NOVARTIS

Global Clinical Development - General Medicine

LIK066

Clinical Trial Protocol CLIK066B1201 / NCT03320941

A randomized, double-blind, dose-finding study to evaluate the change in weight after 12 weeks treatment with 4 doses of LIK066 compared to placebo in Japanese patients with obesity disease

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List of abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ACR	albumin creatinine ratio
AE	Adverse Event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the curve
BL	baseline
BMI	body mass index
BP	blood pressure
β-hCG	β-human chorionic gonadotropin
CFR	US Code of Federal Regulations
CPO	country pharma organization
CRF	Case Report/Record Form (paper or electronic)
CT	computer tomography
CYP3A	cytochrome P450 3A4
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase -4
ECG	electrocardiogram
ED50	effective dose 50
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ENR	enrolled set
[redacted]	[redacted]
eSource	electronic source
EU	European Union
FAS	full analysis set
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GI	gastro-intestinal
GLP-1	glucagon-like peptide-1
[redacted]	[redacted]
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
hsCRP	high sensitive C-reactive protein
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization

[redacted]

IEC	Independent Ethics Committee
IN	investigator notification
INR	international normalization ratio
IRB	Institutional Review Board
LDL	low density lipoprotein
LFT	liver function test
LS	least squares
MAR	missing at random
MDRD	modified diet in renal disease
MedDRA	Medical dictionary for regulatory activities
NIRT	Novartis Interactive Response Technology
NOAEL	no-observed-averse-effect-level
NOEL	no-observed-effect-level
NYHA	New York Heart Association
OAD	oral anti-diabetic drug
OC/RDC	Oracle Clinical/Remote Data Capture
OGTT	oral glucose tolerance test
PCR	protein creatinine ratio
PK	pharmacokinetics
PPS	per-protocol set
[redacted]	[redacted]
PT	prothrombin time
qd	quaque die (once a day)
RAN	randomized set
SAE	Serious Adverse Event
SAF	safety set
SBP	systolic blood pressure
SBW	standard body weight
SD	standard deviation
SFA	subcutaneous fat area
SGLT1	sodium-glucose co-transporter 1
SGLT2	sodium-glucose co-transporter 2
SUSAR	Suspected Unexpected Serious Adverse Reactions
SU	sulfonylurea
T2DM	type 2 diabetes mellitus
TD	study treatment discontinuation
TG	triglycerides
TSH	thyroid stimulating hormone
UGE	urinary glucose excretion
UGT	uridine-5'-diphosphoglucoronosyltransferase
ULN	upper limit of normal
UTI	urinary tract infection
VFA	visceral fat area
VLDL	very low density lipoprotein

[redacted]

WBC	white blood cell
WHO	World Health Organization

[redacted]

Glossary of terms

Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Rescue medication	Rescue medication is medication that can be used to treat those subjects with type 2 diabetes mellitus (T2DM) whose glycemic control is deteriorating. In this protocol a dipeptidyl-peptidase-4 (DPP-4) inhibitor or insulin should be used as rescue medication.
Run-in period	In this study, the run-in period is Epoch 2, where subjects who were successfully screened will receive placebo medication.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

[redacted]

Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 1

Amendment rationale

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

As a precautionary measure, patients with *any* history of ketoacidosis, lactic acidosis, or hyperosmolar coma will be excluded from enrollment into the study as well.

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

Changes to the protocol

Protocol summary and Section 3.1 have been amended regarding the duration of Epoch 1 and Epoch 2, as these epochs are now *approximately* 2 and 4 weeks respectively.

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

The exclusion criterion on ketoacidosis, lactic acidosis or hyperosmolar coma in Protocol summary and Section 4.2 was amended to also exclude any history of the condition. Furthermore, a typo was corrected in this section with regards to the units for hemoglobin, and in addition history of lower limb amputation was added to the exclusion criteria as a precautionary measure.

In Section 5.5.2 overlapping sentence was deleted.

In Section 5.5.4 package was corrected.

Section 5.5.5 was changed to clarify that dose adjustments are not permitted but that interruptions can be done for safety reasons.

In Section 5.6.2 lower limb amputation was added as a condition when study treatment has to be discontinued.

In Table 6-1 some minor typographical corrections were made.

In Section 6.4.1 Subjects must be in underwear or use a hospital gown when their weight is being assessed.

In Section 6.4.4 the definition of overnight fast was updated.

In Section 6.4.5 the use of alternative blood pressure devices is now allowed if an automated device cannot be used (for instance when the cuff on the automated device is too small for the subject's arm).

[redacted]

Section 7.8.2 was improved and clarifications were provided.

In Section 8.3 some minor processes were corrected.

In Section 9 some minor typographical corrections were made.

In Section 10.5 the old name of the audit department was updated to the new name (Global Development Quality Audit).

In Section 12 new references have been added.

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

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

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

[redacted]

Protocol summary

Protocol number	CLIK066B1201
Full Title	A randomized, double-blind, dose-finding study to evaluate the change in weight after 12 weeks treatment with 4 doses of LIK066 compared to placebo in Japanese patients with obesity disease
Brief title	A dose-finding study to evaluate the change in weight after treatment with LIK066 compared to placebo in Japanese patients with obesity disease.
Sponsor and Clinical Phase	Novartis Phase 2b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To evaluate the efficacy, tolerability and safety of LIK066 to support dose selection for Phase 3 development in Japanese adults with obesity disease.
Primary Objective(s)	To examine the dose-response relationship of LIK066 as measured by percent change from baseline (BL) in body weight relative to placebo after 12 weeks of treatment

Secondary Objectives	• To assess the responder rates according to percent decrease in body weight either ≥ 3%, ≥ 5% or ≥ 10%, from BL at Week 12, for the overall population and each of the subgroups [dysglycemic subjects and subjects with type 2 diabetes mellitus (T2DM)]
	• To assess the dose-response relationship for weight loss in dysglycemic subjects and subjects with T2DM after 12 weeks of treatment
	• To evaluate the effect of all LIK066 doses *vs* placebo for the overall population and by subgroups (dysglycemic subjects and subjects with T2DM) after 12 weeks of treatment on:
	  • Waist circumference at umbilical level
	  • Hemoglobin A1c (HbA1c)
	  • Fasting plasma glucose (FPG)
	  • Systolic blood pressure (SBP) and diastolic blood pressure (DBP)
	  • Fasting lipid profile and high sensitivity C-reactive protein (hsCRP)
	  • Uric acid
	  • Urine albumin and urine albumin to creatinine ratio
	  • Visceral fat area (VFA) and subcutaneous fat area (SFA) by computer tomography (CT)
	• To evaluate safety (adverse events (AEs) and laboratory parameters) and tolerability of LIK066 over 12 weeks of treatment
	• To evaluate the pharmacokinetics (PK) of LIK066

Study design	This is a multi-center, randomized, double-blind, parallel-group dose-finding study evaluating the effect on weight, tolerability and safety of 4 doses of LIK066 *vs* placebo. Following a screening visit (Visit 1) and a screening period of approximately 2 weeks (Epoch 1), subjects meeting all eligibility criteria will enter the run-in Epoch 2 at Visit 101.
Population	130 female and male patients with obesity disease ≥ 20 and ≤ 75 years old.

