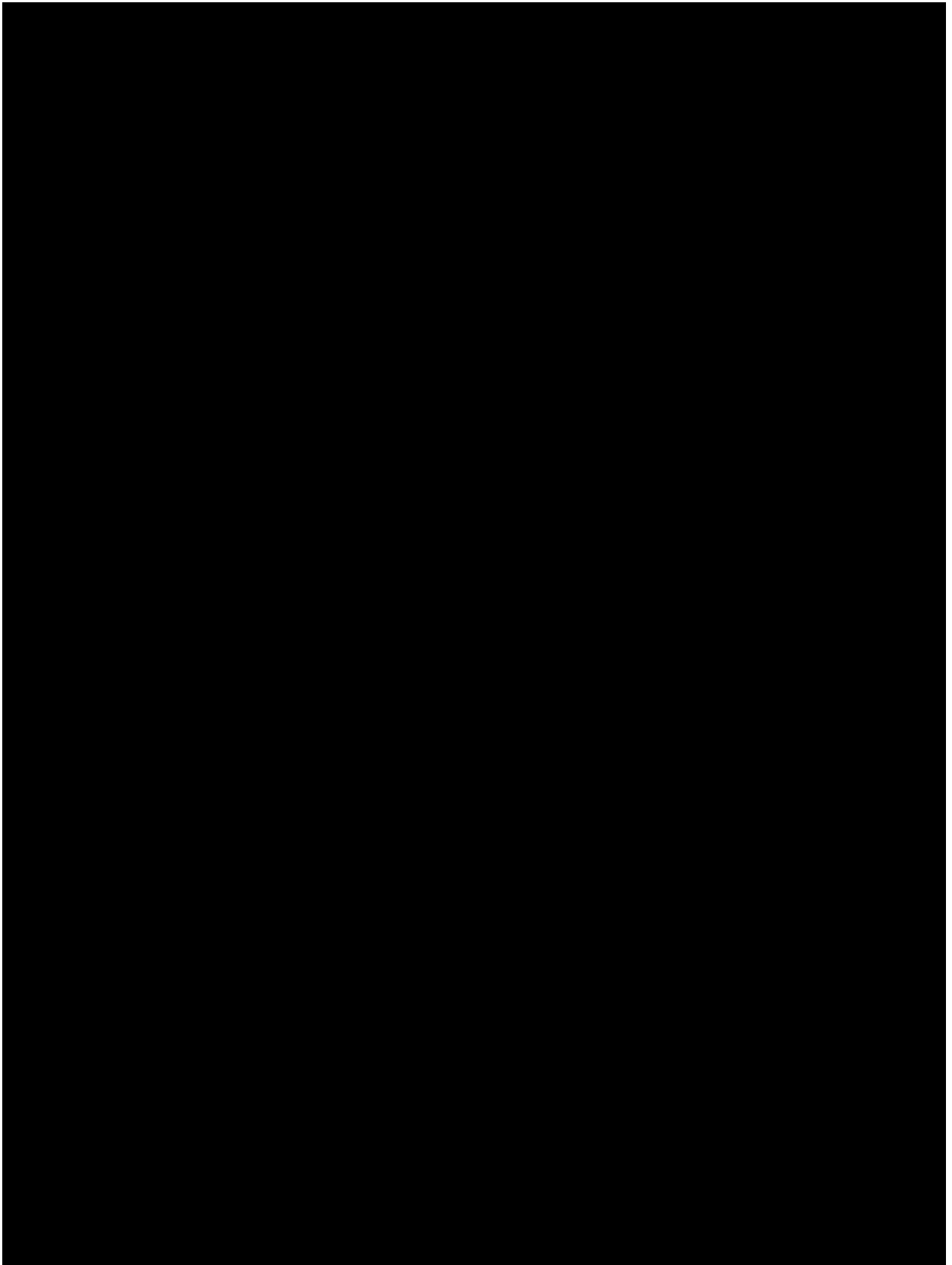
6.5.7 Appropriateness of safety measurements

