NOVARTIS

Clinical Development

LIK066

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

Statistical Analysis Plan (SAP) Amendment 1

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May, 2018	Before DBL	Changes in planned analyses due to the decision of early study termination	Removed the definition of per-protocol set and its relevant content	Sections 2.2, 2.3.1, 2.5.4, 2.6.1, Tables 5-2, 5-3
			Updated subgroup analyses	Sections 2.2.1, 2.3.2, 2.5.4, 2.6.1.2
			Removed “Week 12 Analysis” and “End of Study Analysis” as defined in the study protocol	Throughout the document, wherever applicable
			Updated efficacy analyses	Sections 2.5, 2.6.1.2, 2.7.1.2, 2.8.2
			Removed “on-treatment” safety analyses	Sections 2.6.2.1, 2.6.2.2
			Removed analyses for treatment interruption	Section 2.4.1
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11-Jul-2018	Before DBL	To align with project standard	Updated the definitions of prior and concomitant medications and non-drug therapies	Section 2.4.2

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Updated the definition of Enrolled Set	Section 2.2

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Chemical classification system
bid	bis in diem/twice a day
BMD	Bone Mineral Density
BMI	Body Mass Index
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECHO	Echocardiography
eCRF	Electronic Case Report Form
ENR	Enrolled Set
FAS	Full Analysis Set
FPG	Fasting plasma glucose
Hb1Ac	Glycated hemoglobin
HF	Heart failure
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
LVEF	Left Ventricular Ejection Fraction
NCI	National Cancer Institute
OAD	Oral Antidiabetic Drug
o.d.	Once Daily
[redacted]	[redacted]
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred Term
qd	Qua'que di'e / once a day
[redacted]	[redacted]
RAN	Randomized Set
RAP	Report and Analysis Process
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SCR	Screened Set
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TFLs	Tables, Figures, Listings
TZD	Thiazolidinedione
WHO	World Health Organization

1 Introduction

Due to the early termination of the study, the planned analyses for a full/complete CSR (as outlined in the study protocol) may not provide clinically and/or statistically meaningful results. Therefore, an abbreviated CSR was planned for the study CLIK066B2204. This document provides details of the statistical analyses to support the completion of the abbreviated Clinical Study Report (CSR) for the study CLIK066B2204.

1.1 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 in type 2 diabetes mellitus (T2DM) patients with heart failure (HF).

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.

Patients will be screened at Visit 1. The screening period (Epoch 1) 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. Patients meeting the eligibility criteria 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.

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):

- 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

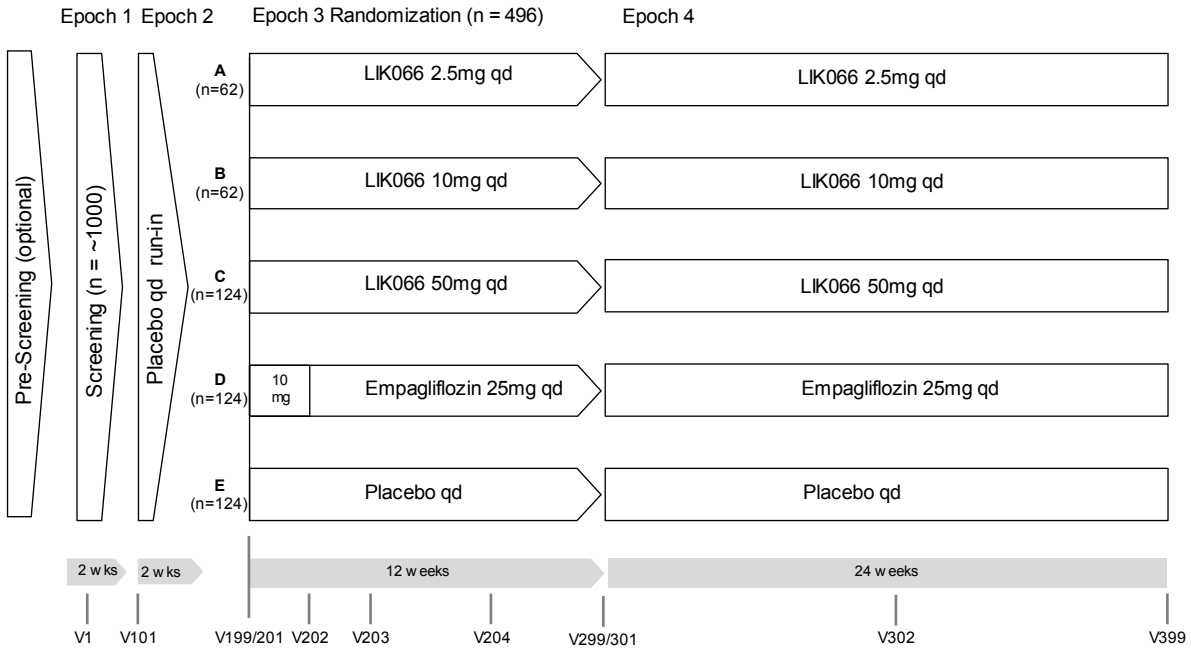
At randomization, patients will be stratified based on geographical region (defined as: North America (Canada, United States), Latin America (Argentina, Guatemala, Mexico), Europe (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Spain, United Kingdom), Asia Pacific and Others (South Korea, Singapore, South Africa, Taiwan)) and the left ventricular ejection fraction (LVEF) measurement at Visit 101: $< 45\%$ versus $\geq 45\%$. 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. The study plans to randomize approximately 496 patients.

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 of the study protocol. During Epoch 3, patients will take the study medication as described in Section 5.5.4 of the study protocol.

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 another 24 weeks to assess long-term efficacy (by HbA1c, echocardiography and NT-proBNP), tolerability and safety.