[redacted]

Key Inclusion criteria	• Male and female, age 20 to 75 years old, both inclusive
	• Patients with obesity disease and inadequately controlled body weight with diet and/or exercise
	  • Body mass index (BMI) ≥ 25 kg/m^2 combined with at least two obesity-related comorbidities
	  • BMI ≥ 35 kg/m^2 at least one obesity-related comorbidity
	• Waist circumference at umbilical level ≥ 85 cm for male, ≥ 90 cm for female
	• Visceral fat area ≥ 100 cm^2
	• Agreement to comply with the study-required life-style intervention and treatment during the full duration of the study

Key Exclusion criteria	• Use of pharmacologically active weight-loss medications, glucagon-like peptide-1 (GLP-1) agonists or sodium-glucose co-transporter 2 (SGLT2) inhibitors, within 3 months of screening, or between screening and randomization. • Use of alpha glucosidase inhibitors within 3 months of Visit 1, or between screening and randomization. • Bariatric surgery • Lack of compliance with lifestyle intervention (defined as weight gain during run-in (Epoch 2)) or with study medication (defined as < 80% study drug intake during Epoch 2), assessed at randomization. • History of ketoacidosis, lactic acidosis, or hyperosmolar coma, or any of these occurring between Visit 1 and Visit 199/201 (randomization). • Symptomatic genital infection or urinary tract infection (UTI) in the 4 weeks prior to screening, or screening and randomization. • Gastro-intestinal (GI) disorders associated with chronic diarrhea. • Congestive heart failure, New York Heart Association (NYHA) class III or IV.
Study treatment	• LIK066 • Placebo
Efficacy assessments	• Body weight • Waist circumference • HbA1c • FPG • Blood pressure • Fasting lipid profile and hsCRP • Uric acid • Urine albumin and urine albumin to creatinine ratio • Visceral fat area and subcutaneous fat area
Key safety assessments	• Physical examinations • Vital signs • Monitoring of laboratory markers in blood and urine • Electrocardiogram • AE monitoring • Liver & renal safety monitoring

[redacted]

Other assessments	• PK (trough) [redacted]
Data analysis	The primary analysis of this study aims to detect a dose response signal for the percentage reduction in body weight after 12 weeks treatment using data from all doses (including placebo) to model the dose-response curve and to provide sufficient information to choose the doses for the further development of the drug. Hence, the following null and alternative hypotheses will be tested: • H_0: There is no dose-response relationship for LIK066 (i.e. the dose response relationship is flat). • H_1: There is a dose-response relationship for LIK066 (i.e. as dose increases, the percent weight decreases). The Multiple Comparison Procedure-Modeling methodology will be used to analyze the primary endpoint of percent change from BL in body weight at Week 12, in order to test these dose-response hypotheses and determine the dose-response relationship. A set of the dose-response candidate models were defined. In order to preserve the family-wise error rate at one-sided significance level of 2.5%, the optimal contrasts derived from the model candidate set will be individually compared to the critical value derived using a multiplicity adjustment that accounts for all tests of comparing LIK066 doses to placebo simultaneously. The rejection of the null hypothesis will be achieved using the maximum test statistic from each estimated contrast test in the candidate set. 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 12 as a response variable, treatment (placebo and all LIK066 doses) and stratification factor (dysglycemic or T2DM) as factors and BL weight as a covariate. Model averaging approach will be used to estimate the dose-response. The primary analysis will be conducted on the full analysis set (FAS). Missing values of body weight at Week 12 will be imputed using the multiple imputation approach under a missing at random (MAR) assumption.
Key words	Obesity disease, T2DM, interventional study, weight loss

[redacted]

1 Introduction

1.1 Background

Obesity represents a rapidly growing threat to the health of populations worldwide. Obesity raises the risk of morbidity from hypertension, dyslipidemia, type 2 diabetes mellitus (T2DM), coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea and respiratory problems, and some cancers. Obesity is also associated with increased risk in all-cause and cardiovascular disease mortality. The biomedical, psychosocial, and economic consequences of obesity have substantial implications for the health and well-being of the person with obesity (AACE 2016). Similar to Western countries, obesity remains an unmet medical need in Asian countries including Japan with increasing numbers of obese patients in recent years. Although obesity is less severe as assessed by body mass index (BMI) in Japan than Western countries, the prevalence of several obesity related diseases is comparable due to accumulation of visceral fat and/or fatty organ dysfunction. Based on that, obesity disease is defined as BMI $\geq$ 25 kg/m^2 with comorbidities in the guidelines in Japan.

Diet and exercise therapies have been shown to be useful in producing clinically relevant, but modest weight loss leading to amelioration of comorbid medical problems. However clinical challenges remain with the magnitude of weight reduction (at least $\geq$ 3%) and the maintenance of the achieved weight loss by behavior modification. Weight loss medication is recommended for obese patients who are inadequately controlled with diet and exercise therapies, but the only drugs available in Japan are mazindol (only approved for severely obese patients with BMI $\geq$ 35 kg/m^2) or the recently approved cetilistat. Weight loss drugs also have limitations for long term use due to central nervous system adverse effects. Therefore, there is a substantial opportunity and real need to develop weight loss medicines which will be more effective and better tolerated.

LIK066 is an inhibitor of the sodium-glucose co-transporter-1 (SGLT1) and sodium-glucose co-transporter-2 (SGLT2). The dual mechanism (renal and intestinal) to reduce re-absorption/absorption of glucose leads to loss of calories (calorie-loss enhancer). It also has the potential to reduce food intake via central mechanisms mediated by an increase in incretin hormones (glucagon-like peptide-1 (GLP-1) and peptide YY). [redacted]

The current study is designed to evaluate the efficacy, tolerability and safety of a dose-range of LIK066 as part of a development program for the use of LIK066 in adults with obese disease.

1.2 Purpose

The purpose of the study is to evaluate the efficacy, tolerability and safety of LIK066 to support dose selection for Phase 3 development in Japanese adults with obesity disease.

[redacted]

2 Study objectives and endpoints

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To examine the dose-response relationship of LIK066 (2.5 mg qd, 10 mg qd, 25 mg qd and 50 mg qd) as measured by percent change from baseline (BL) in body weight relative to placebo after 12 weeks of treatment	• Percent change from BL in body weight at Week 12
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the responder rates according to percent decrease in body weight either ≥ 3%, ≥ 5% or ≥ 10%, from BL at Week 12, for the overall population and each of the subgroups (dysglycemic subjects and subjects with T2DM).	• Responder rates according to percent change in body weight ≥ 3%, ≥ 5%, ≥ 10% from BL at Week 12 (see Section 9.5.1)
• To assess the dose-response relationship for weight loss in dysglycemic subjects and subjects with T2DM after 12 weeks of treatment.	• Dose response relationship for weight loss among subgroups (dysglycemic, T2DM) at Week 12 (see Section 9.5.1)
• To evaluate the effect of all LIK066 doses *vs* placebo for the overall population and by subgroups (dysglycemic subjects and subjects with T2DM) after 12 weeks of treatment.	Change from baseline at Week 12 on (see Section 9.5.1): • Waist circumference at umbilical level • Hemoglobin A1c (HbA1c) • Fasting plasma glucose (FPG) • Systolic blood pressure (SBP) and diastolic blood pressure (DBP) • Fasting lipid profile and high sensitivity C-reactive protein (hsCRP) • Uric acid • Urine albumin and urine albumin to creatinine ratio • Visceral fat area (VFA) and subcutaneous fat area (SFA) by computer tomography (CT)
• To evaluate safety (adverse events (AEs) and laboratory parameters) and tolerability of LIK066 over 12 weeks of treatment.	• AEs including events of special interest • Laboratory parameters • Vital sign • Electrocardiogram (ECG) (see Section 9.5.2)
• To evaluate the pharmacokinetics (PK) of LIK066	• PK (trough) (see Section 6.6.3 and Section 9.5.4).

[redacted]

3 Investigational plan

3.1 Study design

This is a multi-center, randomized, double-blind, parallel-group dose-finding study evaluating the effect on weight, tolerability and safety of 4 doses of LIK066 *vs* placebo (see Figure 3-1 & Section 5.2). Following a screening visit (Visit 1) and a screening period of approximately 2 weeks (Epoch 1), subjects meeting all eligibility criteria will enter the run-in Epoch 2 at Visit 101.

3.1.1 Epoch 2 (run-in)

Subjects meeting the eligibility criteria defined in Section 4 will enter the placebo run-in (Epoch 2). During the approximately 4 weeks duration of Epoch 2, subjects will receive the placebo run-in medication as described in Section 5.1.

At Visit 101, the subject's volume status must be assessed (see Section 6.5.1) and hypovolemia must be corrected during the run-in in the elderly, in subjects with low SBP, or if on diuretics, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).

At the start of Visit 101, all subjects will receive the following advice for lifestyle intervention (Japan Society for the Study of Obesity 2016):

- Subjects with BMI ranging from ≥ 25 to < 35 kg/m^2 will be advised to follow a '25 × standard body weight (SBW)' kcal/day; subjects with BMI ≥ 35 kg/m^2 will be advised to follow a '20 × SBW' to '25 × SBW' kcal/day diet. Consumption of 50 to 60% kcal from carbohydrate, 15 to 20% kcal from protein and 20 to 25% kcal from fat will be recommended.
  Standard body weight (kg) = height (m)^2 × 22
- Subjects will be advised to gradually increase their physical activity to reach a goal of more than 150 min of moderate intensity physical activity per week, preferably distributed over the week.