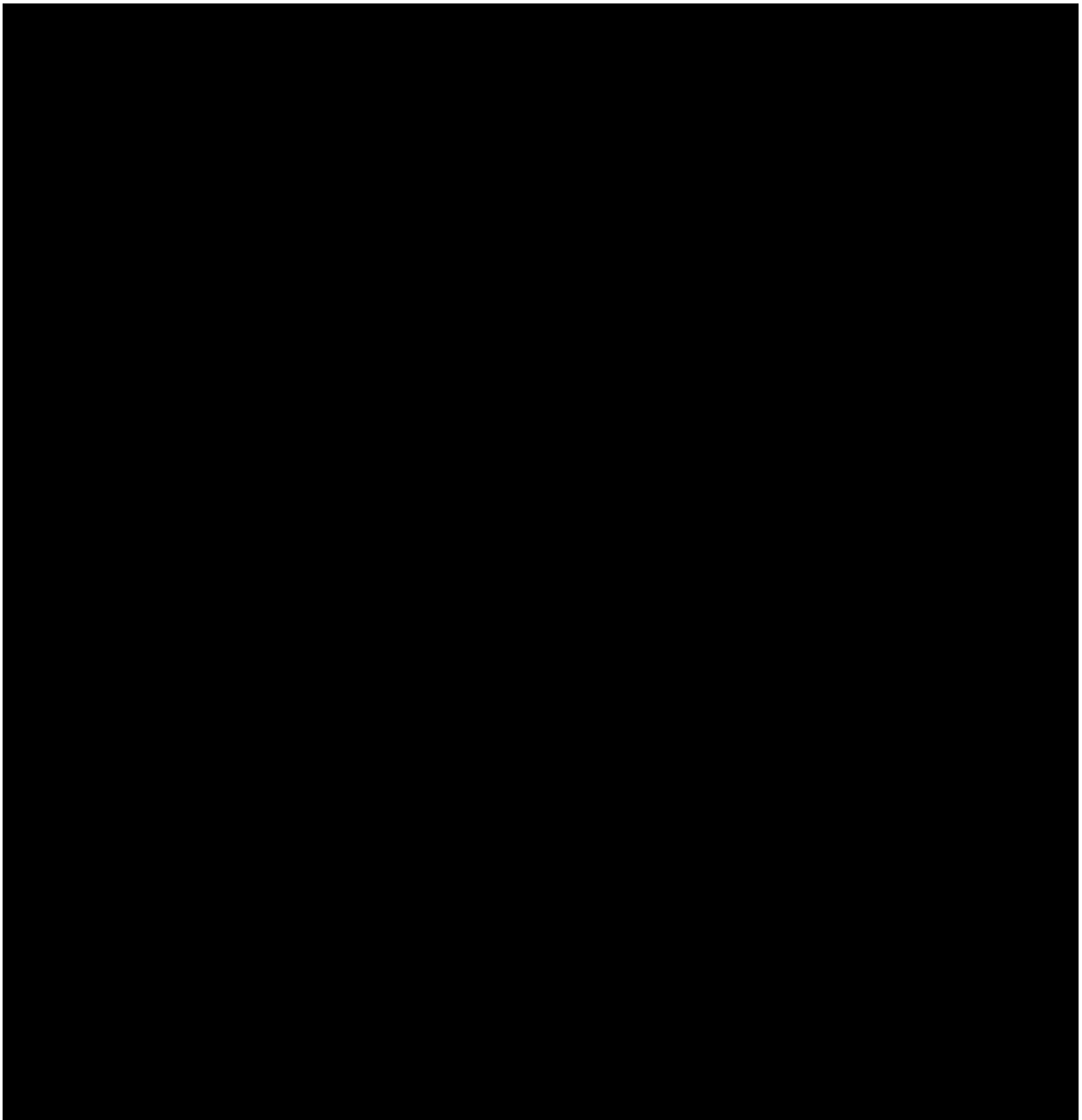
The safety assessments are standard for this indication/subject population. The following additional assessments are included to document and evaluate risks identified with SGLT2 inhibitors or during the LIK066 clinical program:

- Bone biomarkers will evaluate the effect of LIK066 on bone re-modeling
- Renal biomarkers will evaluate whether LIK066 may cause kidney injury due to its dual SGLT1/2 inhibition.

6.6 Other assessments

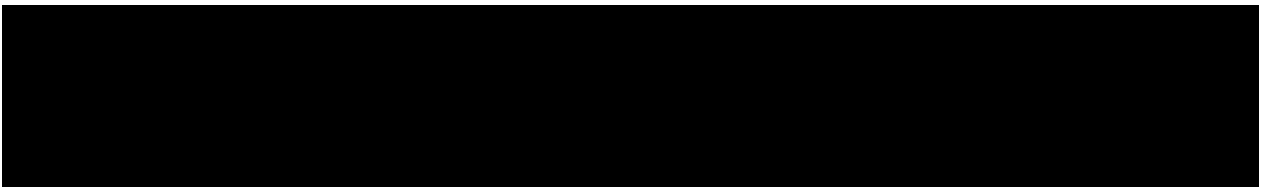






6.6.2 Resource utilization

Not applicable.



7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a patient or clinical investigation patient *after providing written informed* consent for participation in the study (or for participation in the pre-screening, as applicable) until the end of study visit.

For patients who sign the pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in [Section 7.2.1](#) and are reported to be causally related with study procedures (i.e. blood sampling). Once the study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

An AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in [Appendix 1](#).

Adverse events must be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade
 - Mild: usually transient in nature and generally not interfering with normal activities
 - Moderate: sufficiently discomforting to interfere with normal activities
 - Severe: prevents normal activities
- its relationship to the study treatment
 - “No Relationship to study treatment or other investigational treatment” or
 - “Relationship to study treatment” or
 - “Relationship to other investigational treatment” or

- “Relationship to both study treatment and other investigational treatment or indistinguishable“
- its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See [Section 7.2](#) for definition of SAE) and which seriousness criteria have been met.
- action taken regarding investigational treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient’s hospitalization prolonged (see [Section 7.2](#) for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the patient study ICF and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an aggregate safety finding. New information might require an update to the study informed consent and has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient’s personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator’s source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the study informed consent
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

For patients who sign the pre-screening informed consent form, SAEs which occur after signature of this consent will only be captured if they are reported to be causally related with study procedures (i.e. blood sampling).

Every SAE, regardless of causality, occurring after the patient has provided study informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the SAE Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Novartis Chief Medical Office and Patient Safety associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified or reported as serious):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver eCRF pages

Please refer to [Table 14-1 in Appendix 2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in [Table 14-1 of Appendix 2](#) should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in [Table 14-2 in Appendix 2](#).

