NOVARTIS

Clinical Development

LIK066

CLIK066B2201 / NCT03100058

A randomized, double-blind, dose-finding study to evaluate the change in weight after 24 weeks treatment with 8 doses of LIK066 compared to placebo in obese or overweight adults, followed by 24 weeks treatment with 2 doses of LIK066 and placebo

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Apr 12, 2017	Before DBL	Prohibited medication list was updated to align with the protocol	More prohibited medications are included.	Table 2-2
Apr 12, 2017	Before DBL	Updates on PK analyses included in the CSR TFLs.	More PK parameters are included.	Section 2.10
Jun 06, 2017	Before DBL	Stratification variable was missing from the statistical model.	Stratification variable was added.	Section 2.7.2.1
[redacted]				
Jun 27, 2017	Before DBL	Updated the repeated ANCOVA model planned for the subgroup analysis	A simpler statistical model used for the subgroup by glycemic status analysis	Section 2.7.2.1
Jun 27, 2017	Before DBL	Updated planned analyses for diarrhea events	Negative binomial model were to be used for the analysis of diarrhea events on treatment	Section 2.8.1.1
Jul 18, 2017	Before DBL	Baseline definition was updated	Both scheduled and unscheduled assessments are included for baseline consideration.	Section 2.1.1
Sep 21, 2017	Before DBL	Project standard hypoglycemia analysis was updated.	Hypoglycemic events of special interest will also be summarized by third party assistance received	Section 2.8.1.1
Sep 25, 2017	Before DBL	Baseline definition was updated	Clearly defined the baselines for different analysis conducted at Epoch 3 and 4, respectively	Section 2.1.1
Sep 28, 2017	Before DBL	Treatment interruption was better defined.	Treatment interruptions were defined for QD, BID and placebo arms, respectively.	Section 2.4.1
Sep 28, 2017	Before DBL	Unblinding after Epoch 3 need to be addressed	Detailed unblinding plan for Week 24 analysis was added.	Section 5.6
Oct 20, 2017	Before DBL	Anti-diabetic medications at BL was updated	GLP-1 analogues and SGLT2 inhibitors were dropped, and anti-diabetic medication at BL will be analyzed by glycemic status	Section 2.4.2
Oct 26, 2017	Before DBL	ECG normal and abnormal criteria was missing	ECG normal and abnormal criteria was defined	Section 2.8.5

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
Nov 9, 2017	Before DBL	Project-wise updates for PPS definition	PPS included only patients on treatment for at least 22 weeks	Section 2.2
Nov 9, 2017	Before DBL	Project-wise updates for supportive analysis of the primary endpoint	On-treatment data will be used for the primary endpoint analysis	Section 2.5.2
Nov 13, 2017	Before DBL	Project-wise updates for hypoglycemia analysis	Clinically significant hypo events were defined and the way of reporting were updated	Section 2.8.1.1 Section 5.2
Dec 4, 2017	Before DBL	New PD on life style (weight gain>=2kg during run in) was added	The new PD need to be excluded from PP set	Table 5.2 and 5.3
Jan 18, 2017	Before DBL	Single best fit model is less robust	Single best dose response model fit was removed from reporting	Section 2.5.4
Jan 25, 2017	Before DBL	Updated multiple imputation algorithm	MCMC was being implemented.	Section 2.5.3
Feb 14, 2018	Before DBL	Updated Non-PD criteria to exclude subjects from analysis set	Not having informed consent was removed from Non-PD criteria because it was a PD	Section 5.4
Feb 14, 2018	Before DBL	Updated description on PD listing.	The final PDs for the study will be exactly the same as Table 5-2 and Table 5-3	Section 2.2
Feb 14, 2018	Before DBL	Model averaging to obtain the dose responses for qd and bid dosing regimens was updated	A parametric bootstrap-based model averaging approach was being implemented	Section 2.5.2
Mar 22, 2018	Before DBL	Clarified AEs included in the analyses	Updated definitions for treatment emergent AEs and defined on-treatment AEs	Section 2.8.1
Mar 22, 2018	Before DBL	Updated AE listings for reporting	Removed AE listings for Week 24 analysis, and added for overall analysis	Section 2.8.1
May 11, 2018	Before DBL	Reduced the final outputs because of the Week 24 IA results and updated duration of exposure categories for EoS analysis as per decision at the TFL review meeting	Removed subgroup analysis, rescue medication, and treatment interruption for overall treatment period for the EoS analysis, and categories of duration were updated as per TFL.	Section 1.2 Section 2.4.1 Section 2.4.2 Section 2.7.2.2 Section 2.13
May 17, 2018	Before DBL	Updated treatment arms in the safety analysis	For safety analysis other than AE listings only 4 actual treatment arms to be used	Section 2.1.1

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List of abbreviations

AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic classification
AUC	area under the curve
bid	bis in diem/twice a day
BL	baseline
BMI	body mass index
CSR	clinical study report
CTC	common toxicity criteria
CTCAE	common terminology criteria for adverse events
DB	database
DBP	diastolic blood pressure
DMC	data monitoring committee
DSPP	development safety profiling plan
FAS	full analysis set
FPG	fasting plasma glucose
eCRF	electronic case report form
[redacted]	[redacted]
HbA1c	hemoglobin A1c
hsCRP	high sensitivity C-reactive protein
IVR	interactive voice response
IWR	interactive web response
LOCF	last observation carry forward
LS	least squares
MedDRA	medical dictionary for drug regulatory affairs
o.d.	once daily
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetics
PPS	per-protocol set
[redacted]	[redacted]
qd	qua'que di'e / once a day
[redacted]	[redacted]
RAP	report and analysis process
RECIST	response evaluation criteria in solid tumors
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	system organ class
TFLs	tables, figures, listings
T2DM	type 2 diabetes mellitus
UGE	urinary glucose excretion
WHO	world health organization

1 Introduction

The purpose of this document is to outline the planned analyses to be completed to support end of phase 2 meetings with health authorities and the completion of the clinical study report (CSR) for protocol CLIK066B2201.

Note that this version of the statistical analysis plan details the statistical methodology for the analyses planned and agreed to at the time of finalization of the protocol version 00 (original protocol).

1.1 Study design

This is a multi-center, randomized, double-blind, parallel-group dose-finding study evaluating the effect on weight, tolerability and safety of LIK066 vs placebo (see Figure 1-1). The study planned to randomize approximately 432 subjects in total, allocated in the ratio of 1:1:1:1:1:2:1:1:1:2 to the following 10 Epoch 3/Epoch 4 treatment groups:

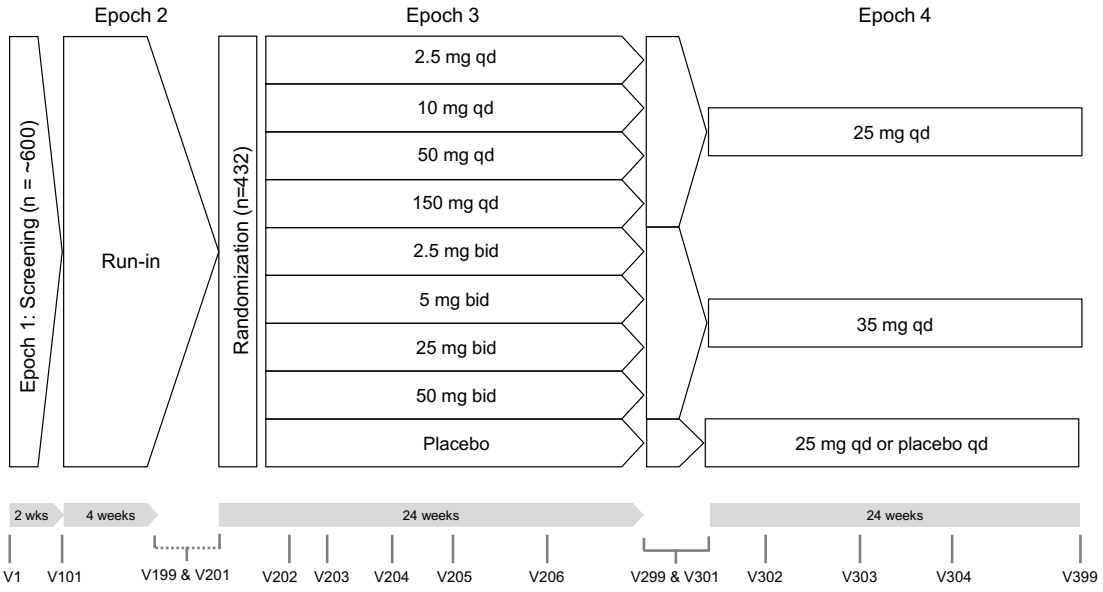
1. placebo/placebo
2. placebo/LIK066 25 mg qd
3. LIK066 2.5 mg qd/25 mg qd
4. LIK066 10 mg qd/25 mg qd
5. LIK066 50 mg qd/25 mg qd
6. LIK066 150 mg qd/25 mg qd
7. LIK066 2.5 mg bid/35 mg qd
8. LIK066 5 mg bid/35 mg qd
9. LIK066 25 mg bid/35 mg qd
10. LIK066 50 mg bid/35 mg qd

The randomization will be stratified by subjects' glycemic status at screening: normoglycemic, dysglycemic and type 2 diabetes mellitus (T2DM).