Compliance with the lifestyle intervention shall be reviewed and re-enforced at every study visit.

Subjects with T2DM

Subjects with T2DM will continue their usual treatment, except for subjects taking sulfonylurea (SU) or insulin. These subjects may be at an increased risk of hypoglycemia due to the combination of the SU or insulin and weight loss, with or without consequent treatment with LIK066 in Epoch 3. Therefore:

[redacted]

- The dose of SUs for subjects with T2DM (see Section 3.1.2 & Section 5.3) using such medication (either as monotherapy or in combination with other oral anti-diabetic drugs (OADs)) may be reduced by up to 50%, or as close to 50% as possible based on dose options available locally, along with following thresholds; glimepiride > 2 mg/day to ≤ 2 mg/day, glibenclamide > 1.25 mg/day to ≤ 1.25 mg/day and gliclazide > 40 mg/day to ≤ 40 mg/day. In case of persistent deterioration in glycemic control, the concomitant background OAD should be initially escalated to the maximal approved dose, followed by addition of rescue medication when required (see Section 5.5.6). To limit the number of subjects with early deterioration of glycemic control who would meet the FPG rescue criteria early after randomization (see Section 5.5.6), an FPG randomization criterion is included in Section 4.2.
- For subjects on insulin, initial dose reduction of the total daily insulin dose by 10% or more may be considered at investigator's discretion based on subject's total daily dose and glycemic control. In case of deterioration in glycemic control, insulin can be up-titrated (see Section 5.5.6).

3.1.2 Epoch 3 (treatment)

After the run-in Epoch 2, eligible subjects will be randomized in the ratio of 2:2:3:3:3 to one of the following regimes at Visit 201 (randomization):

- 2.5 mg qd LIK066
- 10 mg qd LIK066
- 25 mg qd LIK066
- 50 mg qd LIK066
- Placebo.

At Visit 201, subjects will be randomized simultaneously to one of the five Epoch 3 treatment schedules.

At randomization, subjects will be stratified according to their glycemic status at screening using the following criteria (see also Section 5.3):

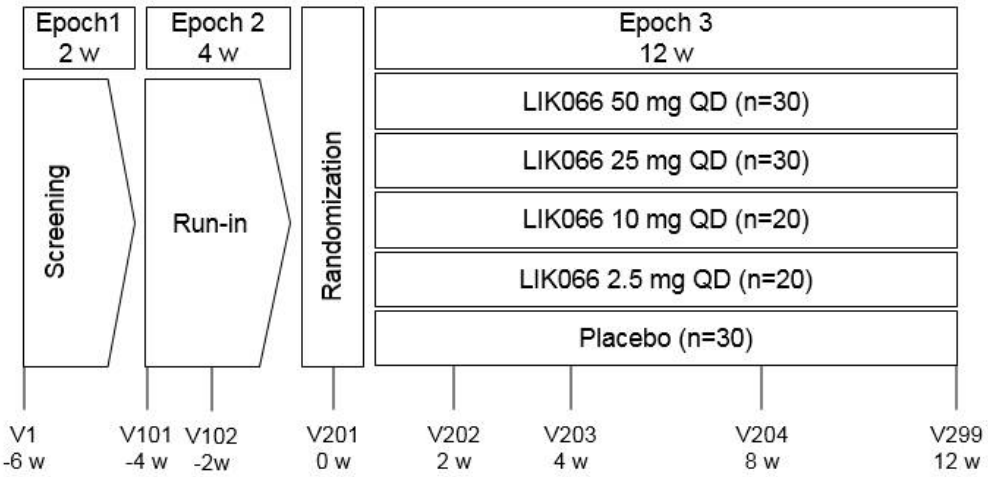
- Dysglycemic: no prior clinical diagnosis of T2DM, FPG ≥ 110 mg/dL and/or HbA1c ≥ 5.6% , except for HbA1c ≥ 6.5% and FPG ≥ 126 mg/dL at Visit 1 (screening).
- T2DM: prior diagnosis of T2DM, or subjects without prior diagnosis of T2DM with HbA1c ≥ 6.5% and FPG ≥ 126 mg/dL at Visit 1 (screening).

Following randomization, subjects will attend study visits in Epoch 3 (12 weeks) for assessment of efficacy, tolerability and safety parameters as defined in Table 6-1. During Epoch 3, subjects will take the study medication as described in Section 5.5.4.

The doses of antidiabetic and antihypertensive medications should be adjusted in patients who, according to the investigator, could be at a safety risk (e.g. repetitive or severe hypoglycemia, symptoms and signs of volume depletion, etc.).

[redacted]

Figure 3-1 Study design



QD: once daily, W: week, V: visit

3.2 Rationale for study design

The study is designed as a standard placebo-controlled, parallel-group study to obtain efficacy, tolerability and safety data in an unbiased fashion and detect signals of the dose-response characteristics of the investigated drug. A single-blind placebo run-in period is included to facilitate the implementation of lifestyle measures, as well as assess the compliance with study treatment. Twelve weeks of treatment in Epoch 3 are considered sufficient to reach sub-maximal or maximal weight loss, and also provide LIK066 safety and tolerability, with collection of trough PK samples in all subjects (see Section 6.6.3). In addition, visceral fat area (VFA) and subcutaneous fat area (SFA) measurement by CT scan will be performed to enable characterization of the efficacy of LIK066 in the studied population.

[redacted]

[redacted]

[redacted]

3.4 Rationale for choice of comparator

A placebo group is a standard comparator in Phase 2 studies and is included to account for study effect and the lifestyle interventions described in Section 3.1.1.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

[redacted]

3.6 Risks and benefits

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

[redacted]

Publications on SGLT2 inhibition in subjects with T2DM treated with selective SGLT2 inhibitors reported higher incidences of urinary tract infections (UTIs) and genital mycotic infections compared with placebo (Bailey et al 2010, Nauck et al 2011, Nyirjesy et al 2012).

[redacted]

SGLT2 inhibition may result in hypotension in elderly subjects, in subjects with low blood systolic pressure, or if on diuretics, ACEi, or ARB. Patients with T2DM treated with antidiabetic agents, especially with sulphonylurea or insulin, may be at an increased risk of hypoglycemia, which can be more pronounced with significant weight loss. In rare cases treatment with SGLT2 inhibitors may be complicated by ketoacidosis (Rosenstock and Ferrannini 2015). [redacted]

Hematology and biochemistry tests will be monitored at each study visit after randomization and study drug can be discontinued for clinically significant laboratory change or abnormality as per investigator's judgment. Detailed criteria for follow-up in case of a liver event are defined in Section 7.3 and Appendix 2. To prevent UTIs and genital infections, subjects will be instructed to pay attention to genital hygiene and have appropriate hydration. If UTI and/or genital infections occur, treatment will be initiated as appropriate at the investigator's discretion.

Benefits to participation in the study may include weight reduction and, potentially, improvement in some cardio-metabolic markers such as blood pressure (BP), lipids or blood glucose.

4 Population

The study population will consist of male and female subjects. Approximately 130 subjects will be randomized. A screening failure rate of about 30% is expected, hence about 190 subjects will be screened.

4.1 Inclusion criteria

Patients/subjects eligible for inclusion in this study must fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female, age 20 to 75 years old, both inclusive at Visit 1
3. Patients with obesity disease and inadequately controlled body weight with diet and/or exercise for three months prior to Visit 1
   - BMI $\geq$ 25 kg/m^2 combined with at least two obesity-related comorbidities* at Visit 1 and 201
   - BMI $\geq$ 35 kg/m^2 at least one obesity-related comorbidity at Visit 1 and 201
     *Obesity-related comorbidities are (Japan Society for the Study of Obesity 2016);
     - Glucose tolerance impaired (T2DM, impaired glucose tolerance etc.)
     - Dyslipidemia

[redacted]

- Hypertension
- Hyperuricemia and gout
- Coronary artery disease: myocardial infarction and angina pectoris
- Cerebral infarction: cerebral thrombosis and transient ischemic attack
- Nonalcoholic fatty liver disease
- Abnormality in menstruation and infertility
- Obstructive sleep apnea syndrome and obesity-hypoventilation syndrome
- Locomotive diseases: Osteoarthritis (knee, hip) and Spinal osteoarthritis, Finger osteoarthritis
- Obesity related glomerulopathy

4. Patients with FPG ≥ 110 mg/dL and/or 5.6% ≤ HbA1c ≤ 10.0%, or T2DM with HbA1c ≤ 10.0% at Visit 1
5. Waist circumference at umbilical level ≥ 85 cm for male, ≥ 90 cm for female at Visit 1
6. Visceral fat area ≥ 100 cm^2 at Visit 102.
7. Agreement to comply with the study-required life-style intervention and treatment during the full duration of the study

4.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days, whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients/subjects participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree atrio-ventricular block without a pacemaker
   - History of familial long QT syndrome or known family history of Torsades de Pointes
4. Patients/subjects taking medications prohibited by the protocol (see Section 5.5.8)
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
6. Pregnant or nursing (lactating) women
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. Basic contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

[redacted]

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps*). For United Kingdom: with spermicidal foam*/gel*/film*/cream*/ vaginal suppository*
- Use of oral, (estrogen and progesterone), injected* or implanted* hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception* or placement of an intrauterine device or intrauterine system. *: not approved in Japan, approved methods should be used.