For the liver laboratory trigger:

- Repeat the liver function test (LFT) within the next week to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats must then be performed at the central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

- Repeat the LFT to confirm elevation as appropriate
- Discontinue the investigational drug if appropriate
- Hospitalize the patient if appropriate
- A causality assessment of the liver event should be made via exclusion of alternative causes (e.g., disease, co-medications)
- Perform an investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate eCRF pages, including the liver event overview eCRF pages.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
 - confirmed (after ≥ 24 h) increase in serum creatinine of $\geq 25\%$ compared to baseline during normal hydration status
- Urine event
 - new onset ($\geq 1+$) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (UACR)
 - new onset ($\geq 1+$), hematuria

Every renal laboratory trigger or renal event as defined in [Table 15-1 in Appendix 3](#) should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

Table 7-1 **Guidance for capturing the study treatment errors including misuse/abuse**

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the study ICF must be reported to Novartis within 24 hours of learning of its occurrence. In such instance, study treatment should be handled as per [Section 5.6.2](#). The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

7.7 Prospective suicidality assessment

Not applicable.

7.8 AEs of special interest

7.8.1 Ketoacidosis

In rare cases, SGLT-2 inhibitors can lead to ketoacidosis. Therefore, investigators must pay close attention for any signs of ketoacidosis. Signs and symptoms of ketoacidosis may include deep and rapid breathing, nausea, vomiting, severe abdominal pain, confusion, unusual fatigue or sleepiness, and coma. All signs and/or symptoms and results from relevant laboratory tests must be reported on the AE eCRF. If ketoacidosis is confirmed, the study treatment should be handled as per [Section 5.6.2](#) and appropriate measures must be taken to correct the acidosis and monitor glucose levels.

Every case of ketoacidosis must be reported to the Ketoacidosis Adjudication Committee (see [Section 8.5](#)), and the Ketoacidosis Adjudication eCRF must be completed by the Adjudication Committee.

7.8.2 Hypoglycemia

Patients with T2DM treated with anti-diabetic agents may be at an increased risk of hypoglycemia due to the expected weight loss. All patients must be educated regarding hypoglycemic symptoms and treatment. This education should include general review of hypoglycemia:

- Explanation of possible triggers of hypoglycemia (e.g., strenuous exercise, delayed meals, changes in meal composition, illness, Ramadan-period, etc.).
- Identification of the symptoms of hypoglycemia (e.g., central symptoms such as dizziness, lightheadedness; adrenergic symptoms such as fast heart rate, palpitations, heart racing/pounding, shakiness; cholinergic symptoms such as sweating, hunger, blurred vision, impairment of motor function, confusion or inappropriate behavior).
- Review of appropriate treatment for events (oral glucose intake).

A home glucose monitor will be provided with all appropriate supplies and its use will be explained to the patient. Blood glucose should be measured each time the patient experiences symptoms which may be suggestive of hypoglycemia, as well as other time points as recommended by the investigator to inform about the need for reducing or discontinuing anti-diabetic treatment to prevent severe hypoglycemic events.

Any time the patient experiences symptoms which they suspect are related to hypoglycemia, the patient should treat the event as appropriate. Patients should record the event in the glycemia study diary, including:

- The glucose value.
- Precipitating factors (strenuous exercise, delayed or missed meals, changes in meal composition, illness, Ramadan-period, etc.).
- Time of occurrence in relation to the last medication and to the last meal intake.
- The treatment used.
- The response to the treatment used.
- Need for assistance to treat the hypoglycemia event.

- Additionally, if a patient performs routine self-monitoring of blood glucose, any asymptomatic plasma glucose < 70 mg/dL (< 3.9 mmol/L) should be treated and recorded in the glycemia study diary.
- The glycemia study diaries will be dispensed at run-in (V101) and at following visits. The patient must return the completed study diary at each following visit.

Data entry

The glycemia study diary will be reviewed by the investigator at each visit and any hypoglycemia must be recorded on the Hypoglycemic Events eCRF.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (ie eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and good clinical practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture/data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the patient's file. The investigator must also keep the ICF(s) signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

The trial will be conducted in a fully validated Data Capture system which conforms to US CRF 21 Part 11 requirements. Investigator site staff will not be given access to the system until they have been trained. Designated investigator staff will 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 will receive copies of the patient data for archiving at the investigational site.

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be 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 will receive copies of the patient data for archiving at the investigational site.

8.3 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 will be 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 will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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

Patients using electronic PROs will fill in their PRO data in a site based tablet. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be

supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be 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.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

A Ketoacidosis Adjudication Committee will review cases suspected for ketoacidosis as defined in the adjudication charter (see also [Section 7.8.1](#)).

9 Data analysis

The main analysis will be 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 to as “*Week 12 analysis*” in sections below). The study remains blinded (see [Section 5.4](#)).

Data collected during Epoch 4 will be analyzed based on the secondary objectives requiring data collection beyond Week 12 and will complement the results from the Week 12 analysis. The analysis performed after study end is referred to 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.

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis. Subjects without valid written study informed consent will be excluded from all analysis sets.

Screened set (SCR) – All patients who signed the study 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 will be analyzed according to treatment received. Treatment received will be 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 will be pre-specified prior to unblinding treatment codes for analyses. A list will be provided in the Clinical Study Report Statistical Analysis Plan.

9.2 Patient demographics and other baseline characteristics

Summary statistics will be 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 will be performed for the FAS.

Continuous variables will be summarized using n, mean, standard deviation (SD), median, Q1 (25th percentile), Q3 (75th percentile), minimum, and maximum. Categorical variables will be summarized using frequency and percentage.

9.3 Treatments

Week 12 analysis

The duration of double-blind treatment exposure in Epoch 3 will be 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 will be summarized by treatment group for duration category.

Prior and concomitant medications/ non-drug therapies will be summarized in separate tables as appropriate for the safety population.

The number and percentage of patients taking rescue medication, and duration of exposure to rescue medication during Epoch 3 will be summarized by treatment group for the SAF. The use of prohibited medication, if any, will also be summarized.

End of study analysis

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

9.4 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 will be performed before all statistical analyses are carried out. The analysis results will then be back-transformed and displayed as percentages for ease of data interpretation.