The analyses for the abbreviated CSR will be carried out after the completion of the study. There will be no interim analysis.

Figure 1-1 Study Design



1.2 Study objectives and endpoints

Table 1-1 Study objectives and endpoints

Objective	Endpoint	Analysis method
Primary objective		

Objective	Endpoint	Analysis method
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	• Change from BL in log-transformed NT-proBNP at Week 12 (i.e., log-transformed ratio of NT-proBNP (pg/mL) collected at Week 12 to BL)	Section 2.5
Secondary objectives		
To evaluate the effect of all LIK066 doses vs placebo at 12 weeks and 36 weeks on: • Change from BL in glycated haemoglobin (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 hs-CRP • 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	• Change from BL in HbA1c • Change from BL in FPG • Change from BL in weight • Change from BL in body composition (total body fat mass, visceral fat mass and lean body mass, assessed by bio-impedance) • Change from BL in body composition (total body fat mass, visceral fat level, lean body mass, assessed by DXA, and body water (calculated), in a subset of patients) • Change from BL in SBP and DBP • 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) • Change from BL in left atrial size and volume assessed by echocardiography	Section 2.6.1

Objective	Endpoint	Analysis method
	• Change from BL in NYHA class	
To evaluate the effect of all LIK066 doses vs empagliflozin at 12 weeks and 36 weeks on: • Change from BL in HbA1c • 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 systolic blood pressure (SBP) and diastolic blood pressure (DBP) • Change from BL in the fasting lipid profile and hs-CRP • Change from BL in 24h urinary glucose and sodium excretion, in a subset of patients	• Change from BL in HbA1c • Change from BL in FPG • Change from BL in weight • Change from BL in body composition (total body fat mass, visceral fat mass and lean body mass, assessed by bio-impedance) • Change from BL in body composition (total body fat mass, visceral fat level, lean body mass, assessed by DXA, and body water (calculated), in a subset of patients) • Change from BL in SBP and DBP • 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)	Section 2.6.1
To evaluate the change from BL to 36 weeks in all LIK066 doses vs placebo on NT-proBNP	• Change from BL in log-transformed NT-proBNP at Week 36 (i.e., log-transformed ratio of NT-proBNP (pg/mL) collected at Week 36 to BL)	Section 2.6.1

Objective	Endpoint	Analysis method
To evaluate safety (adverse events (AEs) and lab parameters) and tolerability of LIK066 over 12 weeks and over 36 weeks for all patients	• Adverse events (AEs) • Deaths • Laboratory data • Vital signs • ECG • Liver events • Renal events	Section 2.6.2
To evaluate 24h urinary calcium and phosphate excretion after 12 weeks and after 36 weeks in a subset of patients	• Change from BL in 24h urinary calcium and phosphate excretion (in a subset of patients)	Section 2.6.2.8
To evaluate bone mineral density (BMD) in a subset of patients	• Change from BL in BMD (in a subset of patients)	Section 2.6.2.9
[redacted]		

Objective	Endpoint	Analysis method
[redacted]		

2 Statistical methods

The following section contains important information on detailed statistical methodology used for analysis and reporting purposes.

2.1 Data analysis general information

Data will be analyzed by Novartis Biostatistics and Statistical Reporting (SR) according to the statistical analysis Section 9 of the study protocol using SAS Version 9.4 or higher. Data collected during the study will be analyzed after the completion of the study. Due to the early termination of the study, the planned analyses for a full/complete CSR (as outlined in the study protocol) may not provide clinically and/or statistically meaningful results. As a result, only limited planned efficacy analyses (as per study protocol) will be performed (see details in Section 2.5, 2.6.1.2, 2.7.1.2). Treatment group in the following sections refers to LIK066 2.5mg qd, LIK066 10gm qd, LIK066 50mg qd, Empagliflozin 25mg qd and Placebo qd unless specified otherwise.

In general, continuous variables will be summarized descriptively by n, mean, SD, median, minimum (min), Q1 (25th percentile), Q3 (75th percentile) and maximum (max), while categorical variables will be summarized descriptively by count and percentage of patients in each category. Graphical presentation of summary data will also be provided as applicable.

2.1.1 General definitions

Study treatment, study medication or study drug

In this document, “study treatment”, “study medication” or “study drug” refers to the investigational, control drug or placebo of this study. Run-in study treatment, study medication or study drug refers to placebo matching LIK066/placebo matching Empagliflozin assigned to the patients during placebo run-in; double-blind study treatment, study medication or study drug refers to LIK066 2.5mg qd, LIK066 10mg qd, LIK066 50mg qd, Empagliflozin (up-titrated from 10mg qd to 25mg qd after 2 weeks) or placebo matching LIK066/placebo matching Empagliflozin assigned to a patient at randomization.

Run-in period

Run-in period refers to Epoch 2 (placebo run-in).

Double-blind period

Double-blind period refers to Epoch 3 (treatment period 1) + Epoch 4 (treatment period 2).

Baseline and study day

Baseline is defined as the last measurement obtained before or at the randomization visit. The first day of administration of randomized study treatment (first dose) is defined as Day 1 for the study. If the date of first administration is missing, then randomization date will be used as Day 1.

All other study days will be labeled relative to Day 1. For event dates on or after Day 1, study day for a particular event date is calculated as [Date of event] – [Date of first dose] + 1. For the dates before Day 1, study day for an event date is calculated as [Date of event] – [Date of first dose]. Duration of an event will be calculated as [Event end date] – [Event start date] + 1. The descriptor "Day 0" will not be used.

2.2 Analysis sets

The following analysis populations will be defined for statistical analysis. Subjects without valid written informed consent will be excluded from all analysis sets. Rules of exclusion criteria of analysis sets are detailed in Appendix 5-4. The analysis sets are defined as follows:

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

Enrolled set (ENR) – All patients who entered the run-in epoch.