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

In case local regulations deviate from the contraception methods listed above, local regulations apply and will be described in the ICF

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

8. Use of pharmacologically active weight-loss medications, GLP-1 agonists or SGLT2 inhibitors, within 3 months of Visit 1, or between Visit 1 and Visit 199/201 (randomization).
9. Use of alpha glucosidase inhibitors within 3 months of Visit 1, or between Visit 1 and Visit 199/201 (randomization).
10. Bariatric surgery.
11. Lack of compliance with lifestyle intervention (defined as weight gain during Epoch 2) or with study medication (defined as < 80% study drug intake during Epoch 2), assessed at Visit 199/201 (randomization).
12. History of ketoacidosis, lactic acidosis, or hyperosmolar coma, or any of these occurring between Visit 1 and Visit 199/201 (randomization).
13. Symptomatic genital infection or UTI in the 4 weeks prior to Visit 1, or between Visit 1 and Visit 199/201 (randomization).
14. GI disorders associated with chronic diarrhea.
15. Congestive heart failure, New York Hart Association (NYHA) class III or IV.
16. Myocardial infarction, stroke, surgery for heart disease, percutaneous coronary intervention in the 6 months prior to Visit 199/201 (randomization).

[redacted]

17. Unstable angina within 3 months of Visit 1, or between Visit 1 and Visit 199/201 (randomization).
18. Acute or chronic liver disease (except liver steatosis), such as hepatitis, cirrhosis or portal hypertension at Visit 1 or Visit 199/201 (randomization).
19. History of hepatitis B or C, or Hepatitis A or B vaccination in the last 3 months prior to Visit 1, or between Visit 1 and Visit 199/201 (randomization).
20. Active substance abuse, alcohol abuse (as defined by consumption of more than 24 alcohol units per week) or history of alcohol-related disease within the past 2 years.
21. Chronic treatment with medication which has a hepatotoxic potential.
22. Chronic use of anti-retroviral therapies.
23. Chronic use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (eg clarithromycin, telithromycin, itraconazole, ketoconazole, voriconazole or posaconazole) or chronic use of strong uridine-5'-diphosphoglucoronosyltransferase (UGT) inhibitors (eg probenecid, valproic acid or mefenamic acid).
24. Concurrent medical conditions that may interfere with the interpretation of efficacy and safety data.
25. Clinically significant thyroid stimulating hormone (TSH) outside of the normal range at Visit 1.
26. For subjects treated with SUs or insulin, self-measured FPG > 13.3 mM (240 mg/dL) on 2 occasions within one week of Visit 199/201 (randomization).
27. Estimated glomerular filtration rate (eGFR, calculated via the modified diet in renal disease (MDRD) formula) < 60 mL/min/1.73 m^2 at Visit 1.
28. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) more than two-fold above upper limit of normal (ULN) (> 2 × ULN), or total bilirubin/direct bilirubin > 1.5 × ULN) at Visit 1, confirmed by repeat measurement within 5 working days of the respective visit.
29. Hemoglobin < 12 g/dL in men, < 11 g/dL in women at Visit 1 (screening).
30. Platelet count < 100 000/µL and/or white blood cell (WBC) count < 4000/µL at Visit 1 (screening).
31. Hematuria determined by dipstick measurement at Visit 1 (screening).
32. Elevated fasting triglycerides (TGs) > 5.6 mM (500 mg/dL), at Visit 1 (screening), confirmed by repeat measurement within 3 working days of the respective visit.
33. Clinically significant laboratory abnormalities which, in the opinion of the investigator, cause the subject to be considered inappropriate for inclusion in the study.
34. History of lower limb amputation (including toe amputation), or if occurring between Visit 1 and Visit 201 (randomization).

[redacted]

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Epoch 2 (placebo run-in)

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

- LIK066 matching placebo tablets

All subjects will take 1 tablet in the morning. The medication will be prepared for the placebo run-in in kits.

Epoch 3 (treatment)

The sponsor will provide the following double-blind study medication for Epoch 3:

- LIK066 2.5 mg tablets
- LIK066 10 mg tablets
- LIK066 25 mg tablets
- LIK066 50 mg tablets
- LIK066 matching placebo tablets

For each treatment arm (see Section 5.2), subjects will receive one of the tablets described above. All subjects will take 1 tablet in the morning.

5.1.2 Additional treatment

No additional treatment beyond investigational drug and placebo are included in this trial.

5.2 Treatment arms

All subjects entering Epoch 2 (run-in) will receive placebo.

At Visit 201 (randomization), subjects eligible for randomization will be assigned 2:2:3:3:3 to one of the following treatment arms in Epoch 3 (see Section 3.1.2):

- 2.5 mg qd LIK066 (approx. 20 subjects)
- 10 mg qd LIK066 (approx. 20 subjects)
- 25 mg qd LIK066 (approx. 30 subjects)
- 50 mg qd LIK066 (approx. 30 subjects)
- Placebo (approx. 30 subjects)

5.3 Treatment assignment and randomization

At Visit 201, all eligible patients/subjects will be randomized via Novartis Interactive Response Technology (NIRT) to one of the treatment arms for Epoch 3. The investigator or his/her delegate will contact the NIRT after confirming that the patient fulfills all the

[redacted]

inclusion/exclusion criteria. The NIRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by a vendor using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified into (see Section 3.1.2):

- Dysglycemic
- T2DM

Efforts will be made by close monitoring of the enrollment through the NIRT system to ensure each of the two stratification sub-groups with at least 45% of total subjects enrolled in the study.

The randomization scheme for patients/subjects will be reviewed and approved by a member of the Randomization Group.

5.4 Treatment blinding

Patient/subjects, investigator staff and persons performing the assessments will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: the randomization codes associated with patients/subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock. (2) the identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Unblinding will only occur in the case of patient emergencies (see Section 5.5.9) and at the conclusion of the study.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

[redacted]

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the NIRT and provide the requested identifying information for the patient to register them into the NIRT. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

If for any reasons the patient fails to be treated with study medication after randomization, the NIRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Run-in epoch Study Disposition CRF.

5.5.2 Dispensing the study drug

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

At Visit 101, investigator staff will identify the study drug package(s) for run-in placebo to dispense to the patient by contacting the NIRT and obtaining the medication number(s).

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to one of the five treatment arms (see Section 5.2). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

5.5.3 Handling of study and additional treatment

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

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

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at each study visit and where applicable, at the time of discontinuation of study treatment.

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

5.5.3.2 Handling of additional treatment

Not applicable.

[redacted]

5.5.4 Instructions for prescribing and taking study treatment

All kits of study treatment assigned by the NIRT will be recorded/databased in the NIRT.

The investigator should ensure that the subject clearly understands the dosing instructions outlined below.

- At Visit 101 (Epoch 2), each subject will be dispensed study drug containing blisters with study medication. The blisters are constructed to easily deliver the daily required number of tablets for the morning dose. The kits contain sufficient medication for the run-in period of up to 4 weeks until Visit 199/201.
- From Visit 201 till Visit 299 (Epoch 3), subjects will be dispensed study drug containing blisters with study medication. The blisters are constructed to easily deliver the daily required number of tablets for the morning dose. The kits contain sufficient medication for the time between each visit according to Table 6-1.