9.4.1 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 will be imputed using a multiple imputation approach as described in [Section 9.4.3](#).

9.4.2 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 will be 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

The null hypothesis of a flat dose-response relationship for the reduction in NT-proBNP compared to placebo will be 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.

Hence, the following null and alternative hypotheses will be tested:

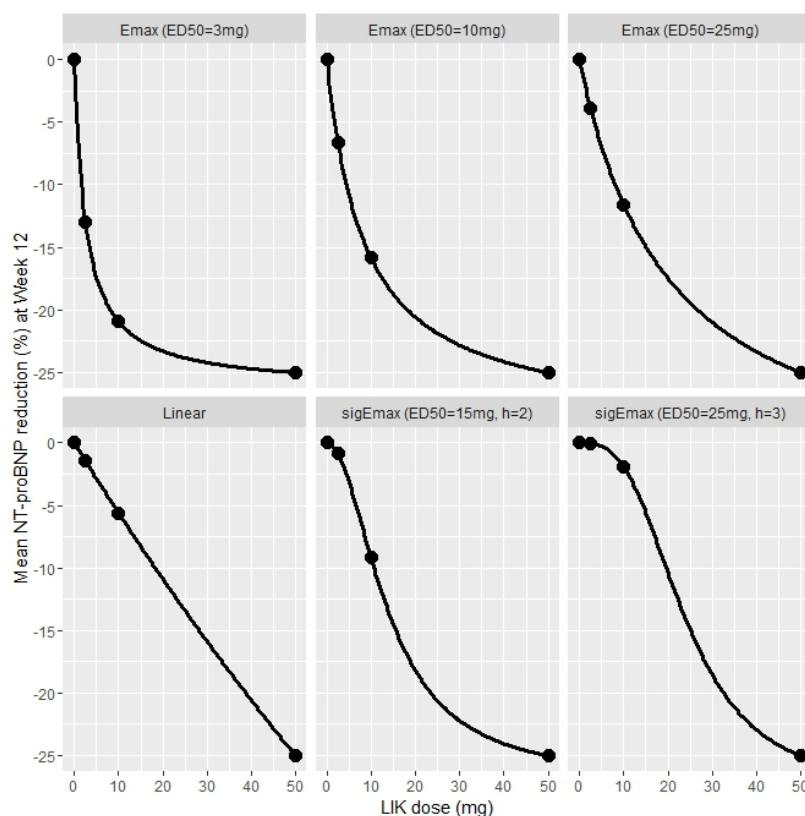
- H_{01} : there is no dose-response relationship or a dose response in the wrong direction for LIK066 after 12 weeks of treatment (i.e. the dose response relationship is flat, or as dose increases, there is less reduction in NT-proBNP from baseline).
- H_{11} : there is a dose-response relationship in the right direction for LIK066 after 12 weeks of treatment (i.e. as dose increases, there is 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, as depicted in Figure 9-1. The candidate models generate a set of six contrasts which will be evaluated using the data to test the above dose-response hypothesis.

- Model 1: 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 $h=2$.
- Model 6: sigmoid Emax with ED50 at 25mg and hill parameter $h=3$.

Figure 9-1 Dose-response curve of candidate models



The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) 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 $\geq 45\%$) as factors, and the baseline in log-transformed NT-proBNP as a covariate. As needed, centers will be pooled according to country and region for the purpose of analysis.

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 as described in [Section 9.4.3](#). In order to account for the imputation uncertainty, this ANCOVA model will be repeated for each imputed dataset, which 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.

The optimal contrasts derived from the candidate model sets will be applied to the combined estimated dose means and covariance matrix to obtain the t statistics for each candidate model and the common critical value $C_{0.025}$. $C_{0.025}$ 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 H_{01} will be rejected and the statistical significance of dose-response in NT-proBNP reduction is established if the $\max(t_1, t_2, t_3, \dots, t_6) \geq C_{0.025}$.

Model averaging to obtain the dose response

The response data in each imputed data set, including relevant covariates, will be used to fit the models in the candidate set. The estimated dose-response will be 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 will be selected as basis for the model averaging.

Model averaging will be carried out for each imputed data set, and the resulting mean efficacy estimates and confidence intervals will be 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 will be 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 will then be 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 will be based on the model averaged dose response estimates of mean NT-proBNP reduction efficacy of LIK066 over the dose range studied in the study.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for the primary endpoint will be imputed using a multiple imputation approach assuming that the missingness mechanism can be retrieved from observed data (missing at random (MAR)). The imputation model will include the longitudinal sequence of NT-proBNP data collected at baseline, Week 4 and Week 12 visits, stratification factors geographical region and LVEF (< 45% versus $\geq 45\%$), and other baseline covariates as appropriate.

The full detailed information about the multiple imputation algorithms will be specified in a separate statistical analysis plan.

9.4.4 Supportive analyses

As a sensitivity analysis, the dose-response modeling as described in [Section 9.4.2](#) will be conducted for the PPS. Results based on the single best dose response model fit will also be reported.

Summary statistics for NT-proBNP will be 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), median, Q1, Q3, minimum and maximum) will be presented by visit and treatment for NT-proBNP and change from BL in NT-proBNP. Figures will be 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. $\geq 45\%$).

In addition, summary statistics for the NT-proBNP will be presented by visit (up to and including week 12 visit) and treatment for observed and imputed values, by the following subgroups:

- LVEF at baseline: $< 45\%$ vs. $\geq 45\%$
- NYHA class at baseline: II vs. III & IV
- NT-proBNP at baseline: $< \text{median}$ vs. $\geq \text{median}$

9.5 Analysis of secondary variables

The secondary efficacy variables will be analyzed in the FAS. Statistical testing of hypotheses on the secondary efficacy endpoints will be performed at the two-sided 0.05 significance level without adjustment for multiplicity. Safety variables will be analyzed in the SAF.