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.

2.2.1 Subgroup of interest

Subgroups will be defined to explore the consistency of treatment effects and safety profiling on selected parameters between the subgroups and the overall population.

In Table 2-1, we have listed all subgroups defined for this study and the ways to derive them. Also note that only important parameters or variables in these analyses will have subgroup analyses. The details about the parameters having subgroup analyses will be presented in the corresponding sections as appropriate. Also, additional subgroups may be formed later for regional or country-wise analyses as applicable.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Baseline LVEF (< 45% vs. ≥ 45%)	Derived, using data at baseline	x	x	x

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

The number and percentage of patients successfully screened will be presented. In addition, the reasons for screen failures will be provided. For patients who are screened more than once, the information from the last screening will be used in the summary.

The number and percentage of patients completed and failed in the run-in period will be summarized. The reasons for run-in failures will be summarized. The analysis set is the ENR.

The number of patients randomized (RAN), included in the full analysis set (FAS) and safety set (SAF) will be presented by treatment group. The number and percentage of patients who have completed Epoch 3 (treatment period 1) and Epoch 4 (treatment period 2), respectively, will be summarized by treatment group using the RAN. The number and percentage of patients who discontinued and the reasons for discontinuation will be presented for each treatment group using the RAN. The number and percentage of patients with protocol deviations as well as non-protocol deviation criteria leading to exclusion from analysis sets will be presented by treatment group for the RAN.

2.3.2 Demographics and baseline characteristics

The following demographic and baseline characteristics will be summarized by randomized treatment group for patients in the FAS population:

- **Continuous variables**
  Age (years)
  Height (cm)

Weight at screening (kg)
BMI at screening (kg/m^2)
SBP at baseline (mmHg)
DBP at baseline (mmHg)
Pulse at baseline (bpm)
Respiratory rate at baseline (bpm)
eGFR at baseline (mL/min/1.73m^2)
LVEF at baseline (%)
NT-proBNP at baseline (pg/mL)
Tobacco consumption (pack year(s))
Alcohol consumption (drink(s) per day)

- **Categorical variables**
  Age (<65 years vs. ≥65 years, <75 years vs. ≥75 years)
  Sex (Male vs. Female)
  Race (Caucasian, Black, Asian, Native American, Pacific Islander, Unknown, Other)
  Ethnicity (Hispanic or Latino, East Asian, Southeast Asian, South Asian, West Asian, Russian, Mixed ethnicity, Not reported, Unknown, Other)
  Region* (North America, Latin America, Europe, Asia Pacific and Others)
  LVEF at baseline (< 45% vs. ≥ 45%)
  NYHA class at screening (Class I, II, III, IV)
  NYHA class at baseline (Class I, II, III, IV)
  NT-proBNP at baseline (< median vs. ≥ median)
  Smoker (Never, Current, Former)
  Alcohol consumption (0, > 0 - 1, >1 - 2, >2 - 3, >3 drink(s) per day)

* Region is defined as follows:
  North America (Canada, United States),
  Latin America (Argentina, Guatemala, Mexico),
  Europe (Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Germany, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Spain, United Kingdom),
  Asia Pacific and Others (South Korea, Singapore, South Africa, Taiwan)

The above analyses will also be performed by subgroup: baseline LVEF (< 45% vs. ≥ 45%).

2.3.3 Medical history

Any condition entered on the medical history CRF will be coded using the MedDRA dictionary. The number and percentage of patients with each medical history condition will be provided by primary system organ class (SOC), preferred term (PT) and treatment group.

The number and percentage of patients with hypertension and dyslipidemia on the protocol solicited medical history CRF page will be summarized by treatment group. Heart failure and diabetes history will be summarized descriptively by treatment group for the following: prior history of heart failure (yes/no), primary HF etiology (ischemic/no-ischemic), prior heart failure hospitalization (yes/no), number of heart failure hospitalization in the last 12 months and type 2 diabetes history (yes/no). The FAS will be used for the above analyses.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The duration of double-blind treatment exposure during double-blind period will be summarized by treatment group both descriptively in days (mean, standard deviation, minimum, Q1, median, Q3, and maximum) and by duration category in weeks (≤2, >2-4, >4-8, >8-12, >12-24, > 24) for the SAF.

- Duration of exposure (days) = date of last dose of double-blind study drug – date of first dose of double-blind study drug + 1
- Duration of exposure (weeks) = (date of last dose of double-blind study drug – date of first dose of double-blind study drug + 1)/7

SAF will be used for the above analyses.

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as any recorded medication taken and stopped prior to the date of the first dose of the double-blind study drug.

Concomitant medications for the double-blind period are any medications given at least once between the day of first dose of double-blind study medication and the end of the double-blind period, including those which started pre-BL and continued into the treatment period.

Similarly, prior non-drug therapies are defined as any recorded non-drug therapy taken and stopped prior to the date of the first dose of the double-blind study drug. Concomitant non-drug therapies for the double-blind period are defined as any recorded non-drug therapy given between the day of first dose of double-blind study medication and the end of the double-blind period.

Prior and concomitant medications will be summarized separately by ATC, PT and treatment group. Prior and concomitant non-drug therapies will be summarized separately by primary SOC, PT and treatment group.

The number and percentage of patients meeting rescue criteria and taking rescue medication, and duration of exposure to rescue medication during double-blind period will be summarized by treatment group.