In Epoch 2 and Epoch 3, subjects will be instructed to take 1 tablet LIK066 (or matching placebo) in the morning, immediately before the meal. Study drug should be taken the same time throughout the study.

No study drug should be taken on the morning of a study visit; subjects with T2DM should not take their anti-diabetic treatment. Subjects should arrive in the fasting state; ie no food or drinks (except water) for a minimum of 8h before the scheduled visit. If the subject has not fasted for an adequate period of time, the collection of fasting laboratory evaluations must be rescheduled. The study drug regimen (and, if applicable, rescue medication as defined in Section 5.5.6) should not be taken prior to obtaining the fasting laboratory test samples.

If a dose is missed and the subject realizes this within 4h, the study drugs should be taken otherwise the subject should take the next scheduled dose.

Previously dispensed study medication blisters, including any remaining study medication, must be returned to the study center at each study visit.

All prescribed dosages and all dose changes during the study must be recorded on the appropriate study drug Dosage Administration Record eCRF(s). All kits of study treatment assigned by the NIRT will be recorded/databased in the NIRT. The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments are not permitted. Dose interruptions are not permitted unless for safety reasons (see Section 7.1).

5.5.6 Rescue medication

During Epoch 3, rescue medication may be used in addition to ongoing study medication for those subjects with T2DM whose glycemic control is deteriorating. The subject must come in for an unscheduled visit to have a sample drawn for FPG measurement performed by the central laboratory if:

[redacted]

- Self-measured FPG on two consecutive occasions exceeds the limits in Table 5-1.
- The result from a blood sample analyzed by the central laboratory exceeds the limits described in Table 5-1.

Table 5-1 Rescue criteria for FPG (subjects with T2DM)

Timeframe	Parameter	Value	Action
Between V201 (Randomization) and V204 (Week 8)	FPG	> 240 mg/dL (13.3 mM)	Unscheduled visit for central laboratory parameter measurement. If elevation confirmed by central laboratory: background OAD may be escalated to the maximum approved dose, followed by addition of another allowed OAD (eg a DPP-4 inhibitor used according to the label or insulin as per the investigator's discretion)
Between V204 (Week 8) and V299 (Week 12)	FPG	> 220 mg/dL (12.2 mM)	

If the results confirm that the limits have been exceeded, first the background OAD should be escalated to the maximal approved dose in steps if clinically indicated, followed by addition of rescue medication.

Rescue medication, a dipeptidyl peptidase-4 (DPP-4) inhibitor or insulin, should be used according to the local label. Rescue medication must be provided locally.

Rescued subjects will continue to participate in the study to allow for assessment of exposure and safety of LIK066.

Use of rescue medication must be recorded on the Rescue Medication eCRF.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications/significant non-drug therapies eCRF.

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

5.5.8 Prohibited medication

Use of following treatments is not allowed for entire study period:

- St. John's wort (strong CYP3A inducer)
- GLP-1 agonists
- SGLT2 inhibitors other than study medication
- Pharmacologically active weight-loss medication (including herbal medication)
- Alpha glucosidase inhibitor

Some medications or products must be used with caution:

[redacted]

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

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the NIRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a communication confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the NIRT at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Patients whose treatment has been unmasked must be discontinued from the study treatment (see Section 5.6.2).

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

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

For subjects who are loss to follow-up, see Section 5.6.4.

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

[redacted]

For all patients/subjects a safety follow-up should be contacted 30 days after last visit. The information to be collected at this follow up includes concomitant medications, adverse events, and survival status.

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator or the sponsor (see Section 5.6.5).

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

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (see Section 6.5.5 and Section 7.6)
- Use of prohibited treatment (see Section 5.5.8)
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following AE: ketoacidosis (see also Section 7.8.1), or lower limb amputation (including toe amputation)
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- Subjects whose study treatment has been unmasked (see Section 5.5.9)
- Withdrawal of consent (see Section 5.6.3)

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

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

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

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

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

If study drug discontinuation occurs because treatment code has been broken, please refer to Section 5.5.9.

[redacted]

5.6.3 Withdrawal of informed consent

Patients/subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore *and*
- Does not want any further visits or assessments *and*
- Does not want any further study related contacts *and*
- Does not allow analysis of already obtained biologic material

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as per Table 6-1.

5.6.4 Loss to follow-up

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

5.6.5 Early study termination by the sponsor

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

[redacted]

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed.

Subjects must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled and the adverse event and concomitant medications reconciled on the CRF.

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

[redacted]

Table 6-1 Assessment schedule

Epoch	**1 Screening**	**2 Run-in**			**3 Treatment**				
Visit	**1**	**101**	**102**	**199**	**201 RND**	**202**	**203**	**204**	**299* TD/ PSD/EOS**
Week	**−6**	**−4**	**−2 - −1**	**0**		**2**	**4**	**8**	**12**
Screening assessments									
Informed consent	X								
Inclusion/exclusion (Section 4)	X			X	X				
Subject demographics (Section 6.2)	X								
Medical history	X								
Medical history: protocol solicited events	X								
Smoking & alcohol history (Section 6.2)	X								
Efficacy									
Height (Section 6.4.1)	X								
Weight (Section 6.4.1)	X	X		X	X	X	X	X	X
Waist circumference (Section 6.4.2)	X	X			X	X	X	X	X
BP (SBP & DBP) (Section 6.4.5)	X	X			X	X	X	X	X
HbA1c (Section 6.4.3)	X				X				X
FPG (Section 6.4.4)	X				X				X
Fasting lipid profile (Section 6.4.6)	X‡				X				X
hsCRP (Section 6.4.6)					X				X
Uric acid (Section 6.4.7)					X				X
Urine albumin and Urine albumin to creatinine ratio (Section 6.4.8)					X				X
VFA and SFA by CT (Section 6.4.9)			X†						X

[redacted]

Epoch	**1 Screening**	**2 Run-in**			**3 Treatment**				
Visit	**1**	**101**	**102**	**199**	**201 RND**	**202**	**203**	**204**	**299* TD/ PSD/EOS**
Week	**−6**	**−4**	**−2 - −1**	**0**		**2**	**4**	**8**	**12**
[redacted]									
Safety									
Complete physical exam (Section 6.5.1)	S								S
Short physical exam (Section 6.5.1)		S		S	S	S	S	S	
Vital signs (Section 6.5.2)	X	X			X	X	X	X	X
Hematology (Section 6.5.3.1)	X				X		X		X
Biochemistry (Section 6.5.3.2)	X				X		X		X
TSH (Section 6.5.3.2)	X								
Pregnancy test (serum, Section 6.5.5)	X								
Pregnancy (urine dipstick, Section 6.5.5)				X	X				X
Hematuria (urine dipstick, Section 6.5.3.3)	X								
Urinalysis (Section 6.5.3.3)					X				X
PK trough (Section 6.6.3)									X
[redacted]									
ECG (Section 6.5.4)	X								X
AEs (Section 7.1)		X		X	X	X	X	X	X
SAEs (Section 7.2)		X		X	X	X	X	X	X
Ketoacidosis AEs (Section 7.8.1)		X		X	X	X	X	X	X
Hypoglycemia AEs (Section 7.8.2)		X		X	X	X	X	X	X

[redacted]

Epoch	**1 Screening**	**2 Run-in**			**3 Treatment**				
Visit	**1**	**101**	**102**	**199**	**201 RND**	**202**	**203**	**204**	**299* TD/ PSD/EOS**
Week	**−6**	**−4**	**−2 - −1**	**0**		**2**	**4**	**8**	**12**
Medication records									
Prior & concomitant medications	X	X		X	X	X	X	X	X
Surgical and medical procedures		X		X	X	X	X	X	X
Dose administration record		X		X	X	X	X	X	X
Administrative procedures									
NIRT system	X	X		X	X	X	X	X	X
Lifestyle instructions (Section 3.1.1)		S			S	S	S	S	
Dispense glucometer (T2DM subjects)		S							
Glycemia diary (T2DM subjects)				S	S	S	S	S	S
Study drug accountability				S	S	S	S	S	S
Screening phase disposition	X								
Run-in phase disposition				X					
Study completion									X

TD = Study treatment discontinuation; PSD = Premature subject discontinuation; X = assessment to be recorded on clinical data base; S = assessment to be recorded on source documentation only; RND = Randomization visit; EOS = end of study; * These assessments are also to be conducted for subjects who prematurely withdraw from the study; † −14 ~ −8 days; ‡ TG only

[redacted]

6.1 Information to be collected on screening failures

All subjects who have signed informed consent but not entered into the next epoch/period will have the study completion page for the screening epoch/period, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

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

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

6.3 Treatment exposure and compliance

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

On-treatment medication

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

Rescue medication

Information regarding the administration of rescue medication as per Section 5.5.6 will be recorded on the appropriate eCRF.