9.5.1 Efficacy variables

9.5.1.1 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
- 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

9.5.1.2 Analysis method

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 will be 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 will be 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) will be presented by visit and treatment for the BL values, post-BL values and changes from BL in NT-proBNP. Figures will be produced 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. \geq 45%).

Analysis of other continuous outcome variables

The following continuous variables will be 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
- 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) will be analyzed using a mixed effect model of repeated measures (MMRM) in which the stratification variables (geographical region and LVEF < 45% vs. \geq 45%), treatment group, visit, and treatment group-by-visit interaction will be 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 will be 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 will be 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 will be 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 will be presented.

In addition, summary statistics (n, mean, SD, median, Q1, Q3, minimum and maximum, and geometric mean for log-transformed variables) for these variables will be 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) will be analyzed using a repeated measures proportional odds cumulative logit model in which the stratification factors (geographical region and LVEF < 45% vs. \geq 45%), treatment group, visit, and treatment group-by-visit interaction will be included as fixed-effect factors, baseline NYHA class will be included as a covariate, and patient will be included as random effects. The analysis will be 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 will be 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 will be 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 will be presented.

In addition, NYHA class will be summarized by visit and treatment group using frequency and percentage. A shift table will be provided to summarize the NYHA class shifting from BL to Week 12 (or Week 36) for *Week 12 Analysis* (or *End of Study Analysis*).

Analysis of outcome variables from a sub-study

Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided by visit and treatment for the outcome variables from a sub-study, for measurement at each visit and change from baseline values.

The following outcome variables from sub-studies will be analyzed using the method as described above:

- Change from BL in body composition (lean body mass, fat mass, visceral fat mass and body water (calculated) assessed by dual-energy x-ray absorptiometry (DXA)) at Week 12 and Week 36
- Change from BL in 24h urinary glucose and sodium excretion at Week 12 and Week 36

9.5.2 Safety variables

The safety assessments are listed below:

- Identified and potential risks
- AEs and SAEs
- Vital signs
- Laboratory evaluations
- ECG
- 24h urinary calcium and phosphate excretion (in a subset of patients)
- BMD (in a subset of patients)

The incidence of treatment emergent AEs (events started on or after the study treatment start date during Epoch 3) will be summarized by primary system organ class and preferred term. Summaries will also be provided by severity and relationship to study medication. The incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term. The number and percentage of patients with AEs related to identified and potential risks will be summarized by treatment.

Laboratory data will be summarized by presenting shift tables, summary statistics of raw data and change from baseline and by flagging of notable values in data listings.

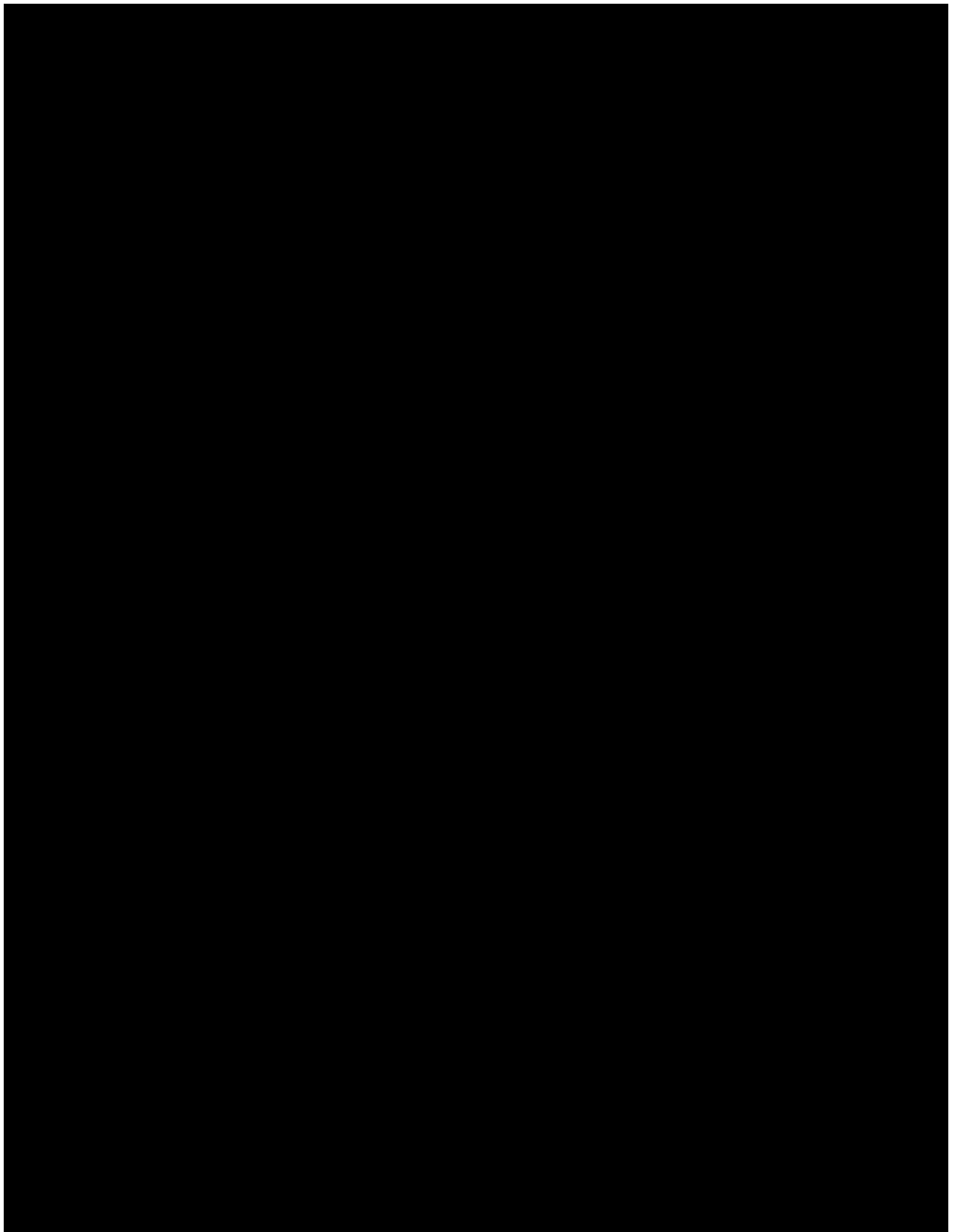
Other safety assessments (e.g., vital signs and ECG) will be summarized descriptively by treatment as appropriate. Data will be listed, notable values will be flagged, and other information collected will be listed as appropriate.