The number and percentage of patients on anti-diabetic medications at baseline (randomization visit) will be summarized by treatment group and medication types as follows:

- Any anti-diabetic medication (insulin or OADs)
  - Insulin
  - OADs (used as single pills)
    - Metformin
    - SU - Sulfonylureas (including Sulfonamides)
    - AGIs
    - TZDs
    - DPP-4 inhibitors
    - GLP-1 analogues
  - Combination of OADs
    - Phenformin + SU
    - Metformin + SU
    - Metformin + TZD
    - SU + TZD
    - Metformin + DPP-4 inhibitor
    - Metformin + AGI
    - DPP-4 inhibitor + TZD
  - Other

The search criteria for the anti-diabetic medications by type are included in Appendix 5.5.

The use of prohibited medications, defined in Table 2-2, will also be summarized.

Table 2-2 Prohibited mediation for reporting

Prohibited Medication	Drug record No. or ATC
SGLT2 inhibitors	A10BK
Clarithromycin	00984601
Telithromycin	01548701
Itraconazole	00780701
Ketoconazole	00532501
Voriconazole	01510101
Posaconazole	01762801
Probenecid	00045101
Valproic Acid	00228501
Mefenamic Acid	00044201

The SAF will be used for the above analyses.

2.5 Analysis of primary objective

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 for ease of data interpretation. The primary endpoint will be analyzed using the FAS.

2.5.1 Primary endpoint

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).

2.5.2 Statistical hypothesis, model, and method of analysis

The Multiple Comparison Procedure-Modeling (MCP-MOD) method (Pinheiro et al, 2006 & Pinheiro et al, 2014) as described in the study protocol will not be performed for the primary endpoint. The following analysis will be performed instead as an exploratory analysis for NT-proBNP. Statistical testing of hypotheses on the endpoint will be performed at the two-sided 0.05 significance level.

The change from baseline in log-transformed NT-proBNP at Week 12 will be analyzed using a mixed effect model of repeated measures (MMRM) in which LVEF at baseline (< 45% vs. ≥ 45%), treatment group, visit, and treatment group-by-visit interaction will be included as fixed-effect factors, and baseline log-transformed NT-proBNP 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 log-transformed NT-proBNP at all post-baseline scheduled visits up to Week 12 and based on likelihood method with an assumption of missing at random (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 log-transformed NT-proBNP at Week 4 and at Week 12 for each treatment group, and for the adjusted mean difference at Week 4 and at Week 12.

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. The analysis results will be back-transformed for ease of data interpretation.

2.5.3 Handling of missing values/censoring/discontinuations

No imputation will be performed for missing NT-proBNP values.

2.5.4 Supportive analyses

Summary statistics (n, mean, standard deviation (SD), median, Q1, Q3, minimum, maximum, geometric mean and its 95% confidence interval) will be presented by visit and treatment for NT-proBNP and change from BL in NT-proBNP in the double-blind period, for all patients and by baseline LVEF (< 45% vs. ≥ 45%). Figures will be produced to visually show the mean changes by visit over 12 weeks of Epoch 3 for each treatment group, for all patients and by LVEF group (< 45% vs. ≥ 45% at baseline).

2.6 Analysis of secondary objectives

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.

2.6.1 Efficacy variables

2.6.1.1 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 (total body fat mass, visceral fat mass and lean body mass, assessed by bio-impedance)
- Change from BL in body composition (total body fat mass, visceral fat level, lean body mass, assessed by DXA, and body water (calculated), 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

2.6.1.2 Analysis method

Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by visit and treatment for the following variables in the double-blind period, for measurement at each visit and change from baseline values:

- HbA1c

- FPG
- SBP and DBP
- Weight
- Body composition (total body fat mass, visceral fat level and lean body mass, assessed by bio-impedance)
- Body composition (total body fat mass, visceral fat mass, lean body mass, assessed by DXA, and body water (calculated), in a subset of patients)
- 24h urinary glucose and sodium excretion (in a subset of patients)
- Left atrial size and volume assessed by echocardiography

In addition, summary statistics will be provided for left atrial size and volume by baseline LVEF (< 45% vs. ≥ 45%).

For the analysis of NT-proBNP, please see details in Section 2.5.

Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum and maximum) will be provided by visit and treatment for the following variable in the double-blind period, for measurement at each visit and percentage change from baseline values:

- Fasting lipid profile (TG, total cholesterol, HDL cholesterol, LDL cholesterol, calculated VLDL cholesterol and non-HDL cholesterol, lipoproteins (apolipoprotein A-I, apolipoprotein B))

Summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum, geometric mean and its 95% confidence interval) will be provided by visit and treatment for hs-CRP in the double-blind period, for measurement at each visit and change from baseline values.

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. NYHA class (I/II/III/IV) will be summarized by visit and treatment group using frequency and percentage. A visit-based shift table will be provided to summarize the NYHA class shifting from BL

All secondary efficacy data will be listed at the individual patient level.

2.6.2 Safety analyses

The safety analyses described in this section will be performed for the SAF.

2.6.2.1 Adverse events (AEs)

Treatment emergent adverse events (TEAEs) during the double-blind period are defined as any AE with start date on or after the start date of the first dose of the study drug during the double-blind period.

The number and percentage of patients with the following types of treatment emergent adverse events during the double-blind period will be provided by primary SOC, PT and treatment group

in separate tables: AEs, SAEs, AEs leading to study drug discontinuation, AEs suspected to be study drug related, and AEs leading to study drug interruption. TEAEs during the double-blind period will also be summarized by primary SOC, PT, maximum severity and treatment group. The most common TEAEs (>=10% in any treatment group) during the double-blind period will be presented by PT in descending order of frequency in the investigational study drug arm, LIK066 50 mg qd.

The following rules apply to the above AE summaries:

- If a patient has multiple AEs within a primary system organ class during the double-blind period, the patient will be counted only once in that primary system organ class
- If a patient has multiple occurrences of an AE with the same PT during the double-blind period, this patient will be counted only once at that PT level.
- An AE with increased severity should be considered and recorded as a new AE.