6.4 Efficacy

6.4.1 Weight

Body weight will be measured to the nearest 0.1 kg at visits indicated in Table 6-1 on a calibrated scale provided by the sponsor. The measurement will be performed with the study subject in underwear (or a hospital gown) and without shoes. Voiding before weight measurement is required.

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

[redacted]

6.4.2 Waist circumference

Waist circumference will be measured to the nearest 0.1 cm at visits indicated in Table 6-1 in a standing position, at the end of a normal expiration, using a tape at the level of umbilicus.

6.4.3 HbA1c

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

6.4.4 FPG

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

6.4.5 BP

Arterial BP, pulse rate readings and signs and symptoms of orthostasis will be assessed with an automated BP device. If an automated device cannot be used, the BP will be measured with an alternative device.

Three sitting BP measurements and one standing BP measurement will be performed at visits indicated in Table 6-1. Every effort should be made to have the same staff member obtain BP measurements for a given subject, at the same time of day, using the same equipment, at each visit.

Sitting BP and standing measurements must be performed prior to any procedure (eg blood draw) or medication intake. At Visit 1 (screening) BP must be measured at both arms. The arm with the higher SBP reading must be used for the BP measurements at Visit 1 and the same arm must be used at all subsequent visits. The arm used at each visit must be documented in the source documentation.

The subject should be in a relaxed setting and measurements should not be taken immediately after exertion or the consumption of coffee. At each study visit, after the subject has been sitting for 5 minutes with the back supported and both feet placed on the floor, SBP and DBP will be measured three times using the BP device and an appropriate size cuff. The bladder of the cuff should be large enough to encircle 80% of the arm. The cuff should be placed so its bottom is 1 to 2 cm above the elbow and the arm should be supported so that the bottom of the cuff is at the level of the heart. The tube should run down the center of the arm, approximately in line with the middle finger. The subject should be asked to relax his/her arm and turn the palm upward. The subject should not speak or move their arm during the measurement deflation of the cuff. Three separate sitting BP should be obtained with a full two-minute interval between measurements and with the cuff fully deflated between measurements. The subject will then stand, and after standing for two minutes, one BP measurement will be taken (see also Section 6.5.2).

All 3 sitting BP measurements and the single standing measurement will be recorded and documented in the eCRF and in the subject's source documents. All 3 sitting BP readings will be used for evaluation of sitting BP.

[redacted]

6.4.6 Fasting lipid profile & inflammation biomarkers

Fasting lipid profile, TG and hsCRP as described in Table 6-2 will be measured on blood samples obtained after an overnight fast at visits indicated in Table 6-1 and analyzed at a central laboratory.

Table 6-2 Fasting lipid profile, TG & inflammation biomarkers

Category	Parameter(s)
Fasting lipid profile & TGs	TG, total cholesterol, HDL cholesterol, LDL cholesterol (calculated, direct), lipoproteins (apolipoprotein A-I, apolipoprotein B), calculated VLDL cholesterol and non-HDL cholesterol.
Inflammation biomarkers	hsCRP

6.4.7 Uric acid

Uric acid will be measured from a blood sample at visits indicated in Table 6-1 and analyzed at a central laboratory.

6.4.8 Urine albumin and Urine albumin to creatinine ratio

Urine albumin and urine albumin to creatinine ratio will be measured from urine sample at visits indicated in Table 6-1 and analyzed at a central laboratory.

6.4.9 VFA and SFA

VFA and SFA by CT scan will be measured at visits indicated in Table 6-1 and evaluated centrally. VFA and SFA results will not be communicated to the study sites or the Novartis study team to avoid unmasking. Details on FA assessment by CT scan are explained in the separate manual.

6.4.10 Appropriateness of efficacy assessments

Measurements of weight, waist circumference, HbA1c, FPG, BP and fasting lipids are standard measures to assess the efficacy of a weight loss drug and its effect on cardio-metabolic parameters. Fat area measurement allows for evaluation of LIK066's primary mode of action's contribution to weight loss.

6.5 Safety

6.5.1 Physical examination

A complete physical examination will be performed at visits indicated in Table 6-1 and includes the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities (including feet), vascular status, neurological status and volume status (see Section 3.1.1). If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed.

A short physical exam will include the examination of general appearance (including feet) and assessments described in Section 6.4.5. They will be performed at all scheduled visits indicated in Table 6-1 and at unscheduled study visits.

[redacted]

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

6.5.2 Vital signs

BP will be measured as described in Section 6.4.5 at visits indicated in Table 6-1. The pulse rate from the last sitting BP measurement will be recorded. Respiratory rate will also be measured. Clinically notable vital signs are defined in Appendix 1.

6.5.3 Laboratory evaluations

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

6.5.3.1 Hematology

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

Table 6-3 Hematology evaluations

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

6.5.3.2 Clinical chemistry

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

Table 6-4 Clinical chemistry

Category	Parameter(s)
Biochemistry	ALT, albumin, alkaline phosphatase (ALP), AST, bicarbonates, bilirubin (direct, total), blood urea nitrogen (BUN), calcium (total), chloride, creatinine, cystatin C, eGFR (MDRD), magnesium, phosphates, potassium, protein (total), sodium, uric acid, γ-GT, amylase, lipase
Chemistry (TSH)	TSH
Chemistry (pregnancy)	Serum β-HCG

6.5.3.3 Urinalysis

Urine samples will be collected for analysis of parameters listed in Table 6-5 at visits indicated in Table 6-1. Urine will be used to assess pregnancy and hematuria (dipstick) at visits indicated in Table 6-1 as well. Glucosuria results will not be communicated to the study sites or the Novartis study team to avoid unmasking.

[redacted]

Table 6-5 Urinalysis

Category	Parameter(s)
Urinalysis	pH, specific gravity, protein, glucose, ketones, nitrites, blood, leucocytes
Urinalysis	Urine albumin, urine albumin to creatinine ratio (spot urine)
Urine (dipstick)	Hematuria
Urine (dipstick)	Pregnancy test (β-hCG)

[redacted]

6.5.4 Electrocardiogram (ECG)

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

Single 12 lead ECGs are collected and interpreted by the principal investigator or their designee. The Fridericia QT correction formula should be used to assess the QT interval.

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

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

6.5.5 Pregnancy and assessments of fertility

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

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

6.5.6 Appropriateness of safety measurements

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

[redacted]

[redacted]

6.6 Other assessments

[redacted]

6.6.2 Resource utilization

Not applicable

6.6.3 Pharmacokinetics

PK trough sampling will be performed in all subjects at time-points indicated in Table 6-1. At the morning of the visit, subjects must be in a fasting state (see Section 5.5.4). Details on PK

[redacted]

trough sample collection, numbering, processing and shipment is explained in the laboratory manual.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

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

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
  - Yes
  - No
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

[redacted]

- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met.
- action taken regarding [investigational] treatment

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

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

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

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

[redacted]

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

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

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

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

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *study treatment*, complete the SAE Report Form in English, and submit the completed form within 24 hours to

[redacted]

Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

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

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

7.3 Liver safety monitoring

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

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

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

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

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

For the liver laboratory trigger:

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

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

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

[redacted]

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

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

7.4 Renal safety monitoring

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

- Serum event:
  - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - new onset (≥ 1+), hematuria or glycosuria

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

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

[redacted]

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

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

7.6 Pregnancy reporting

To ensure patient safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

7.7 Prospective suicidality assessment

Not applicable.

7.8 AEs of special interest

7.8.1 Ketoacidosis

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

Every case of ketoacidosis must be reported to the Ketoacidosis adjudication committee (see Section 8.5), and the Ketoacidosis Adjudication eCRF must be completed.