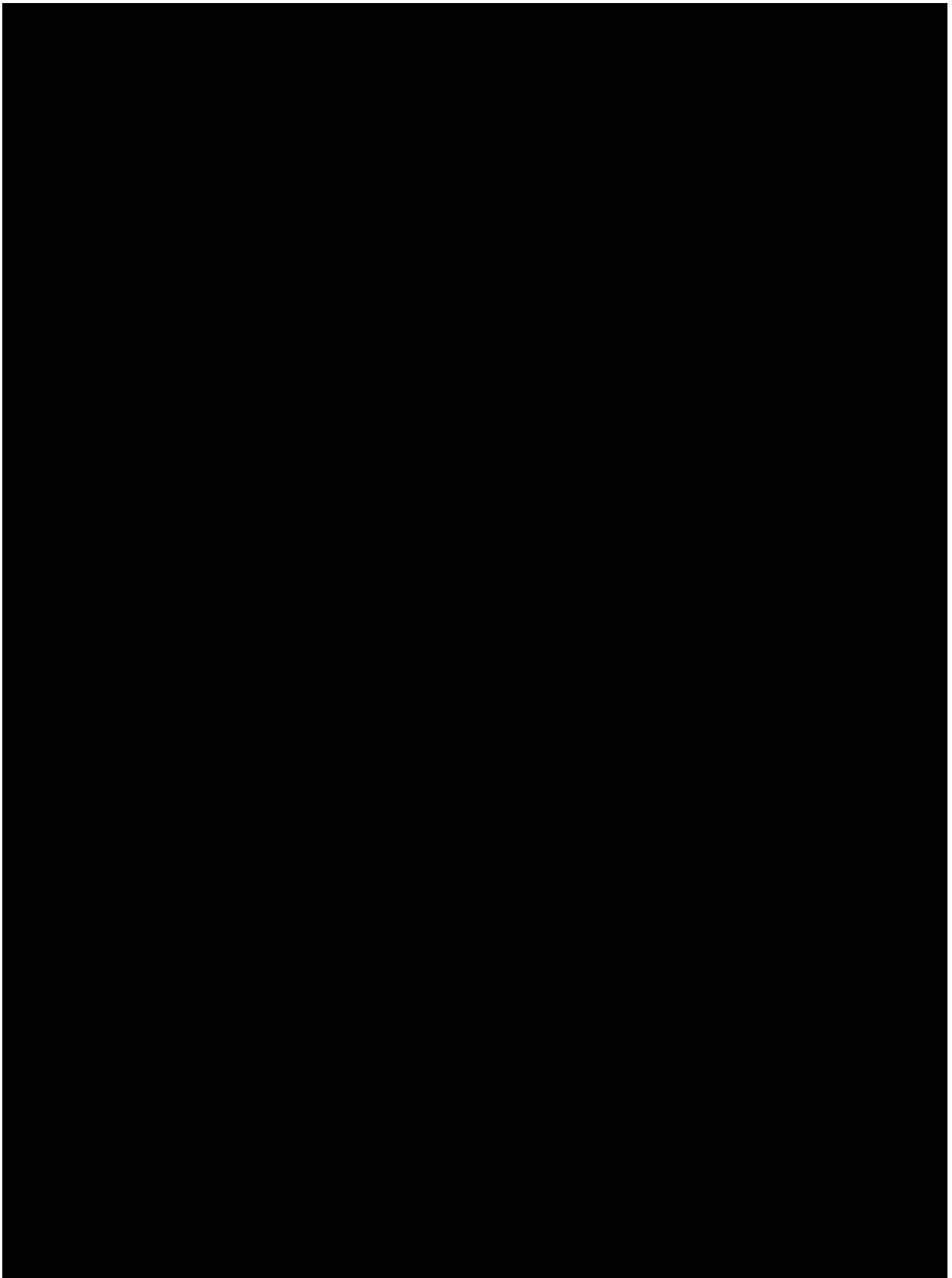
Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be provided by visit and treatment for the 24h urinary calcium, phosphate excretion and BMD from the sub-study, for measurement at each visit and change from baseline values.

The above analyses will be performed for the SAF for data collected during Epoch 3 for *Week 12 analysis*. For *End of study analysis*, these analyses will be carried out for data collected during Epoch 3 + Epoch 4.