There will be no interim analysis for the study. The main analysis will be performed at the end of Epoch 3 when all subjects complete their treatment at Week 24 after randomization and data collected up to and including Week 24 (Visit 299) are cleaned (referred to as "*Week 24 analysis*" in sections below). The main analysis will be summarized in a report which will be used for internal and external decision making and will serve as the basis of end of phase 2 discussions with the health authorities.

Data collected during Epoch 4 will be analyzed after the study ends (referred to as "*End of study analysis*" in sections below). Both Week 24 analysis and end of study analysis will be presented in the CSR.

Figure 1-1 Study design



1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary objective		
To determine the dose-response signal and assess the dose-response relationship of two dose regimens of LIK066 as measured by the percent change from baseline (BL) in body weight relative to placebo after 24 weeks of treatment	Percent change from BL at Week 24 in body weight	Section 2.5.2
Secondary objectives		
To assess the responder rates according to percent decrease in body weight either ≥5% or ≥10%, from BL at Week 24, for the overall population and each of the subgroups (normoglycemic subjects, dysglycemic subjects, and subjects with T2DM)	Proportion of patients with percent change from BL at Week 24 in body weight: • ≤ - 5% • ≤ - 10%	Section 2.7.2.1
To assess the dose-response relationship for weight loss in normoglycemic subjects, dysglycemic subjects and subjects with T2DM after 24 weeks of treatment	Percent change from BL at Week 24 in body weight	Section 2.7.2.1
To evaluate the effect of all LIK066 doses and regimens vs placebo for the overall population	Change from BL at Week 24 in:	Section 2.7.2.1

and by subgroups after 24 weeks of treatment on: • Waist circumference • Change from BL in glycated hemoglobin A1c (HbA1c) • Change from BL in fasting plasma glucose (FPG) • Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) • Percent changes in the fasting lipid profile and high sensitivity C-reactive protein (hsCRP) • 24-h urinary glucose excretion (UGE) in a subset of subjects	• Waist circumference • HbA1c • FPG • SBP and DBP • 24-h UGE Percent change from BL at Week 24 in: • Lipid parameters • log_{10} transformed hsCRP	
To evaluate the change in weight and other efficacy parameters listed above in the overall population by LIK066 treatment vs placebo between Week 24 and Week 48	Change from Week 24 at Week 48 in efficacy parameters listed above	Section 2.7.2.2
To evaluate safety (adverse events (AEs) and laboratory parameters) and tolerability of LIK066 over 24 weeks of treatment and over 48 weeks of treatment for all subjects	Safety outcomes include: • AEs/SAEs • Death • Laboratory data • Vital signs • ECG • Liver events • Renal events • Bone and renal biomarkers	Section 2.8.1 Section 2.8.2 Section 2.8.3 Section 2.8.4 Section 2.8.5 Section 2.8.6 Section 2.8.7 Section 2.12
To evaluate AEs of interest and laboratory data in subjects treated with LIK066 25 mg qd, 35 mg qd or placebo between Week 24 and Week 48 (during Epoch 4)	AE of special interest, diarrhea, ketoacidosis, hypoglycemic event, etc.	Section 2.8.1
To evaluate 24-h urinary calcium and phosphorus excretion after 24 weeks of treatment and after 48 weeks of treatment in a subset of subjects	Change from BL at Week 24 and at Week 48 in the 24-h urinary calcium and phosphorus excretion	Section 2.8.3

To evaluate the pharmacokinetics (PK) of LIK066	• Concentration • Lapsed time	Section 2.10
[redacted]		

2 Statistical methods

2.1 Data analysis general information

Data will be analyzed by Novartis according to the data analysis Section 9 of the study protocol. Important information is given in the following sections and details are provided, as applicable, in Appendix 16.1.9 of the CSR. SAS Version 9.4 or higher will be used to perform all the statistical analyses in the report.

Unless otherwise stated, summary tables/figures/listings will be on all subjects included in the population under consideration.

In general, for continuous data, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum will be presented. Categorical data will be presented as frequencies and percentages of patients in each category. For categorical variable summaries, an additional category 'Missing' will be presented if there are missing values for that variable.

If not otherwise specified, p-values will be presented for two-sided hypothesis testing and two-sided confidence intervals will be displayed; the level of significance will be 5% unless otherwise stated.

2.1.1 General definitions

Baseline (Week 0) for Week 24 analysis and overall analysis including both Epoch 3 and Epoch 4 data will be defined as the last measurement before or at the randomization visit. Baseline for End of study analysis including Epoch 4 data only will be defined as the last measurement in Epoch 3.

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.

For Week 24 analysis, the treatment groups presented are:

- LIK066 2.5 mg qd
- LIK066 10 mg qd
- LIK066 50 mg qd
- LIK066 150 mg qd
- LIK066 2.5 mg bid
- LIK066 5 mg bid
- LIK066 25 mg bid
- LIK066 50 mg bid
- Placebo
- Total (if applicable)

For End of study analysis, unless specified otherwise, the following treatment grouping strategy will be used, expressed as per the Epoch 3 treatment/Epoch 4 treatments a subject is assigned to at randomization:

- LIK066 qd any dose/LIK066 25 mg qd, shortened as LIK066 qd/LIK066 25 mg qd
- LIK066 bid any dose/LIK066 35 mg qd, shortened as LIK066 bid/LIK066 35 mg qd
- Placebo/LIK066 25 mg qd
- Placebo/placebo, shortened as Placebo
- Total (if applicable)

For End of study AE listings, the 10 randomized treatments will be used, as shown in Section 1.1 study design, along with the additional two pooled groups:

- LIK066 qd any dose/LIK066 25 mg qd, shortened as LIK066 qd/LIK066 25 mg qd
- LIK066 bid any dose/LIK066 35 mg qd, shortened as LIK066 bid/LIK066 35 mg qd
- Total (if applicable)

For overall analysis including both Epoch 3 and Epoch 4 treatment, the 10 randomized treatment grouping strategy will be used, as shown in Section 1.1 Study design.

For the Week 24 analyses, data collected up to the end date of Epoch 3 will be included. For AEs and concomitant medications, this means that events with start dates prior to the end of Epoch 3 dates are included.

2.2 Analysis sets

Screened set (SCR): the SCR consists of all subjects who signed the ICF.

Randomized set (RAN): All subjects who have received a randomization number, regardless of receiving trial medication.

Run-in set (RUN): All subjects who enter the run-in epoch.

Full analysis set (FAS): the FAS comprises all subjects to whom study treatment has been assigned, except those who are not qualified for randomization but were inadvertently randomized into the study and did not take any study drug. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization.

Safety set (SAF): the SAF includes all subjects who received at least one dose of study medication. Subjects will be analyzed according to treatment received. Note that the safety set allows the inclusion of non-randomized subjects who received the study drug in error.

Per-protocol set (PPS): the PPS is a subset of the FAS. It consists of all randomized subjects in the FAS who have been exposed to study medication for at least 22 weeks and have no major protocol deviations (PDs) affecting the primary endpoint analysis.

Randomized set – Epoch 4 (RAN-Epoch 4): all randomized subjects who have been assigned a treatment in Epoch 4.

Full analysis set – Epoch 4 (FAS-Epoch 4): all RAN-Epoch 4 subjects, excluding those who did not take any Epoch 4 study medication.

Safety set – Epoch 4 (SAF-Epoch 4): all SAF subjects who received at least one dose of Epoch 4 study medication.

Protocol deviations will be pre-specified prior to un-blinding treatment codes for analyses. See Appendix Table 5-2 and Table 5-3 for list of protocol deviations and criteria that lead to exclusion from analysis sets, and related rules of exclusion criteria of analysis sets.

2.2.1 Subgroup of interest

Subgroups of interest include:

- Glycemic status (dysglycemic, normoglycemic, and T2DM)
- Age (<65, ≥65)
- Sex (Male, Female)
- BMI (<30, ≥30; <35, ≥35)
- Region (North America, Europe)

Table 2-1 provides an overview of how subgroups are defined/derived and what type of analyses may be performed. Details are specified in relevant sections below.