7.8.2 Hypoglycemia

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

[redacted]

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

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

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

- The glucose value.
- Precipitating factors (strenuous exercise, delayed or missed meals, changes in meal composition, illness, ramadan-period, etc.).
- Time of occurrence in relation to the last medication and to the last meal intake.
- The treatment used.
- The response to the treatment used.
- Need for assistance to treat the hypoglycemia event.
- Additionally, if a subject performs routine self-monitoring of blood glucose, any asymptomatic plasma glucose < 70 mg/dL (< 3.9 mM) should be treated and recorded in the glycemia study diary.
- The glycemia study diaries will be dispensed at run-in (Visit 101) and at following visits. The subject must return the completed study diary at each following visit.

Subjects without diabetes must have the symptoms of hypoglycemia explained and will be asked to report them at every study visit, if such occur. These subjects will not be provided with blood glucose meters or diaries.

Data entry

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of

[redacted]

ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

Readings of VFA/SFA will be processed centrally and the results will be sent electronically to Novartis.

[redacted]

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using the NIRT. The database will be sent electronically.

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

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

A Ketoacidosis adjudication committee will review cases suspected for ketoacidosis as defined in the adjudication charter (see also Section 7.8.1).

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

The following analysis sets will be used for the statistical analyses:

Enrolled set (ENR): all subjects who signed the ICF.

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

[redacted]

Full analysis set (FAS): the FAS comprises of 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.

The **per-protocol set** (PPS) is a subset of the FAS. It consists of all randomized subjects in the FAS who took at least one dose of study medication and have no major protocol deviations affecting the primary endpoint analysis.

Major protocol deviations will be pre-specified prior to un-blinding treatment codes for analyses.

9.2 Patient demographics and other baseline characteristics

The number of enrolled subjects, randomized subjects and screen failed subjects, as well as the number of subjects in each analysis set will be summarized.

Demographics, baseline 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 (SD), 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).

9.3 Treatments

The duration of double-blind treatment exposure (days) in Epoch 3 will be summarized by treatment group both descriptively (i.e. mean, standard deviation, median, Q1 (25^{th} percentile), Q3 (75th percentile), minimum and maximum) and by duration category for the safety set.

The number and percentage of subjects receiving prior and concomitant medications will be summarized by treatment group and overall in SAF in separate tables according to the hierarchy levels of the WHO coding dictionary. Prior medications are defined as drugs taken and stopped prior to first dose of study medication. Any medication given at least once between the day of first dose of double-blind study medication and the end of Epoch 3 visit will be a concomitant medication, including those which were started pre-BL and continued into the treatment period. Subjects' background anti-diabetic medications at baseline will be summarized by treatment and medication type.

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 use of prohibited medication, if any, will also be summarized.

[redacted]

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary analysis variable is the percent change in body weight (kg) from BL at Week 12. BL is defined as the last body weight value measured prior to or at the randomization visit (Visit 201). This analysis will be carried out on the FAS, with missing Week 12 values imputed as described in Section 9.4.3.

9.4.2 Statistical model, hypothesis, and method of analysis

The primary objective will be evaluated by the methodology using an optimally weighted contrast test (Pinheiro et al 2006, Pinheiro et al 2014). To this end, a candidate model set is defined corresponding to the range of expected mean response. 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 to the control group is used, hence a multiplicity adjustment is applied that accounts for the multiple possible dose response behavior considered. 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.

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_0: There is no dose-response relationship for LIK066 (i.e. the dose response relationship is flat).
- H_1: There is a dose-response relationship for LIK066 (i.e. as dose increases, the percent weight decreases).

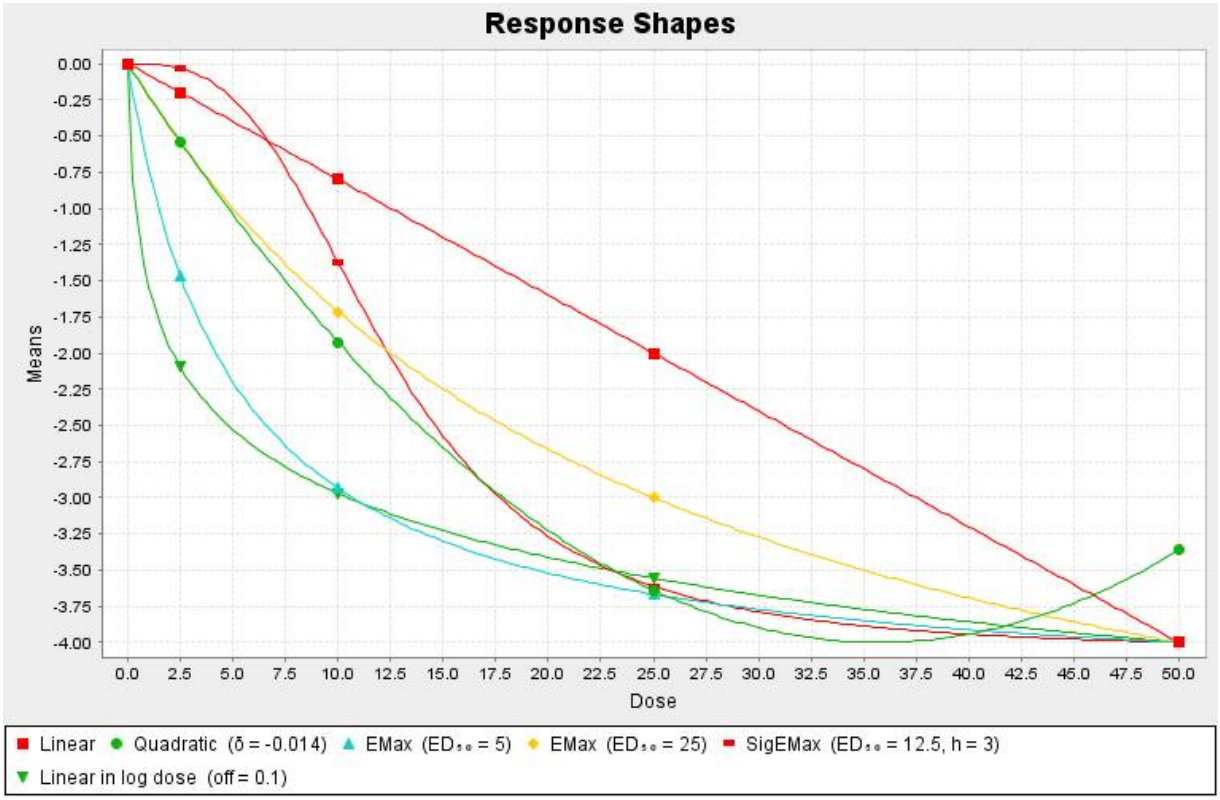
In order to preserve the family-wise error rate at one-sided significance level of 2.5%, the optimal contrasts derived from the model candidate set will be individually compared to the critical value derived using a multiplicity adjustment accounting for all tests comparing LIK066 doses to placebo. The rejection of the null hypothesis will be achieved using the maximum test statistic from each estimated contrast test in the candidate set.

The candidate models generating the contrast weights are described below and depicted in Figure 9-1:

- E_{max} model: ED_{50} = 5 mg
- E_{max} model: ED_{50} = 25 mg
- Linear
- Quadratic: $\delta = -0.014$
- Sigmoid E_{max} model: ED_{50} = 12.5 mg, h = 3
- Linear on log dose, with offset value = 0.1

[redacted]

Figure 9-1 Dose-response curve of candidate models



The analysis to derive the test statistics is based on an analysis of covariance (ANCOVA) model with the percent change in body weight from BL, to Week 12 as a response variable, treatment (placebo and all LIK066 doses), stratum indicator (dysglycemic /T2DM) as factors and BL weight as a covariate.

The response variable of percent change in body weight from BL to Week 12 used in the above ANCOVA is from an imputed dataset, where the missing Week 12 weight is imputed using the multiple imputation method as described in Section 9.4.3. In order to account for the imputation uncertainty, this ANCOVA model will be repeated for each imputed dataset, which results in a set of least squares (LS) mean estimates for all dose groups and the related covariance matrices. Rubin's rule will be used to combine the multiple sets of LS mean estimates and the related covariance matrices to a single set of LS mean estimates of percent changes of body weight at Week 12 for all dose groups and the related covariance matrix.

The optimal contrasts derived from the candidate model sets will be applied to the combined estimated dose means and covariance matrix to obtain the t statistics for each candidate model and the common critical value $C_{0.025}$. $C_{0.025}$ is the common critical value derived from the reference multivariate t-distribution with the 6x6 correlation matrix induced by testing the candidate dose response models with respect to comparing each LIK066 dose to the placebo group.