All TEAEs during the double-blind period will be summarized descriptively by primary SOC, PT and treatment in the following subgroups: baseline LVEF < 45% vs. ≥ 45%.

All AEs will be listed at the individual patient level. The listings will include those AEs reported during the screening and run-in period, and AEs reported after study discontinuation for those who discontinue the study prior to the end of the study.

Deaths occurred during the double-blind period will be summarized descriptively (using number and percentage of patients) by primary SOC and principal cause of death. All deaths will be listed.

2.6.2.2 Adverse events of special interest / grouping of AEs

AEs of special interest that are defined in the Development Safety Profiling Plan (DSPP) can be found in the electronic case retrieval sheet (eCRS) stored in GPS.

The pre-defined issues of special interest for LIK066 including identified risks, potential risks and special assessments are listed below:

- Bone fractures
- Cardiotoxicity
- Diarrhea
- Electrolyte disturbances
- Genital infections
- Hepatotoxicity
- Hypersensitivity
- Hypoglycemia
- Impaired renal function
- Increased LDL
- Intravascular volume depletion

- Ketoacidosis
- Lower limb amputation
- Pre-amputation events
- Malignancy
- Pancreatitis
- Urinary tract infections
- Venothrombotic and embolic events

Treatment-emergent AEs of special interest will be summarized for double-blind period, by risk category, preferred term and treatment group. Treatment emergent AEs of special interest during the double-blind period will also be summarized descriptively by risk category, preferred term and treatment group in the following subgroups: baseline LVEF < 45% vs. ≥ 45%.

Additional analyses for the pre-defined risks of diarrhea, ketoacidosis and hypoglycemia will be performed as described below:

Diarrhea events

Number of days with diarrhea events will be calculated for all patients with at least one diarrhea incidence and will be summarized descriptively by treatment.

- Number of days for one diarrhea incidence = AE end date – AE start date +1.
- Number of days with diarrhea events for a patient = sum of days on diarrhea over all incidences that occurred in the double-bind period.

The number and percentage of patients with diarrhea events during the double-blind treatment period will also be summarized by treatment over time in the following time window: 0 - < 2, 2 - < 4, 4 - < 8, 8 - < 12, 12 - < 16, 16 - < 24, >=24 weeks.

Ketoacidosis events of special interest

All cases of ketoacidosis will be adjudicated by an independent committee. The frequencies and percentages of the adjudication confirmed ketoacidosis events will be provided by treatment.

The site-reported ketoacidosis events will also by summarized by treatment. In addition, the ketoacidosis events will be listed at individual patient level, with the site-reported event profile and symptoms and the adjudication outcome displayed as well.

Hypoglycemic events of special interest

Hypoglycemic events entered into the study Hypoglycemic event eCRF are included in all of the AE summaries in Section 2.6.2.1.

In addition, there are two categories of clinically significant hypoglycemic events defined:

- **Severe hypoglycaemia**: An event, requiring assistance of another person (third party assistance) to actively administer carbohydrate, glucagon, or other corrective actions, confirmed or not by a blood glucose measurement

- **Other clinically significant hypoglycaemia**: Plasma glucose < 3.0 mmol/l (54 mg/dl) with or without typical symptoms of hypoglycaemia, and which is handled by the subject himself/herself.

Hypoglycemia classification is included in the Appendix Table 5-1.

Patients reporting at least one clinically significant hypoglycemic event, and the subgroup of patients reporting ≥2 such events, patients discontinued study medication or withdrew from the study due to clinically significant hypoglycemic events, patients reporting severe hypoglycemic events, and patients reporting other clinically significant hypoglycemic events will be summarized by numbers and percentages in each treatment group. The exposure-adjusted incidence rates, relative risks and the related 95% confidence intervals of LIK groups versus placebo for the overall, severe and other clinically significant hypoglycemic incidences will be calculated respectively, and presented along with other safety risks/events of interest.

The clinically significant hypoglycemic events will also be summarized by event profile as follows:

- Severity (Mild, Moderate, Severe)
- Meeting the definition of an SAE (Yes, No)
- Seriousness (Death, Life threatening, Requires or prolongs hospitalization, Congenital anomaly or birth defect, Significant disability, Other medically important serious event)
- Discontinuation due to hypoglycemic events (Yes, No)
- Relationship to the study treatment (No, Investigational treatment, Other study treatment, Both and/or indistinguishable)
- Action taken with study treatment (Dose increased, Dose not changed, Dose reduced, Drug interrupted, Drug withdrawn, Unknown, Not applicable)
- Medication or therapy taken (Yes, No)
- Outcome (Not recovered/not resolved, Recovered/resolved, Recovered/Resolved with sequelae, Fatal, Unknown)
- Time of the day in 24-hour clock (>00:00–06:00, >06:00–12:00, >12:00–18:00, or >18:00–24:00)
- Time between last meal and event
- Time between last dose and event
- Precipitating factors (None, Missed/delayed meal, Strenuous exercise, Alcohol consumption, Other)
- Third party assistance (Yes, No)
- Medical assistance received (Yes, No)

A listing of AEs of special interest will be presented by treatment group and patient number.

2.6.2.3 Laboratory data

2.6.2.3.1 Hematology, Biochemistry and Urinalysis

Each laboratory parameter in Table 2-3 will be summarized descriptively by visit and treatment group for actual and change from baseline values. The summary will be provided separately for biochemistry, hematology and urinalysis laboratory parameters.

Shift tables based on the standard ranges for each laboratory parameters will be provided by treatment group at each visit to present incidence of transitions from a baseline high, normal or low laboratory value to a post-baseline high, normal or low value.