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Glycemic status (dysglycemic, normoglycemic, and T2DM)	Screening	X	X	X
Age groups: (<65, ≥65 years)	Screening (derived)		X	X
Sex (Male/Female)	Screening		X	X
BMI (<30, ≥30; <35, ≥35)	Baseline		X	
Region (North America, Europe)*	Screening (pooled countries)		X	

* North America: USA and Canada; Europe: Austria, Czech Republic, Hungary, Slovakia and United Kingdom.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Demographics and other baseline characteristics

Week 24 analysis

Demographics, BL characteristics, disease history and medical history will be summarized overall (total) and by treatment group for the FAS. Descriptive statistics (mean, Q1, median, Q3, standard deviation, minimum and maximum) will be presented for continuous variables for each treatment group and for all subjects (total). The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects (total). Demographics and BL characteristics will be similarly summarized by the stratification factor (glycemic status at screening) as well.

Continuous variables:

- Age
- Height
- Weight
- Body mass index (BMI)
- Waist circumference (cm)
- Smoking pack years
- Baseline pulse (bpm)
- Baseline systolic blood pressure (mmHg)
- Baseline diastolic blood pressure (mmHg)
- Baseline HbA1c (%)
- Baseline FPG (mg/dL)

- Baseline eGFR MDRD mL/min/1.73m2

Categorical variables

- Age category (< 65, ≥ 65)
- Gender
- Subjects of child bearing status (females only)
- Race
- Ethnicity
- Smoking status at baseline
- Alcohol history (0, 1, 2, >=3 drinks/day)
- BMI (<30, ≥30; <35, ≥35)
- Glycemic status (dysglycemic, normoglycemic, and T2DM)
- Baseline HbA1c category (<6.5, ≥6.5 - < 8%, ≥8%)
- Baseline eGFR MDRD category (<60, ≥60 mL/min/1.73m2)

BMI will be calculated using the following formula:

$$\text{BMI} = (\text{body weight in kilograms}) / (\text{height in meters})^2$$

For BMI, the last value of height and body weight prior to randomization will be used.

Medical history will be coded with the medical dictionary for regulatory activities terminology (MedDRA) using the most recent version at the time of database lock. The number and percentage of subjects with each medical condition will be provided by treatment group, primary system organ class, and preferred term.

The protocol solicited medical history events (hypertension, dyslipidemia, prediabetes, sleep apnea, type II diabetes, bariatric surgery, lactic acidosis, urinary tract infection, myocardial infarction, stroke and unstable angina) will be summarized by event type, event status (yes, no, unknown), and treatment.

End of study analysis

Demographics and other BL characteristics including medical history will be similarly summarized for FAS subjects who enter the study Week 24 to Week 48 period (Epoch 4) as for the Week 24 analysis.

2.3.2 Patient disposition

RAN will be used for the summary and listing of patient disposition.

Week 24 analysis

Based on the SCR, the number and percentage of patients screened will be presented. In addition, the primary reasons for screen failures will be summarized by presenting number and

percentage of screen failed patients by category. The number and percentage of subjects entered, completed, and failed in run-in will be summarized using the RUN. The reasons for run-in failures will be provided. The number and percentage of randomized subjects who completed the Epoch 3, who discontinued the Epoch 3 and the reasons for discontinuation will be presented for each treatment group using the RAN.

The number of randomized subjects included in each analysis set (FAS, SAF, and PPS) will be presented by treatment group. The number and percentage of subjects with protocol deviations as well as the criteria leading to exclusion from analysis sets will be presented in separate tables for the RAN. Subject exclusion from analysis sets will be listed with reasons for exclusion.

The number of randomized subjects included in each analysis set (FAS, SAF, and PPS) will also be presented by treatment group and glycemic status.

End of study analysis

The number of RAN subjects who entered Epoch 4, completed Epoch 4, and who discontinued Epoch 4 and the reasons for discontinuation will be presented for each treatment group.

Subject randomization number and whether they completed or were discontinued from Epoch 3 and/or Epoch 4 will be listed, with date of last dose and primary reason for discontinuation, including unblinding date if applicable, by 10 randomized treatment arms. Flags will be included to indicate misrandomized patients and forced randomization.

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

2.4.1 Study treatment / compliance

Week 24 analysis

The duration of double-blind treatment exposure in Epoch 3 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, >12-16, >16-20, >20-24, and >24) for the SAF.

- Duration of exposure (days) = last dose date of Epoch 3 – first dose date + 1
- Duration of exposure (weeks) = (last dose date of Epoch 3 – first dose date + 1)/7

Overall subject-years on-treatment in Epoch 3 will be reported by each treatment group.

- Overall subject-years on-treatment = sum of duration of treatment exposure (in days) from all subjects / 365.25

The duration of double-blind treatment exposure excluding treatment interruptions in Epoch 3 will also be summarized descriptively and by duration categories as above.

- Duration of exposure excluding treatment interruptions (days) = last dose date of Epoch 3 – first dose date + 1– number of days of treatment interruption

Treatment interruptions will be considered as following:

- For BID doses – patients taking 0 tablets for both morning and evening doses,
- For QD doses – patients taking 0 tablets for the morning dose,
- For Placebo – patients taking 0 tablets for both morning and evening doses.

Number and percentage of subjects with treatment interruption and permanent treatment discontinuations in Epoch 3 will be provided by reason for treatment interruption or discontinuation.

Duration of treatment interruption, frequency and duration of the PD after meal dose intake will also be summarized as appropriate.

End of study analysis

The duration of Epoch 4 will be summarized by treatment group both descriptively in days and by duration-category in weeks (≤4, >4-12, >12-24, and >24) for subjects in the safety set who enter the study Week 24 to Week 48 period (Epoch 4), respectively.

- Epoch 4 duration of exposure (days) = last dose date – first dose date of Epoch 4 + 1
- Epoch 4 duration of exposure (weeks) = (last dose date – first dose date of Epoch 4 + 1)/7

Duration of treatment interruption, frequency and duration of PD after meal dose intake will also be summarized as appropriate.

The duration of overall treatment period (Epoch 3 + Epoch 4) will also be summarized by 10 randomized arms both descriptively in days and by duration-category in weeks (≤4, >4-12, >12-24, >24-36, >36-48, and >48), respectively.

- Overall duration of exposure (days) = last dose date – first dose date + 1
- Overall duration of exposure (weeks) = (last dose date – first dose date + 1)/7

Number and percentage of subjects with treatment interruption and permanent treatment discontinuations in overall treatment period will be provided by reason for treatment interruption or discontinuation. Frequency and duration of PD after meal dose intake will be included for reporting as well.

2.4.2 Prior, concomitant and post therapies

Week 24 analysis

Prior medications are defined as any drugs taken and stopped prior to the first dose of study medication. Concomitant medications for Epoch 3 are any medications given at least once between the day of first dose of double-blind study medication and the end of Epoch 3, including those which started pre-BL and continued into the treatment period.

The number and percentage of subjects receiving prior and concomitant medications will be summarized by treatment group and overall in the SAF in separate tables by therapeutic class and preferred term.

The number and percentage of subjects taking rescue medication, and duration of exposure to rescue medication during Epoch 3 will be summarized by treatment group.

The number and percentage of subjects on anti-diabetic medications at BL (randomization visit) will be summarized by treatment, glycemic status, and medication types:

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

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

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

Table 2-2 Prohibited medication for reporting

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

Prohibited Medication	Drug record No. or ATC
GLP-1 receptor agonists	A10BJ
Weight loss medication	A08A

End of study analysis

Concomitant medications for Epoch 4 are any medications given at least once between the start and the end of Epoch 4, including those which started before and continued into Epoch 4. Concomitant medications subjects take during Epoch 4 will be similarly summarized for subjects in SAF who enter Epoch 4.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary analysis variable is the percent change in body weight (kg) from BL at Week 24. BL is defined as the last body weight value measured prior to or at the randomization visit (Visit 201). The analysis will be carried out on the FAS, with missing Week 24 values imputed as described in section 2.5.3.

2.5.2 Statistical hypothesis, model, and method of analysis

The objective of determining a dose response signal and dose-response relationship in either qd or bid dosing regimen compared to placebo will be evaluated using an optimally weighted contrast test following the methodology described in Pinheiro et al. (2006) and Pinheiro et al. (2014). To this end, a candidate model set is defined corresponding to the range of expected mean response in each of the dosing regimen. The candidate model set is used to generate a set of weights for the calculation of optimal contrasts between the responses in the studied dose groups and the placebo group. A statistical test comparing all doses in the different dosing regimens simultaneously to the control group is used, hence a multiplicity adjustment is applied that accounts for the multiple possible dose response behavior considered as well as the common placebo between the dosing regimens. A critical value is derived from a multivariate t-distribution using the correlation matrix induced by the correlations between the weights corresponding to the candidate sets as well as the correlation between the tests of shapes in the dosing regimens to the common placebo group.