9.5.4 DNA

Not applicable





9.7 Interim analyses

Not applicable

9.8 Sample size calculation

The study planned to randomize approximately 496 patients in total, allocated in the ratio of 1:1:2:2:2 to the LIK066 2.5mg qd, 10mg qd, 50mg qd, empagliflozin and placebo treatment groups, respectively.

The following power calculations are based on the primary efficacy variable of log-transformed ratio of NT-proBNP at Week 12 to baseline. Due to the lack of available data in this patient population there is uncertainty on the standard deviation (SD) of the log-transformed ratio of week 12 to BL in NT-proBNP. Therefore calculations are provided for assumptions of SD in the range of 0.8, 0.85 to 0.9 to reflect the impact of this uncertainty on the power estimation. Based on the data from the PARAMOUNT HF study (data on file), a SD of 0.85 was considered a reasonable estimate.

Assuming a one-sided 2.5% significance level (with adjustments for multiple comparisons using the MCP-MOD), a sample size of approximately 496 patients (124 each in placebo and LIK high dose; 62 each in LIK low doses; 124 in empagliflozin that is not included in the dose-response modeling) will provide a mean power (over all candidate models) of 75%(or 90%) to detect a dose response signal, assuming that the underlying true maximum NT-proBNP reduction on LIK066 vs placebo is 25% (or 30%), and the standard deviation (on the log scale) is 0.85.

Table 9-1 Power for detecting a significant dose response signal*

Effect size for best dose	SD	Average power	Minimum power [†]
20%	0.8	58%	54%
20%	0.85	53%	49%
20%	0.9	48%	45%
25%	0.8	80%	76%
25%	0.85	75%	71%
25%	0.9	70%	66%
30%	0.8	93%	91%
30%	0.85	90%	88%
30%	0.9	87%	84%

* Assumes 372 patients in LIK066 and placebo arms with effective sample size of 336 patients due to an effect of missing data equivalent to 10% fewer patients. Calculations were performed using the DoseFinding package in R.

† Power for a significant dose-response contrast test across all scenarios in [Figure 9-1](#). The candidate model Emax with ED50 of 3mg has the lowest power.

Power consideration for assessing the glucose-lowering potential at Week 12

To explore the glucose-lowering potential of LIK066 vs. placebo or empagliflozin (EMPA), the treatment difference in HbA1c change from BL to Week 12 will be considered.

Table 9-2 Comparison of LIK versus placebo (at 2-sided alpha of 0.05)

	Expected treatment difference	SD	Power
LIK high dose (n=124) versus placebo (n=124)*	0.5%	1	96%
Any LIK low dose (n=62) versus placebo (n=124)*	0.5%	1	85%

*assuming 10% information loss due to drop-out.

Table 9-3 Comparison of LIK versus empagliflozin

	Expected treatment difference	SD	Probability of the 95% confidence interval upper bound < 0.4%
LIK high dose (n=124) versus EMPA (n=124)	0	1	84%
Any LIK low dose (n=62) versus EMPA (n=124)	0	1	68%

*assuming 10% information loss due to drop-out.

The calculations in [Table 9-2](#) and [9-3](#) were performed using nQuery 7.0. No multiple testing adjustment was applied.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with 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.

10.2 Informed consent procedures

Eligible patients may only be included in the pre-screening or in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the pre-screening and/or the study, as applicable, to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate

assent form. Informed consent must be obtained before conducting any pre-screening or study-specific procedures (e.g. pre-screening assessments/all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in separate documents proposed pre-screening and study informed consent forms that comply with the ICH GCP guideline and regulatory requirements and are considered appropriate for pre-screening and for participation in the study. Any changes to the proposed consent forms suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form(s), consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Global Development Quality Audit, a group independent from those involved in conducting,

monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 7](#) Safety Monitoring must be followed.

12 References

- Bailey CJ, Gross JL, Pieters A, et al (2010) Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet*; 375: 2223-33.
- Bay M, Kirk V, Parner J, et al (2003) NT-proBNP: a new diagnostic screening tool to differentiate between patients with normal and reduced left ventricular systolic function. *Heart* 2003; 89:150–154.
- Chun S, Tu J, Wijeyesundera H et al, (2012). Lifetime analysis of hospitalizations and survival of patients newly admitted with heart failure. *Circ Heart Fail*; 5: 414-421
- Ferrannini E, Mark M et Mayoux E (2016) CV Protection in the EMPA-REG OUTCOME Trial: A “Thrifty Substrate” Hypothesis. *Diabetes Care* DOI: 10.2337/dc16-0330; published ahead of print
- Fitchett D, Zinman B, Wanner C et al, (2016) Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME trial. *Eur Heart J*; doi:10.1093/eurheartj/ehv728 (published ahead of print)
- Green CP, Porter CB, Bresnahan DR, Spertus JA (2000). Development and evaluation of the Kansas City cardiomyopathy questionnaire: a new health status measure for heart failure. *Journal of the American College of Cardiology*; 35 (5):1245-55.
- Herdman M, et al (2011) Development and preliminary testing of the new five-level version of the EQ-5D (EQ-5D-5L). *Qual Life Res*; 20 (10): 1727-1736.
- Kaznick J, Drzewoski M (2014) Heart failure in the diabetic population – pathophysiology, diagnosis and management. *Arch Med Sci*; 10, 3: 546–556
- Komajda M, Carson PE, Hetzel S, et al (2011) Factors associated with outcome in heart failure with preserved ejection fraction: findings from the Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE). *Circ Heart Fail*; 4: 27–35.
- Masson S, Latini R, Anand IS, et al. (2006). Direct Comparison of B-Type Natriuretic Peptide (BNP) and Amino-Terminal proBNP in a Large Population of Patients with Chronic and Symptomatic Heart Failure: The Valsartan Heart Failure (Val-HeFT) Data. *Clinical Chemistry*; 52: 1528-1538
- Nauck MA, Del Prato S, Meier JJ, et al (2011) Dapagliflozin vs glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin. *Diabetes Care*; 34(9): 2015-22.
- Neal B, Prekovic V, Mahaffey KW, et al. (2017) Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *NEJM*; doi: 10.1056/NEJMoa1611925.
- Nichols GA, Gullion CM, Koro CE et al, (2004). The incidence of congestive heart failure in Type 2 Diabetes. *Diabetes Care* 27:1879–1884
- Nyirjesy P, Zhao Y, Ways K, et al (2012) Evaluation of vulvovaginal symptoms and *Candida* colonization in women with type 2 diabetes mellitus treated with canagliflozin, a sodium glucose co-transporter 2 inhibitor. *Current Medical Research and Opinion*; 28(7): 1173-8.