The number and percentage of patients with clinically notable laboratory results post baseline will be presented in accordance with Table 2-4.

Table 2-3 Laboratory parameters

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

Table 2-4 Clinically notable laboratory values

Parameter	Criteria (based on a percent change from baseline)
Hematology	
RBC (total)	>50% increase, >20% decrease
WBC (total)	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
Clinical chemistry	
ALT	>150% increase
AST	>150% increase
BUN	≥50% increase
Creatinine	≥50% increase
Total bilirubin	>100% increase
ALP	>100% increase
Sodium	>5% increase or >150, or decrease <130 mmol/L

Potassium	absolute values < 3.0 mmol/L, > 5.9 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease and hyper - > 2.6,
Uric acid	>50% increase
Plasma glucose	>50% increase
Plasma glucose	< 3.0 mmol/L (54 mg/dL)

2.6.2.3.2 Bone and renal biomarkers

Serum samples for bone and renal biomarkers will be collected from the patients participating in sub-study 2 at visits indicated in Table 6-1 of the study protocol.

Urine samples for bone and renal biomarkers from the patients participating in the sub-study will be assessed from 24h urine collection.

Table 2-5 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, Ca2+, Mg2+, phosphates (see also Table 6-4 of the study protocol)
Renal biomarkers	Serum cystatin C, urinary cystatin C (24h urine sample), urinary creatinine (24h urine sample), urinary albumin (24h urine sample),

For each biomarker in Table 2-5, the test values and the change from baseline values will be summarized by visit and treatment group using n, mean, geometric mean and its 95% confidence interval, minimum, Q1, median, Q3, and maximum. The analyses will be performed in the SAF population.

2.6.2.4 Vital signs

Sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP) and sitting pulse will be descriptively summarized (by n, mean, standard deviation, median, Q1, Q3, minimum and maximum) for actual value and change from baseline values for each scheduled assessment visit and treatment group. A listing of all patients with notable vital sign values and changes (as defined in Table 2-6) will be provided.

Table 2-6 Vital signs notable range deviations

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

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

2.6.2.5 ECG

The following variables will be descriptively summarized by visit and treatment: QT_cF duration (msec), heart rate (beats/min), PR duration (msec), RR duration (msec), and QRS duration (msec).

The number and percentage of patients meeting the following criteria will be summarized by visit and treatment group for the double-blind period:

- $QT_cF > 500$ msec
- $QT_cF > 480$ msec
- $QT_cF > 450$ msec
- QT_cF increases from baseline ≥ 30 msec
- QT_cF increases from baseline ≥ 60 msec
- PR > 200 and $\leq$ 220 msec
- PR > 220 msec
- PR increases from baseline > 25% (PR > 200 msec)
- QRS > 110 and $\leq$ 120 msec
- QRS > 120 msec
- QRS changes from baseline > 25 % (QRS > 110 msec)
- Heart rate > 100 beats/min
- Heart rate < 50 beats/min

In addition, a visit-based shift table will be provided to summarize the shifting from BL for each ECG parameter.

Cutoff points below are used to define normal or abnormal criteria in the above ECG shift table:

- QTcF: >450 or =<450 msec for male, or, >460 or =<460 msec for female
- QRS: >120 or =<120 msec
- PR: >200 or =<200 msec
- HR: >100 or =<100 beats/min

A listing of ECG parameters together with newly occurring or worsening abnormalities will be provided.

2.6.2.6 Liver events

The liver event and laboratory trigger definitions are specified in the Appendix 2 of the study protocol. Liver event data will be listed.

The number and percentage of patients who meet the liver toxicity criteria in Table 2-7 post baseline will be summarized by treatment group for the double-blind period. Listings of patients with clinically notable LFT values will be provided.

Table 2-7 Criteria for evaluating liver toxicity

Parameter	Criterion
ALT or AST	ALT or AST > 3xULN
	ALT or AST > 5xULN
	ALT or AST > 8xULN
	ALT or AST > 10xULN
Hy's category	ALT or AST >3x ULN and TBL >1.5x ULN
	ALT or AST > 3xULN & TBL > 2xULN
	ALT or AST > 5xULN & TBL > 2xULN
	ALT or AST > 8xULN & TBL > 2xULN
	ALT or AST > 10xULN & TBL > 2xULN
	ALT or AST > 3xULN & TBL > 2xULN & ALP ≤ 2xULN
TBL&ALP	TBL >1.5x ULN and ALP >2x ULN
	TBL >2x ULN and ALP >2x ULN
Isolated TBL	TBL >1.5x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN
	TBL >2x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN
	TBL >3x ULN & ALT and AST ≤3x ULN and ALP ≤2x ULN
Isolated ALP	ALP >1.5x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN
	ALP >2x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN
	ALP >3x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN
	ALP >5x ULN & ALT and AST ≤3x ULN and TBL ≤1.5x ULN