Test of the dose response signal

The null hypothesis of a flat dose-response relationship for the percentage reduction in body weight 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 percent body weight.

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

- H_{01}: there is no dose-response relationship for LIK066 given qd
- H_{11}: there is a dose-response relationship for LIK066 given qd
- H_{02}: there is no dose-response relationship for LIK066 given bid

- H_{12}: there is a dose-response relationship for LIK066 given bid

Given that we suspect the dose-response may behave differently between qd and bid regimens based on the data we have seen from the proof-of-concept study LIK066X2201, we define separate sets for the dose-response candidate models for each dosing regimen. 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 for each dosing regimen will be individually compared to the critical value derived using a multiplicity adjustment accounts for all tests of comparing LIK066 doses to placebo across regimens simultaneously as described above. The rejection of the null hypothesis for each dosing regimen will be achieved using the maximum test statistic in each dosing regimen from each estimated contrast test in the candidate set.

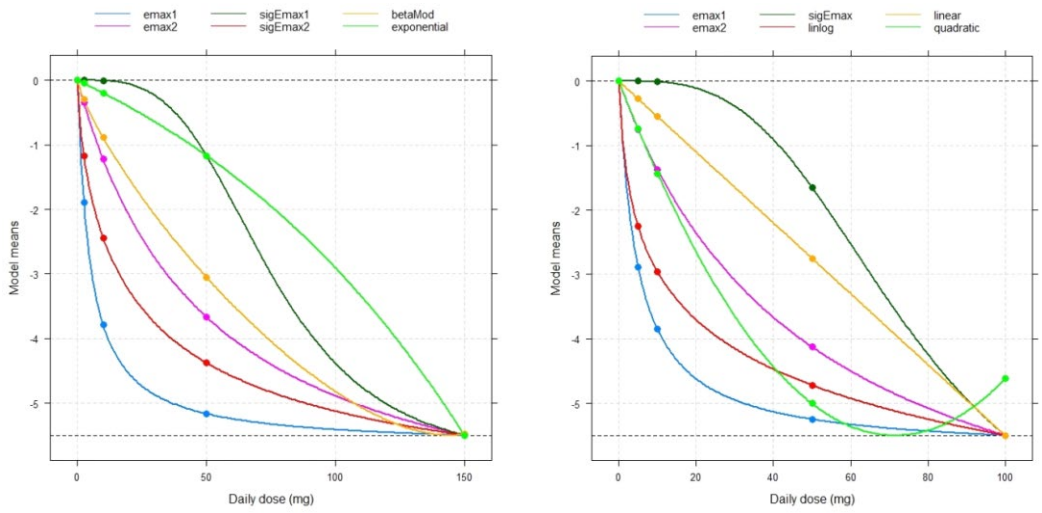
The candidate models generating the contrast weights are described in table 2-3 and depicted in Figure 2-1, with the doses used to define parameters of interest being defined as total daily dose.

The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) model with the percent change in body weight from BL to Week 24 as a response variable, treatment (placebo and all LIK066 doses from each regimen), stratum indicator (dysglycemic/ normoglycemic/T2DM) and region as factors and BL weight as a covariate. Centers will be pooled according to country and region for the purpose of analysis.

Table 2-3 Candidate dose-response models in consideration

#	Candidate models for qd regimen	Candidate models for bid regimen
1	E_{max} model: ED_{50} = 5 mg	E_{max} model: ED_{50} = 5 mg
2	E_{max} model: ED_{50} = 50 mg	E_{max} model: ED_{50} = 50 mg
3	Sigmoid E_{max}: ED_{50} = 75 mg, H = 3.5	Sigmoid E_{max}: ED_{50} = 75 mg, H = 3.2
4	Sigmoid E_{max}: ED_{50} = 25 mg, H = 0.7	Linear log-dose: null, c = 0.8
5	β-model: α = 0.8, β = 0.2, scale = 180	Linear
6	Exponential: λ = 125	Quadratic: δ = -0.007

Figure 2-1 Dose-response curve of candidate models (left panel: qd regimen)



The response variable of percent change in body weight from BL to Week 24 used in the above ANCOVA is from an imputed dataset, where the missing Week 24 weight is imputed using the multiple imputation method as described in Section 2.5.3. 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 for the two regimens 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 percent changes of body weight as Week 24 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 in the two regimens and the common critical value $C_{0.025}$. $C_{0.025}$ is the common critical model derived from the reference multivariate t-distribution with the 12 × 12 correlation matrix induced by testing the candidate dose response models with respect to comparing all candidate models in both dosing regimens to the common placebo group.

The intersection hypotheses H_{01} and H_{02} will be rejected and the statistical significant of dose-response in body weight reduction established if the max (t1, t2, t3, …, t11, t12) $\geq C_{0.025}$. In other words, the intersecting null hypothesis requires the rejection of either H_{01} or H_{02}.

Model averaging to obtain the dose responses for qd and bid dosing regimens

A parametric bootstrap-based model averaging approach will be implemented to obtain the dose response estimates for qd and bid dosing regimens according to the following steps:

1. The parametric bootstrap procedure will draw a sample of mean percent changes in body weight from baseline to Week 24 for all doses (including placebo) from a multivariate normal distribution, with mean and covariance matrix was determined using Rubin's rule, as described earlier. This sample corresponds to the mean response for each dose (including placebo).
2. Model selection will be performed as follows: general dose-response models as specified in Table 2-3 will be fit to this bootstrap sample for qd and bid regimen separately, i.e. Emax, Sigmoid Emax, β-model and Exponential model will be fit to mean response data from placebo and qd doses, and Emax, Sigmoid Emax, Linear log-dose, Linear and Quadratic model will be fit to mean response data from placebo and bid doses. The best model based on the gAIC criterion will be selected for qd and bid regimen separately.
3. After selecting the best models for qd and bid separately, a combined model with parameters corresponding to the individually selected models but with a single parameter for the placebo group will be fitted to the bootstrap sample, i.e. the sampled mean responses for all doses (including placebo).
4. The dose response estimate will be calculated for each dose group, including placebo, using this combined model. The difference in estimated dose response between each dose and placebo will also be calculated. The target doses of interest in each dosing regimen will be calculated based on this common model as well.

5. The above procedure (steps 1-4) will be repeated 5,000 times. The mean dose-response estimates by dose group and mean differences of dose-response estimates between each LIK dose and placebo, the target doses of interest, as well as their 95% confidence intervals will be calculated based on the quantiles (median, 2.5th and 97.5th percentiles) of these multiple sets of dose-response and target dose estimates generated in step 4.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for the primary endpoint will be imputed using a multiple imputation approach that assumes that the missingness mechanism can be retrieved from observed data (missing at random; MAR). The imputation model will be fitted within each treatment and stratum, using MCMC method, based on the longitudinal sequence of body weight data collected at each visit up to and including Week 24.

2.5.4 Supportive analyses

As a sensitivity analysis, the dose-response modeling as described in Section 2.5.2 will be conducted in the PPS as well. In addition, the same dose-response modeling will be conducted in the FAS using on-treatment weight data only. On-treatment data refer to those collected during the double-blind period, and prior to or within 7 days of the final study medication intake date in Epoch 3.

Summary statistics for body weight will be presented by visit and treatment for observed and imputed values. The summary statistics n, mean, standard deviation, median, minimum, maximum, Q1 and Q3 will be presented for the BL values and similarly for absolute values at post-BL and percent changes from BL to the post-BL visits. Summary statistics for body weight will also be presented by visit and treatment for observed values by subgroups of interest: age group, gender, BMI categories and region.

Figures will be produced to visually show the raw and the imputed mean percent changes as well as the estimated mean percent changes from the dose response modeling by visit over 24 weeks of Epoch 3 for each treatment group.

In addition, the individual patients' percent change in body weight from BL at Week 24 will be depicted by waterfall plot as appropriate.

2.6 Analysis of the key secondary objective

There is no key secondary objective for the study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

2.7.1.1 Week 24 analysis variables

- Responder rates based on percent decrease in body weight from BL at Week 24 ≥ 5 %, or ≥ 10 %.
- Dose-response relationship in normoglycemic subjects, dysglycemic subjects and subjects with T2DM after 24 weeks of treatment.

- Change from BL at Week 24 in waist circumference.
- Change from BL at Week 24 in HbA1c.
- Change from BL at Week 24 in FPG.
- Change from BL at Week 24 in SBP and DBP.
- Percent changes from BL at Week 24 in the fasting lipid profile (TG, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, lipoproteins, calculated very low density lipoprotein (VLDL) cholesterol and non-HDL cholesterol).
- Percent change from BL at Week 24 in hsCRP (log_{10} transformed).
- Change from BL at Week 24 in 24-h UGE.