Pinheiro J, Bornkamp B, Bretz F (2006) Design and analysis of dose finding studies combining multiple comparisons and modeling procedures. *Journal of Biopharmaceutical Statistics*; 16: 639-56.

Pinheiro J, Bornkamp B, Glimm E, et al (2014) Model-based dose finding under model uncertainty using general parametric models. *Statistics in Medicine*; 33: 1646-661

Ponikowski P, Voors AA, Anker SD, et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016 Jul 14;37(27): 2129-200. doi: 10.1093/eurheartj/ehw128. Epub 2016 May 20

Rosenstock J and Ele Ferrannini (2015) Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. *Diabetes Care*; 38:1638–1642

Sattar N, McLaren J, Kristensen S et al, 2016 SGLT2 Inhibition and cardiovascular events: why did EMPA-REG Outcomes surprise and what were the likely mechanisms? *Diabetologia*; 59:1333–1339

Solomon SD, Zile M, Pieske B, et al (2012) The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomized controlled trial. *Lancet*; 380: 1387–95

Solomon SD, Claggett B, Desai AS, et al (2016) Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction: The Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Trial. *Circ Heart Fail*; 9:e002744. doi: 10.1161 (published ahead of print)

Stabin M (2016) RADAR medical procedure radiation dose calculator and consent language generator (Internet) Accessed 10 Oct 2016. Available from: <http://www.doseinfo-radar.com/RADARDoseRiskCalc.html>.

Taegtmeyer H, McNulty P, Young M (2002) Adaptation and maladaptation of the heart in diabetes. *Circulation*; 105:1727-1733

Turk E, Zabel B, Mundlos S, Dyer J, et al (1991) Glucose/galactose malabsorption caused by a defect in the Na/glucose cotransporter. *Nature*; 350: 354–356

van Reenen et Janssen, April 2015. EQ-5D-5L Userguide, Version 2.1 http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/EQ-5D-5L_UserGuide_2015.pdf

Ware J, Sherbourne C (1992). The MOS 36-Item Short –Form Health Survey (SF-36): Conceptual framework and item selection. *Medical Care*, 30 (6): 473-483.

Yancy CW, Jessup M, Bozkurt B et al, (2013) 2013 ACCF/AHA Guideline for the Management of Heart Failure: Executive Summary. *Circulation*;128:1810-1852

Zinman B, Wanner C, Lachin JM, et al, (2015) Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *NEJM*; 373:2117-28

13 Appendix 1: Clinically notable laboratory values and vital signs

Vital signs range deviations are defined as per [Table 13-1](#).

Table 13-1 Vital signs notable range deviations

Vital sign		Notable abnormalities
Pulse (beats/min)		either ≥ 120 + increase $\geq 25^*$ or > 130 either ≤ 50 + decrease $\geq 30^*$ or < 40
BP (mmHg)	systolic	either ≥ 180 + increase $\geq 30^*$ or > 200 either ≤ 90 + decrease $\geq 30^*$ or < 75
	diastolic	either ≥ 105 + increase $\geq 20^*$ or > 115 either ≤ 50 + decrease $\geq 20^*$ or < 40

* Refers to post-BL value as compared to BL value.

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	<ul style="list-style-type: none"> • $3 \times \text{ULN} < \text{ALT} / \text{AST} \leq 5 \times \text{ULN}$ • $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
LIVER EVENTS	<ul style="list-style-type: none"> • $\text{ALT or AST} > 5 \times \text{ULN}$ • $\text{ALP} > 2 \times \text{ULN}$ (in the absence of known bone pathology) • $\text{TBL} > 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) • $\text{ALT or AST} > 3 \times \text{ULN}$ and $\text{INR} > 1.5$ • Potential Hy's Law cases (defined as $\text{ALT or AST} > 3 \times \text{ULN}$ and $\text{TBL} > 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) • Any clinical event of jaundice (or equivalent term) • $\text{ALT or AST} > 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and $\text{INR} > 1.5$	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
$> 5 \text{ to } \leq 8 \times \text{ULN}$	<ul style="list-style-type: none"> • Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms ^b	<ul style="list-style-type: none"> Discontinue the study treatment immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient 	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF 	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient 	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> Discontinue the study treatment immediately Hospitalize the patient Establish causality Complete liver CRF 	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution ^c (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> Consider study treatment interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF 	Investigator discretion

^aElevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

^b(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

^cResolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

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:	
<p><u>Document contributing factors in the CRF:</u> co-medication, other co-morbid conditions, and additional diagnostic procedures performed</p> <p>Monitor patient regularly (frequency at investigator's discretion) until either:</p> <p>Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or</p> <p>Event stabilization: sCr level with \pm10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with \pm50% variability over last 6 months.</p>	