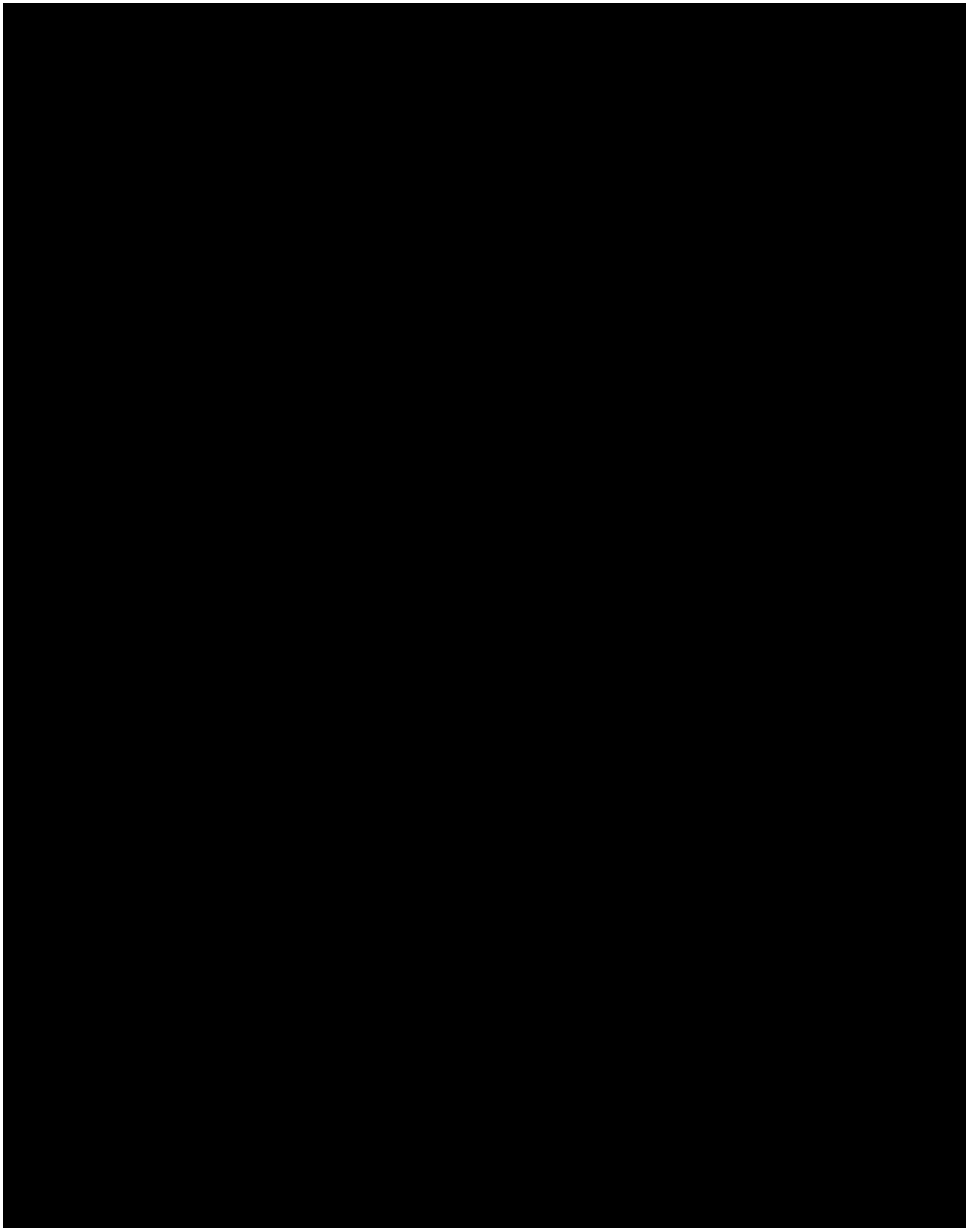
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBL: total bilirubin; ULN: upper limit of normal.

2.6.2.7 Renal events

The specific renal alert criteria and actions are defined in the Appendix 3 of the study protocol. Renal event data will be listed.

2.6.2.8 Other safety analyses (24h urinary calcium and phosphate excretion, bone mineral density (BMD))

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



2.9 Interim analysis

Not applicable

3 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 3-1 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%

Effect size for best dose	SD	Average power	Minimum power†
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 2-1. 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 3-2 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 3-3 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 3-2 and 3-3 were performed using nQuery 7.0. No multiple testing adjustment was applied.

4 Change to protocol specified analyses

Due to the early termination of the CLIK066B2204 study, the following major changes to the protocol specified analyses have been made in the SAP amendment 1:

- "Week 12 Analysis" and "End of Study Analysis" as defined in the study protocol are no longer applicable. The analyses for the abbreviated CSR will be carried out after the completion of the study.
- MCP-Mod will not be performed for the primary endpoint change in log-transformed NT-proBNP at Week 12. Instead, MMRM will be performed as an exploratory analyses for NT-proBNP. See details in Section 2.5.
- Summary statistics will be provided for selected efficacy endpoints. All efficacy endpoints will be listed. See details in Sections 2.5, 2.6.1.2, 2.7.1.2.
- Subgroup analyses will only be performed for demographics and baseline characteristics, primary and key secondary efficacy endpoints summary statistics, AEs and AEs of special interest, in the subgroups LVEF <45% vs. >= 45%.

5 Appendix

The missing or partially missing AE start/end date and concomitant medication start/end date will be imputed using the Novartis ADaM Governance Board (AGB) global standard approach. Details will be provided in the study Programming Datasets Specifications.

5.1.1 Study drug

Any partial dates will be imputed as the earlier day of

- The last day in the month and
- The end day of the corresponding epoch

5.1.2 AE date imputation

AE end date imputation

1. If 'month' is missing, the end date will be set to the earliest of the (min (last visit date, last dose date), 31DECYYYY, and date of death).
2. If 'day' is missing, the end date will be set to the earliest of the (min (last visit date, last dose date), 31MONYYYY, and date of death).
3. If 'year' is missing or AE is ongoing, the end date will not be imputed.

AE start date imputation

Before imputing AE start date, find the AE start reference date.