2.7.1.2 End of study analysis variables

Changes from Week 24 to study end in each efficacy variable, body weight, FPG, HbA1c, SBP, DBP, lipid parameters, hsCRP (log_{10} transformed), 24-h UGE and waist circumference.

2.7.2 Statistical model and method of analysis

All analyses on secondary variables will be performed using the FAS.

2.7.2.1 Week 24 analysis

Responder analysis

For the responder analysis, a logistic regression model will be performed using the percent decrease in body weight from BL at Week 24 ≥ 5% or ≥ 10% (yes/no) as a response variable, treatment, glycemic stratification factor and region as fixed factors and BL body weight as a covariate, respectively. The Week 24 missing values will be imputed using the multiple imputation method as described in Section 2.5.3. In order to account for the imputation uncertainly, this logistic regression model will be repeated for each imputed dataset, which results in a set of estimated odds ratio and associated 95% confidence intervals for each LIK066 dose vs placebo contrast, for all dose groups and regimens. Rubin's rule will be used to combine the multiple sets of odds ratios and 95% confidence intervals to a single set of odds ratio and its 95% confidence interval of an LIK066 dose vs placebo. Similar analysis by glycemic status stratification factor will be performed to assess the responder rate for each of the subgroups (normoglycemic subjects, dysglycemic subjects and subjects with T2DM).

In addition, subjects meeting the predefined response criteria (percent decrease in body weight from BL at Week 24 ≥ 5 % or ≥ 10 %) will be summarized by treatment for all subjects and by glycemic stratification factor. A Cochran-Mantel-Haenszel-test will be performed to compare each qd or bid dose to the common placebo.

Dose-response relationship by glycemic stratification factor

For the dose-response relationship in normoglycemic subjects, dysglycemic subjects and subjects with T2DM, the dose-response modeling with the same candidate model sets for the

primary variable as described in Section 2.5.2 will be performed on percent change of body weight from BL at Week 24 for these three subsets of subjects separately.

Summary statistics for body weight will be presented by visit and treatment for observed and imputed values by glycemic stratification factor. Figures will be produced to visually show the raw mean percent changes and the adjusted mean percent changes from the dose response modeling by visit over 24 weeks of Epoch 3 for each treatment group by glycemic stratification factor as well.

Other secondary endpoints

For changes from BL at Week 24 in HbA1c, FPG, SBP, DBP, waist circumference and 24-h UGE, a repeated measure ANCOVA model with treatment, visit, stratification factor (normoglycemic, dysglycemic, and T2DM), pooled center or region, and treatment by visit interaction as fixed-effect factors, BL and BL by visit interaction as covariates, and a common unstructured covariance matrix among visits between treatments will be performed separately for each variable. The adjusted mean changes at Week 24 within each treatment, the differences in mean changes at Week 24 between the LIK066 and placebo treatments, and their 95 % confidence intervals obtained from the above model will be presented. The analysis is based on likelihood method with an assumption of MAR for missing data.

The same repeated measure ANCOVA model will be fitted for each stratum (normoglycemic, dysglycemic, and T2DM) as well, and the adjusted mean changes at Week 24 within each treatment, the differences in mean changes at Week 24 between the LIK066 and placebo treatments for each stratum, and their 95% confidence intervals obtained from the above models will be presented by strata for each efficacy endpoint.

Similar repeated measure ANCOVA models will be performed for percent changes of lipid parameters and $\log_{10}$ transformed hsCRP from BL at Week 24.

Summaries of absolute values and change from BL by treatment group and visit will be presented for all secondary efficacy variables for all subjects and by strata. Figures will be produced to visually show the raw mean changes by visit over 24 weeks of Epoch 3 for each treatment group, for overall and by strata separately.

2.7.2.2 End of study analysis

All analyses will be performed in subjects in the FAS who enter Epoch 4.

A repeated measure ANCOVA model with treatment, visit, pooled center or region, and treatment by visit interaction as fixed-effect factors, BL and BL by visit interaction as covariates, and a common unstructured covariance matrix among visits between treatment will be performed separately for the changes from Week 24 to study end in each efficacy variable (body weight, FPG, HbA1c, SBP, DBP, lipid parameters, hsCRP in $\log_{10}$ transformation, 24-h UGE and waist circumference). The adjusted mean changes from Week 24 to Week 48 within each treatment, the differences in mean changes from Week 24 to Week 48 between the LIK066 and placebo treatments, and their 95% confidence intervals obtained from the above models will be presented. The analysis is based on likelihood method with an assumption of MAR for missing data.

Note that for lipid parameters and hsCRP in log_{10} transformation, the percent changes (instead of absolute change) from Week 24 to study end will be used as a response variable in the above repeated measure ANCOVA model. For HbA1c and FPG, the repearted measure ANCOVA will be fitted for each stratum (normoglycemic, dysglycemic, and T2DM); and for 24-h UGE, the repeated measure ANCOVA will be fitted for both overall population and for each stratum.

Summaries of absolute values and changes (and/or percent changes for body weight and lipid parameters) from Week 24 by treatment group and visit will be presented for all efficacy variables, for all subjects, and by stratification strata if applicable.

2.7.3 Handling of missing values/censoring/discontinuations

Missing body weight at Week 24 will be imputed using the multiple imputation method as described in Section 2.5.3.

Repeated measure ANCOVA models, which use all available data, will be used to analyze other secondary variables. The approach yields valid results, i.e. confidence intervals with correct coverage and tests with the correct size under a missing at random (MAR) process (Siddiqui et.al. 2009).

2.8 Safety analyses

All Week 24 safety analyses will be performed in the SAF, and all End of study safety analyses will be performed for subjects in the SAF who enter Epoch 4.

2.8.1 Adverse events (AEs)

Week 24 analysis

A treatment-emergent AE for Week 24 is defined as any AE in Epoch 3 that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment. Following the definition, AEs occurring after treatment discontinuation will also be considered as treatment-emergent AEs. Treatment emergent AEs will be summarized for Week 24 analysis. The number and percentage of subjects having AEs will be summarized by system organ class, preferred term, and treatment group. Unless otherwise specified, primary system organ will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the investigational study drug arm (LIK066 150 mg qd). If a patient reported more than one AE with the same preferred term, the AE will be counted only once. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once at the system organ class level. The number and percentage of subjects having AEs will be summarized by system organ class, preferred term, treatment group, and subgroups of interest (glycemic status, age group and sex) as well.

The most frequent AEs (>=2% in any treatment group) will be presented by preferred term in descending order of frequency in the investigational study drug arm, LIK066 150 mg qd.

AEs will also be presented by greatest severity. If a patient reported more than one AE with the same preferred term, the highest severity will be presented. All AEs will be summarized by highest severity, primary system organ class, preferred term, and treatment. If a patient reported

more than one AE within the same primary system organ class, only one AE will be counted for that patient at the highest severity level in the total row for each primary system organ class. Missing severity will be assumed to be severe in the summary table.

AEs suspected to be related to study drug, serious AEs, fatal AEs, and AEs leading to study drug discontinuation, study drug interruption will be summarized by presenting number and percentage of patients with an event by primary system organ class, preferred term, and treatment.

Week 24 on-treatment AEs are defined as any treatment-emergent AEs occurred while patients were on Epoch 3 treatment (captured using treatment start and end date). On-treatment AEs, serious AEs, fatal AEs, AEs leading to study drug discontinuation, and AEs of special interest will also be summarized.

End of study analysis

A treatment-emergent AE for the End of study analysis is defined as any AE that develops after the start of Epoch 4 or any event already present in Epoch 3 that worsens following exposure to the study treatment during Epoch 4. AEs occurring after treatment discontinuation will also be considered as treatment-emergent AEs. The number and percentage of subjects having AEs, SAEs, AEs leading to study medication permanent discontinuation and study drug interruption occurring after start of Epoch 4 will be summarized and presented, in similar way as for the Week 24 analysis.

Overall treatment emergent AEs for the overall 48 weeks of Epoch 3 plus Epoch 4 by 10 randomized treatments will be generated.

All AEs in the database will be listed by 10 randomized arms. The listings will include those AEs reported during the run-in epoch, and AEs reported after study completion or discontinuation.

Legal requirement for AE reporting

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent AEs which are not SAEs with an incidence greater than 2% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class, preferred term, and 10 randomized treatment arms on the SAF for overall study duration.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment/non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.1.1 Adverse events of special interest / grouping of AEs

AEs of special interest, such as risks defined in the development safety profiling plan (DSPP), or topics of interest regarding signal detection or routine analysis, are defined in the electronic case retrieval sheet (eCRS) that is 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
- Malignancy
- Pancreatitis
- Urinary tract infections
- Venothrombotic and embolic events
- Lower limb amputation

Week 24 analysis

Treatment-emergent AEs of special interest which occur during Epoch 3 will be summarized by risk category and preferred term, by treatment. The AEs of special interest will be summarized by risk category, preferred term, treatment, and subgroups of interest (glycemic status, age group, and sex) as well.