- If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
- Else AE start reference date = treatment start date

After finding the AE start reference date:

1. If 'year' is missing, the date uncertainty is too high; therefore the imputed AE start date will be set to NULL.
2. If 'year' is less than the treatment start date 'year', the AE started before treatment; therefore:
    a. If 'month' is missing, the AE start date will be set to 01JULYYYY.
    b. If 'day' is missing, the AE start date will be set to 15 MONYYYY.
3. If 'year' is greater than the treatment start date 'year', the AE started after treatment; therefore:
    a. If 'month' is missing, the AE start date will be set to 01JANYYYY.
    b. IF 'month' is not missing, the AE start date will be set to the later of (01MONYYYY, AE start reference date + 1).
4. If 'year' is equal to the treatment start date 'year'
    a. If 'month' is missing, the AE start date will be set to the AE reference start date +1.
    b. If 'month' is less than the treatment start 'month', the AE start date will be set to 15MONYYYY.
    c. If 'month' is equal to or greater than the treatment start 'month', the AE start date will be set to the later of (01MONYYYY, AE start reference date+1).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, imputed AE start date will be set to the (imputed) AE end date.

5.1.3 Concomitant medication date imputation

CM end date imputation

1. If 'day' is missing and 'month/year' are non-missing then impute date as the earlier of (treatment end date, and 31MONYYYY).
2. If 'day/month' are missing and 'year' is non-missing then impute date as the earlier of (treatment end date, and 31DECYYYY).
3. If imputed end date is less than the start date, use the start date as the imputed end date.

CM start date imputation

1. If 'year' is missing, the start date will be set to one day prior to treatment start date.
2. If 'year' is less than treatment start 'year', the CM started before treatment. Therefore:

a. If 'month' is missing, the start date will be set to 01JULYYYY.

b. If 'month' is non-missing, the start date will be set to 15MONYYYY.

3. If 'year' is greater than treatment start 'year', the CM started after treatment. Therefore

   a. If 'month' is missing, the start date will be set to 01JANYYYY.

   b. If 'month' is non-missing, the start date will be set to 01MONYYYY.

4. If 'year' is equal to the treatment start date 'year'

   a. If 'month' is missing or equal to the treatment start 'month', then the start date will be set to one day prior treatment start date.

   b. If 'month' is less than the treatment start 'month', the start date will be set to 15MONYYYY.

   c. If 'month' is greater than the treatment start 'month', the start date will be set to 01MONYYYY.

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date will be set to the (imputed) end date.

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See section 5.1.3.

5.2 AEs coding/grading

AEs will be coded according to MedDRA dictionary. The MedDRA version used for reporting will be described in the footnotes.

Safety topics of interest, defined in the Safety Profiling Plan are defined in the Program Case Retrieval Sheet. Missing severity will be assumed to be severe in the summary table.

Hypoglycemia classification is presented in Table 5-1.

Table 5-1 Hypoglycemia classification

Category	Definition	Criteria as specified in the Hypo eCRF
Severe hypoglycemia	An event, requiring assistance of another person (third party assistance) to actively administer carbohydrate, glucagon, or other corrective actions, confirmed or not by a BG measurement	An event with answer = 'YES' for any one of the two questions: • Was third party assistance required? • Was medical assistance received?

Category	Definition	Criteria as specified in the Hypo eCRF
Other clinically significant hypoglycemia	Plasma glucose < 3.0 mmol/l (54 mg/dl)* with or without typical symptoms of hypoglycaemia, and which is handled by the subject himself/herself.	An event with answer = 'YES' to the question 'Glucose measurement taken' and the plasma glucose < 3.0 mmol/l (54 mg/dl), and answer = NO to both questions: • Was third party assistance required? • Was medical assistance received?

*Blood glucose values need to be converted to plasma glucose values.
A plasma glucose of 3.0 mmol/L (54 mg/dL) corresponds to a whole blood glucose of 2.7 mmol/L (48 mg/dL)
Plasma glucose = blood glucose * 1.12.

5.3 Laboratory parameters derivations

Not applicable

5.4 Rule of exclusion criteria of analysis sets

Criteria defining protocol deviations are referenced in the "Protocol Deviations' tab of the Data Review Plan document. Protocol deviations will be classified into 5 categories as appropriate:

- Selection criteria not met
- Treatment deviation
- Prohibited concomitant medication
- Subject not withdrawn as per protocol
- Other

The protocol deviations leading to the exclusion of patients from analysis sets are outlined in Table 5-2. In addition, the non-protocol deviation criteria leading to the exclusion of patients from analysis sets are outlined in Table 5-3. Table 5-2 and Table 5-3 may be updated according to Data Review Plan document before data base lock.

Table 5-2 Protocol deviations leading to exclusion of patients from analysis sets

Deviation ID	Description of Deviation	Exclusion from Analysis set(s)
INCL01a INCL01b	Informed consent not obtained Informed consent not signed	SCR, ENR, RAN, FAS, SAF
OTH07	Misrandomized in IRT	FAS

Table 5-3 Non-protocol deviation criteria leading to exclusion of patients from analysis sets

Description of Deviation	Exclusion from Analysis set(s)
No study drug taken during double-blind	SAF

5.5 Search criteria for the anti-diabetic medications by type:


Combos - Codes match.pptx


List of _ingredients_anti

Category	Type	ATC code or drug code
Insulin	All insulin A10A	A10A (all insulin), and within this group: A10AB, A10AC, A10AD, A10AE and A10AF
OADs – used as single pills	Metformin	A10BA Biguanides
	SU	A10BB Sulfonylureas A10BC Sulfonamides (heterocyclic)
	AGIs	A10BF Alpha glucosidase inhibitors
	TZDs	A10BG Thiazolidinediones
	DPP-4i	A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors
	GLP-1 analogues	A10BJ Glucagon-like peptide-1 (GLP-1) analogues
Combinations of OADs	See details in the above pptx document Combos – Codes.pptx. Exclude Metformin + SGLT-2i and DDP-4i + SGLT-2i for this study	
Other		A10BX Other

6 Reference

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(5): 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(10): 1646-661.