In addition, exposure-adjusted incidence rates per 100 patient years regardless of study drug relationship, by treatment will be provided by risk category and preferred term. The 95% confidence interval for the overall exposure-adjusted incidence rates per 100 patients will also be presented for each risk category, along with relative risk and 95% confidence interval.

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

Diarrhea events of special interest

Number of days with on-treatment diarrhea events will be calculated for all patients with at least one incidence of on-treatment diarrhea 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 Epoch 3.

The number and percentage of patients with diarrhea events during the double-blind treatment period (while patients on study medication) will also be summarized by treatment over time in the following time window: 0 - <2, 2 - <4, 4 - <8, 8 - <12, 12 - < 16, 16 - < 20 and >= 20 weeks.

The number of days with diarrhea events while on-treatment in Epoch 3 will be analyzed using a generalized linear model assuming a negative binomial distribution. The negative binomial model accounts for any over dispersion that may result from assuming a Poisson distribution by allowing a different Poisson rate for each patient and assuming that these rates as a set are distributed across subjects according to a gamma distribution. The log(overall days on study medication) will be used as the offset variable in the model. The model will be adjusted for treatment, glycemic status, and region.

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 be 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 2.8.1.

In addition, there are two categories clinically significant of 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, Requires or prolongs hospitalization, Life threatening, Congenital anomaly or birth defect, Significant disability, Other medically importance 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)

In addition, for pre-defined risk and selected AEs including hypotension, hypoglycemia, hyperkalemia, diarrhea, genital infections and UTIs, a by-stratification factor of BL glycemic status subgroup analysis will be provided.

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

End of study analysis

The AEs of interest collected during Epoch 4 will be summarized as appropriate separately.

2.8.2 Deaths

Any deaths up to and including Week 24 will be included in a separate AE table by treatment group for Week 24 analysis summarizing fatal events. Additional deaths in Epoch 4 will be included in a separate AE table similarly for the End of study analysis.

Deaths will also be listed by treatment groups for both Week 24 analysis and End of study analysis.

2.8.3 Laboratory data

Table 2-4 Laboratory data

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, creatinine, cystatin C, eGFR (MDRD), magnesium, phosphates, potassium, protein (total), sodium, uric acid, γ-GT, amylase, lipase
Urinalysis	pH, specific gravity, protein, glucose, ketones, nitrites, blood, leucocytes, Urine albumin to creatinine ratio (spot urine)

All laboratory samples will be processed through the central laboratory. Laboratory data consist of hematology, clinical chemistry, and urinalysis.

Hematology data are collected at Visit 1, 201, 205, 299/301, 302, 303, and 399; clinical chemistry data are collected at Visit 1, 201, 203, 205, 299/301, 302, 303, and 399; and Urinalysis are collected at Visit 201, 205, 299/301, 303, and 399.

Week 24 analysis

Descriptive summary statistics including for the change from BL to each study visit up to and including Week 24 visit will be presented by treatment group for each laboratory parameter, as well as for the maximum change from BL. In addition, shift tables will be provided for all parameters with available ranges to compare a subject's BL laboratory evaluation relative to the most extreme post-BL value. For the shift tables, normal ranges as well as specifically defined clinically notable/abnormality limits, if available – will be used.

A listing of all patients with notable laboratory values will be provided.

Urinary calcium and phosphorus excretion will be collected for a subset of subjects participating in the PK analysis. The change from BL in the 24-h urinary calcium and phosphorus excretion will be descriptively summarized by treatment and visit.

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline are shown in Table 2-5.

Table 2-5 Clinically notable laboratory abnormalities for selected tests

Parameter	Criteria (based on a percent change from baseline or 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, >150 mmol/L, <130 mmol/L
Potassium	absolute values < 3.0 mmol/L, > 5.9 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease, hyper > 2.6 mmol/L
Uric acid	>50% increase
Plasma glucose	>50% increase
Plasma glucose	< 3.0 mmol/L (54 mg/dL)

End of study analysis

Descriptive summary statistics including for the change from Week 24 to each post-Week 24 study visit during Epoch 4 will be presented by treatment group for each parameter, as well as for the maximum change from BL. In addition, shift tables will be provided for all parameters with available ranges to compare a subject's Week 24 laboratory evaluation relative to the most extreme post-Week 24 value.

The change from Week 24 in the 24-h urinary calcium and phosphorus excretion will be descriptively summarized by treatment and visit (for post-Week 24 visits only) for a subset of subjects participating in the PK analysis.

A listing of all patients with notable laboratory values will be provided as well.

2.8.4 Vital signs

Week 24 analysis

For vital sign data collected during Epoch 3, descriptive statistics will be provided for absolute values and change from baseline at each assessment time point by treatment group as appropriate.

The number and percentage of patients with newly occurring or worsening notable values, including notable change from baseline will be summarized by vital sign parameter at each

assessment time point by treatment group. Notable absolute values and notable changes from baseline for each vital sign parameter are defined in Table 2-6 and Appendix 1 of the protocol.

A listing of all patients with notable vital sign values and changes will be provided.

End of study analysis

Similar analysis to that done at Week 24 will be conducted for the end of study analysis for vital sign data collected during Epoch 4.

Table 2-6 Vital signs notable range deviations

Vital signs		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.

2.8.5 ECG

The following quantitative variables will be summarized: QT_cF duration (msec), Heart rate (beats/min), PR duration (msec), RR duration (msec), and QRS duration (msec).

Week 24 analysis

Changes from baseline for ECG variables will be provided; for QTcF and heart rate, inferential statistics will be generated as well.

The number and percentage of subjects with the following criterion will be presented.

- 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 ≤ 220 msec
- PR > 220 msec
- PR increases from baseline > 25% and to a value > 200 msec
- QRS > 110 and ≤ 120 msec
- QRS > 120 msec
- QRS changes from baseline > 25 % and to a value > 110 msec

- Heart rate > 100 beats/min
- Heart rate < 50 beats/min

In addition, shift tables comparing baseline ECG results (normal, abnormal, not available, total) with the maximum on-study result (normal, abnormal, not available, total) will be provided for each variable.

Cutoff points below are used to define normal or abnormal criteria:

- QTcF: >450 or =<450 msec for male and >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.

End of study analysis

Similar analyses outlined for Week 24 will be provided for the End of study analysis.

2.8.6 Liver events

Week 24 analysis

Liver events and laboratory trigger definitions and follow-up requirements are defined in Appendix 2 of the protocol.

The laboratory parameters for liver function will be shown in the laboratory standard tables as discussed in Section 2.8.3. In addition, summary tables will be provided on the number and percentage of subjects who meet the following liver toxicity criteria post baseline by Week 24.

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

Parameter	Criterion
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.

End of study analysis

Summary tables will be provided on the number and percentage of subjects who meet the liver toxicity criteria after Week 24 until end of the study (Epoch 4).

2.8.7 Renal events

Week 24 analysis

The overall frequency of events and percentage of patients with renal events during the treatment period will be provided for the Week 24 analysis. Furthermore, the frequency and percentage of patients with renal events during Epoch 3 will be provided by treatment and the first identified criterion. The frequency of patients with renal events and percentage will be provided for clinical signs and symptoms by the treatment.

Renal event overview data, pathology data, and imaging data will be provided in listings.

The renal function lab data will be analyzed in Section 2.8.3 Laboratory data.

End of study analysis

Similar analyses will be conducted for the End of study analysis for those patients who entered Epoch 4 of the study.

Table 2-8 Specific renal alert criteria

Criteria	Action required
Serum event	
Serum creatinine increase 25 – 49 % compared to BL	Confirm 25 % increase after 24-48h Follow up within 2-5 days
Acute kidney injury: serum creatinine increase ≥50 % compared to BL	Follow up within 24-48h if possible Consider study treatment interruption Consider subject hospitalization /specialized treatment
Urine event	
New dipstick proteinuria ≥ 1+	Confirm value after 24 to 48-h

Albumin- or protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR

2.9 Pharmacokinetic endpoints

Not applicable.

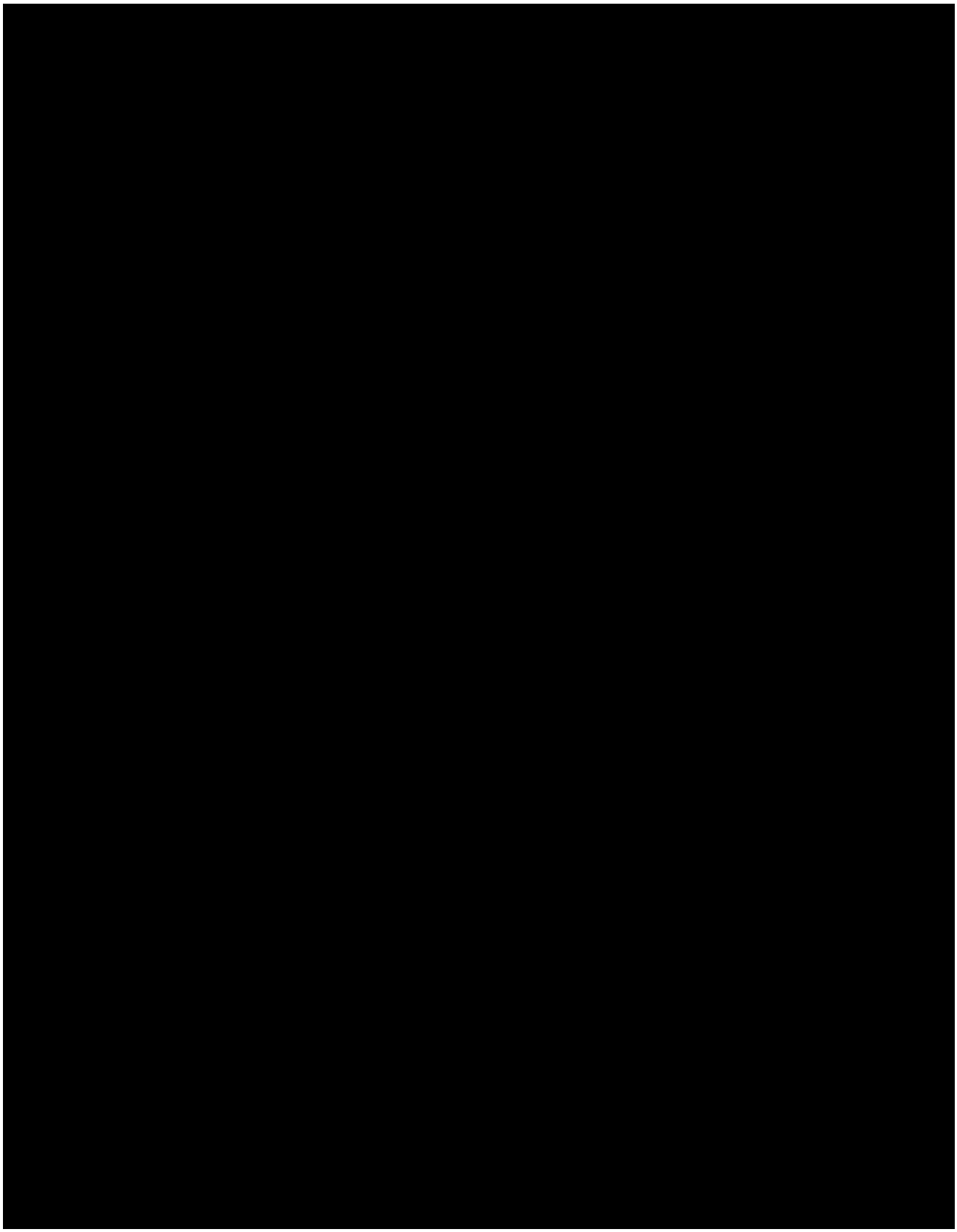
2.10 PK analyses

PK sampling will be performed at visits 205, 299/301, and 303. Blood samples will be collected at time-points: 0h (pre-dose) and approximately 1h, 2h, 4h, and 6h post dose.

Plasma concentration of LIK066 and scheduled time from dosing will be summarized by treatment and visit/sampling time point. PK parameters (Cmax, Tmax, AUClast, AUC0-t) will be listed and summarized. Descriptive statistics includes n, mean, standard deviation, minimum, median, maximum, coefficient of variation (%) for arithmetic mean, geometric mean, and coefficient of variation (%) for geometric mean.

Concentrations below the lower limit of quantification (LLOQ) will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Individual LIK066 plasma concentration data will be listed by treatment, subject, and visit / sampling time point.



2.12 Biomarkers

Serum samples for bone and renal biomarkers, and urine bone biomarkers will be collected from subjects who participate in the PK substudy. Biomarkers are collected at Visit 201, 205, 299/301, 303, and 399. Data will be analyzed based on SAF.

Table 2-9 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, estradiol, calcium, magnesium, phosphates
Renal biomarkers	Serum cystatin, urinary cystatin cystatin C/creatinine ratio (spot urine)

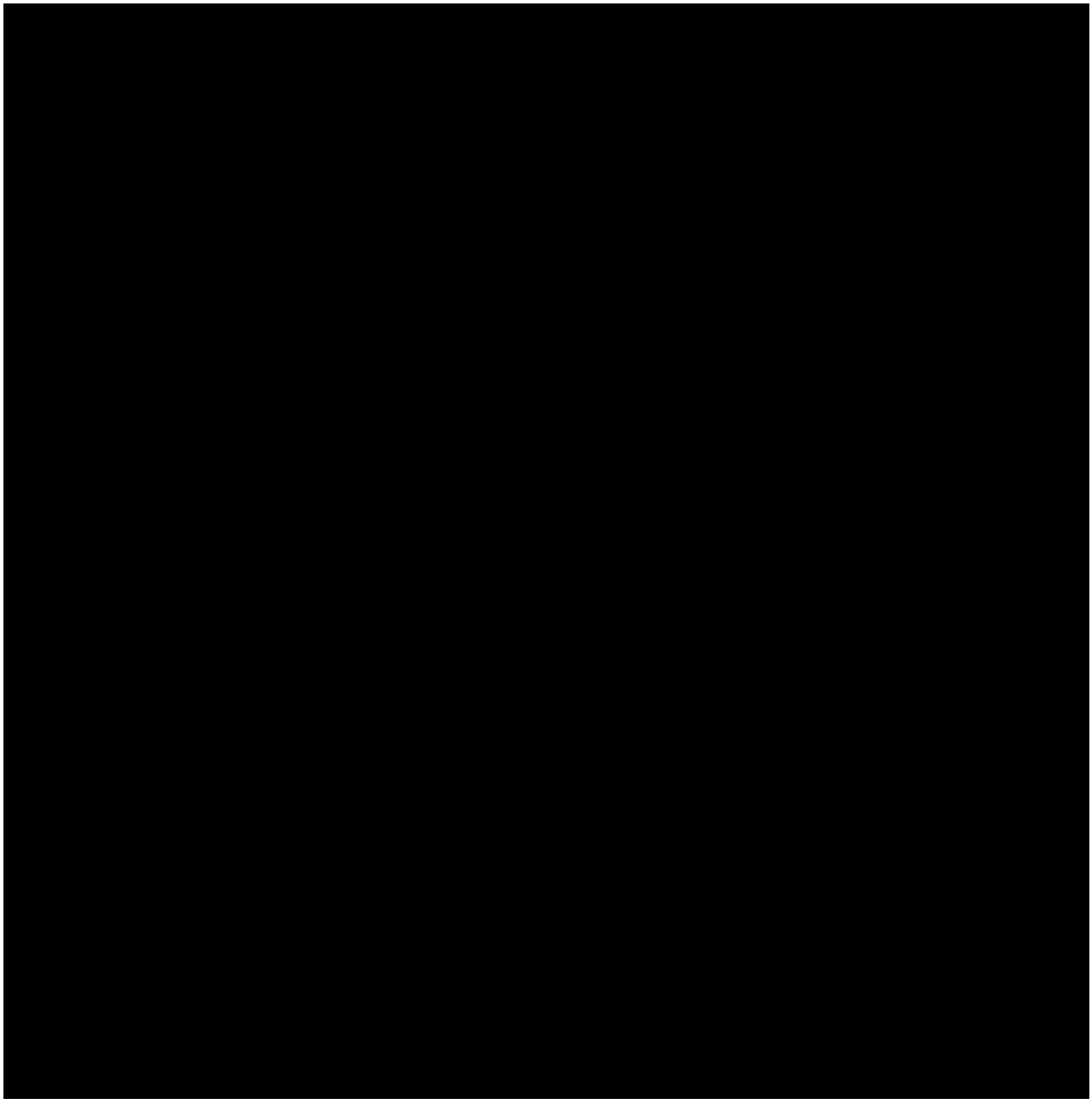
Week 24 analysis

Summaries of absolute values and change from BL in each of the bone, renal, and inflammatory biomarkers by treatment group and visit will be presented using statistics: n, mean, SD, median, minimum, maximum, Q1, Q3, geometric mean and coefficient of variation. Figures will be

produced to visually show the mean values by visit over 24 weeks of treatment in Epoch 3 for each treatment group.

End of study analysis

The absolute values and change from Week 24 in each of the bone, renal and inflammatory biomarkers will be similarly summarized and depicted as for the Week 24 analysis.



2.14 Interim analysis

Not applicable.

3 Sample size calculation

The study planned to randomize approximately 432 subjects in total, allocated in the ratio of 1:1:1:1:1:2:1:1:1:2 to the following 10 Epoch 3/Epoch 4 treatment groups:

1. placebo/placebo
2. placebo/LIK066 25 mg qd
3. LIK066 2.5 mg qd/25 mg qd
4. LIK066 10 mg qd/25 mg qd
5. LIK066 50 mg qd/25 mg qd
6. LIK066 150 mg qd/25 mg qd
7. LIK066 2.5 mg bid/35 mg qd
8. LIK066 5 mg bid/35 mg qd
9. LIK066 25 mg bid/35 mg qd
10. LIK066 50 mg bid/35 mg qd

This randomization scheme implies that the Epoch 3 treatment and Epoch 4 treatment for a specific subject is determined simultaneously at randomization visit. The randomization will be stratified by subjects' glycemic status at screening: normoglycemic, dysglycemic and T2DM.

As the dose-response assessment is conducted in qd and bid regimens separately (while an overall family-wise type I error is controlled at a one-sided significance level of 2.5 %), power calculation was done for testing dose-response signal by regimen as well. Table 3-1 summarizes the average power and the lowest power across the candidate dose response shapes in Figure 2-1 by regimen, under different scenarios with the assumptions on effect size of body weight loss (percent change from BL) for the dose of maximum effect, and the related standard deviations.

Note that a dose-response signal is detected (ie the primary objective is met) as long as either of the dose-response signals for the two regimens is detected. Therefore, the overall study power is at least the maximum of the powers between two regimens for each scenario considered.

Table 3-1 Power for detecting a significant dose response signal*

Dose regimen	Effect size for best dose	SD	Average power**	Minimum power†
Qd	5 %	5.5 %	99.99 %	99.98 %
	5 %	6.5 %	99.71 %	99.57 %
	6 %	5.5 %	99.99 %	99.99 %
	6 %	6.5 %	99.99 %	99.98 %
Bid	5 %	5.5 %	99.16 %	95.84 %
	5 %	6.5 %	96.50 %	86.79 %
	6 %	5.5 %	99.90 %	99.43 %
	6 %	6.5 %	99.28 %	96.36 %

Dose regimen	Effect size for best dose	SD	Average power**	Minimum power†

* Assumes 432 subjects in LIK066 and placebo arms with effective sample size of 367 subjects due to an effect of missing data equivalent to 15 % fewer subjects. Calculations were performed using the DoseFinding package in R.

† Power for a significant dose-response contrast test across all scenarios within each regimen in Table 3-1. The candidate model #5 in bid regimen has the lowest power.

It was assumed that the effect of losses to follow-up is equivalent to effectively having 15 % fewer subjects than randomized, even if the multiple imputation approach used to handle missing values should be able to recover some information for such subjects.

4 Change to protocol specified analyses

[redacted]

In protocol section 9.5.1.1 change from BL at Week 24 in hsCRP was listed as one of the secondary efficacy variables, and this has been modified to percent change from BL at Week 24 in hsCRP in $\log_{10}$ transformation in the SAP.

5 Appendix

5.1 Imputation rules

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 date imputation need to be done twice, once for Week 24 analysis, and once for the End of study analysis.

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 date imputation need to be done twice, once for Week 24 analysis and once for the End of study analysis.

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. 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?
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

Protocol deviations are identified prior to clinical database lock/unblinding and entered into a dedicated data panel as part of the locked database. Details are provided in the PD Specs and Edit Checks tab of LIK066B2201 Edit Check Specification document.

The protocol deviations resulting in exclusion of subjects from an analysis population are outlined in Table 5-1 below.

Table 5-2 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Informed consent not obtained	Excluded from SCR, RUN, RAN, FAS, SAF, and PPS
TRT19	Subject withdrew consent and not discontinued from the study	Data collected after withdrawal of IC, excluded from FAS and SAF
TRT34	Patients mis-randomized in IRT	Excluded from FAS and PPS
INCL03	BMI not within range or BMI missing	Excluded from PPS
EXCL04	Subject taking prohibited medication	Excluded from PPS
EXCL05	Patient with a history of malignancy	Excluded from PPS
EXCL06	Pregnant patient	Excluded from PPS
EXCL08	Use of active weight-loss medications	Excluded from PPS
EXCL09	Bariatric surgery	Excluded from PPS
EXCL10b	Not compliant with lifestyle intervention	Excluded from PPS
EXCL19	Substances or alcohol abuse	Excluded from PPS
TRT06	Study treatment adjusted	Excluded from PPS
TRT11	Study treatment unmasked and subject not discontinued from the study	Excluded from PPS
TRT15	Use of prohibited medication and not discontinued from the study	Excluded from PPS
TRT22	Use of another investigational drug while on study	Excluded from PPS
TRT35	Study medication taken after the morning or evening meal	Excluded from PPS
TRT28	Misdispensed medication and taken by patient	Excluded from PPS

Table 5-3 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
SCR	INCL01	Not having screening epoch disposition page

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
RUN	INCL01	Not in ENR; Not having run-in epoch disposition page
RAN	INCL01	Not randomized
FAS	INCL01, TRT19, TRT34	Not in RAN;
PPS	INCL01, INCL03, EXCL04, EXCL05, EXCL06, EXCL08, EXCL09, EXCL10b, EXCL19, TRT06, TRT11, TRT15, TRT22, TRT35, TRT 28, and TRT34	Not in FAS; Overall exposure on DB medication < 22 weeks unless premature discontinuation due to adverse events
SAF	INCL01, TRT19	No double-blind study drug taken

5.5 Anti-diabetic medications search criteria

The documents attached detail the search criteria of anti-diabetic medications for reporting.


Combos - Codes match.pptx


List of _ingredients_anti

5.6 Unblinding plan at the Week 24 database lock

5.6.1 Unblinding plan for the Week 24 analysis at the 24-week DBL

The unblinding plan for the Week 24 (Epoch 3) analysis was specified in Section 5.4 “Treatment blinding” of the study protocol. The logistic and operational details of this unblinding plan were provided here.

- A restricted study folder will be set up in the Global Programming System (GPS) for the Week 24 analysis activities.
- Access to this GPS restricted folder is given only to statisticians and programmers (analysis group 1) who are directly involved in performing Week 24 analyses. This analysis group 1 will not be involved in any study conduct activities related to the study Week 24 to Week 48 period (Epoch 4) after the unmasking.
- A separate analysis group (analysis group 2, including final analysis TS and TP), who does not have access to the analysis results and the identity of treatments at Week 24 analysis, will perform the pre-planned final analysis at the end of the study.
- The randomization datasets will be uploaded to the 24-week restricted folder by Novartis Randomization Office upon the DBL for the Week 24 analysis;
- When the analysis group 1 runs the Week 24 analyses using the actual treatment code in the GPS restricted folder, they must keep all the outputs confidentially.
- It was not planned to generate patient listings for the Week 24 analysis.

- 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 24 to Week 48 period (Epoch 4), will not have access to the subject level data with identity of treatments such as subject listings at Week 24 analysis.
- In general, the Global Program Medical Director (GPMD) will not have access right to the patient listings. However, for the preparation of the future study(s) and other internal decision making, the GPMD may request analysis group 1 to provide the patient listings to review for specifically selected and interested safety parameters and may request additional analysis for further investigation.
- For scientific and management discussions and presentations, the GPMD can decide which group of people and at what extent the group can receive the Week 24 analysis results and the results from additional post-hoc analysis.
- Investigators and patients will not be allowed to access to any unblinded patient level data or analysis results until the end of the entire study.

5.6.2 Documentation of outputs

All outputs for the Week 24 analysis will be stored in the GPSII restricted folder, as described in section 5.6.1.

The outputs related to summary results will be imported and stored in a restricted folder in Novartis Documentation System webEDI. Relevant summary reports based on the Week 24 analysis results will be stored in the restricted folder in webEDI as well. The study leader, on behalf of the GPMD, will be in charge of the access to this restricted folder in the webEDI.

The restriction to these resctricted-acess folders will be removed after the final DB lock at the end of the study.

5.6.3 List of unblinded personnel

A separate document to include the list of names for personnel who are unblinded to the Week 24 analysis data and outputs will be created and stored in the study folder in webEDI.

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.

Siddiqui O, Hung J HM, and O'Neill R (2009) MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. Journal of Biopharmaceutical Statistics; 19(2):227-246