The hypothesis H_0 will be rejected and the statistical significance of dose-response in body weight reduction is established if the max (t1, t2, t3, t4, t5, t6) $\geq C_{0.025}$.

[redacted]

Model averaging to obtain the dose responses

The response data in each imputed data set, including relevant covariates, will be used to fit the models in the candidate set. The estimated dose-response will be derived by using model averaging methods on a subset of candidate models, for which the associated contrast tests are statistically significant. Model averaging will be carried out for each imputed data set, and the resulting mean efficacy estimates and confidence intervals will be derived using the combination variance that accounts for the uncertainty of the imputed data using Rubin's combination rules.

Target dose selection will be based on the model averaged dose response estimates of mean weight lowering efficacy of LIK066 over the dose range studied in this study.

9.4.3 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 include the longitudinal sequence of body weight data collected at each visit up to and including Week 12 visit as response variable, and treatment, visit and BL covariates (e.g. stratification factor, baseline body weight, height and gender) as independent variables.

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

9.4.4 Sensitivity analyses

The dose-response modeling as described in Section 9.4.2 will be conducted in the PPS as well.

Results based on the single best dose response model fit will also be reported.

Summary statistics for body weight will be presented by visit by treatment for observed and imputed values. The summary statistics n, mean, SD, median, minimum, maximum, Q1 and Q3 will be presented for the BL values and similarly for absolute values at and changes from BL to the post-BL visits. Figures will be produced to visually show the raw and the imputed mean changes by visit over 12 weeks of Epoch 3 for each treatment group, for all subjects and by strata separately.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Variables

- Responder rates based on percent decrease in body weight from BL at Week 12 $\geq$ 3%, $\geq$ 5%, or $\geq$ 10%
- Dose-response relationship in dysglycemic subjects and subjects with T2DM after 12 weeks of treatment.
- Change from BL at Week 12 in waist circumference at umbilical level.
- Change from BL at Week 12 in HbA1c

[redacted]

- Change from BL at Week 12 in FPG
- Change from BL at Week 12 in SBP and DBP
- Changes from BL at Week 12 in the fasting lipid profile (TG, total cholesterol, HDL cholesterol, LDL cholesterol, lipoproteins, calculated VLDL cholesterol and non-HDL cholesterol) and hsCRP
- Change from BL at Week 12 in uric acid
- Change from BL at Week 12 in urine albumin
- Change from BL at Week 12 in urine albumin to creatinine ratio
- Change from BL at Week 12 in fat area parameters (VFA and SFA)

Analysis method: responder analysis

For the responder analysis, a logistic regression model will be performed using the percent decrease in body weight from BL at Week 12 ≥ 3%, ≥ 5% or ≥ 10% (yes/no) as a response variable, treatment, and glycemic stratification factor as fixed factors and BL body weight as a covariate, respectively. The Week 12 missing values will be imputed using the multiple imputation method as described in Section 9.4.3. In order to account for the imputation uncertainty, this logistic regression model will be repeated for each imputed dataset, which results in a set of estimated odds ratio and its 95% confidence interval of an LIK066 dose *vs* placebo for all dose groups. 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 across each of the subgroups (subjects with dysglycemic and subjects with T2DM).

In addition, subjects meeting the pre-defined response criteria (percent decrease in body weight from BL at Week 12 ≥ 3%, ≥ 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 dose to the placebo.

Analysis method: dose-response relationship by glycemic stratification factor

For the dose-response relationship in subjects with dysglycemic and subjects with T2DM, the dose-response modeling with the same candidate model sets for the primary variable as described in Section 9.4.2 will be performed on percent change of body weight from BL at Week 12 for these two subsets of subjects separately.

Analysis for other secondary endpoints

For changes from BL at Week 12 in waist circumference, HbA1c, FPG, SBP, DBP, uric acid, urine albumin and urine albumin to creatinine ratio, a repeated measure ANCOVA model with treatment, visit, and treatment by visit interaction as fixed-effect factors and BL as a covariate, and a common unstructured covariance matrix among visits between treatments will be performed separately for each variable. The adjusted mean changes at Week 12 within each treatment, the differences in mean changes at Week 12 between the LIK066 and placebo treatments, and their 95% confidence intervals obtained from the above model will be

[redacted]

presented. The analysis is based on likelihood method with an assumption of MAR for missing data.

In addition, a repeated measure ANCOVA model with treatment, visit, stratification factor (dysglycemic, T2DM) and treatment by visit, treatment by stratification factor and treatment by visit by stratification factor interactions as fixed-effect factors and BL as a covariate, and a common unstructured covariance matrix among visits between treatments will be performed for the primary and secondary efficacy variables, respectively. The adjusted mean changes at Week 12 within each treatment, the differences in mean changes at Week 12 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 fat area parameters, and $\log_{10}$-transformed hsCRP from BL to Week 12.

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 12 weeks of Epoch 3 for each treatment group, for overall and by strata separately.

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

9.5.2 Safety variables

All safety analyses will be performed in the SAF.

AEs

Treatment emergent AEs will be summarized. A treatment-emergent AE is defined as any AE that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment. The number and percentage of subjects having AEs will be presented by treatment group and different hierarchy levels of the MedDRA coding dictionary. Summaries will also be presented by greatest severity, for AEs suspected to be related to study drug, serious AEs, AEs leading to discontinuation, to dosage adjustment, to death and other significant AEs. The hypoglycemic events will be similarly summarized. Further information related to hypoglycemic events (eg if third party assistance required, was medical assistance received, etc.) may be provided as well.

AEs related to identified and potential risks as specified in the development safety profiling plan will be summarized and presented separately.

The frequencies and percentages of the adjudication confirmed ketoacidosis events will be provided by treatment.

In addition, for selected AEs including hypotension, hypoglycemia, hyperkalemia, diarrhea, and genital and urinary tract infection, a by-stratification factor of BL glycemic status subgroup analysis will be provided.

Laboratory data, vital signs and ECG

Descriptive summary statistics including for the change from BL to each study visit up to and including Week 12 visit will be presented by treatment group for each laboratory parameter,

[redacted]

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.

The vital sign and ECG data collected during Epoch 3 will be descriptively summarized by treatment as appropriate.

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Individual LIK066 plasma concentration data will be listed by treatment, subject, and visit. Concentrations below the lower limit of quantification will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

9.5.5 DNA

Not applicable.

[redacted]

[redacted]

[redacted]

9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

The study planned to randomize approximately 130 subjects in total, allocated in the ratio of 3:2:2:3:3 to the following Epoch 3 treatment groups:

1. placebo
2. LIK066 2.5 mg qd
3. LIK066 10 mg qd
4. LIK066 25 mg qd
5. LIK066 50 mg qd

This randomization scheme implies that the Epoch 3 treatment for a specific subject is determined simultaneously at randomization visit. The randomization will be stratified by subjects' glycemic status: T2DM and dysglycemic (see Section 3.1.2).

Sample sizes are considered from two viewpoints. One is that this study should be statistically powered to identify the dose-response relationship regarding the effect of LIK066 on weight loss. The other is that this is the first study to enroll Japanese patients, and that the highest dose arms, 25 mg and 50 mg qd arms, and the placebo arm as a control, should include more patients to obtain sufficient information on safety and/or tolerability of LIK066 in Japanese patients. The detail of the first viewpoint will follow.

Table 9-1 summarizes the average power and the lowest power across the candidate dose-response shapes in Figure 9-1, 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. In power evaluation, it was also assumed that dose-response is assessed with controlling the overall family-wise type I error at a one-sided significance level of 2.5%.

It was assumed that the effect of losses to follow-up is equivalent to effectively having 10% 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.

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

Effect size for best dose	Standard deviation	Average power	Minimum power**
3.5%	3%	99.70%	99.52%
3.5%	3.5%	98.11%	97.28%
4.0%	3%	99.97%	99.94%
4.0%	3.5%	99.59%	99.35%

* Assumes 130 subjects in total with effective sample size of 117 subjects due to an effect of missing data equivalent to 10% fewer subjects. Calculations were performed using R Dose Finding package.

** Power for a significant dose-response contrast test across all scenarios mentioned in Section 9.4.2. The quadratic model has the lowest power.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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

10.3 Responsibilities of the investigator and IRB/IEC

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

[redacted]

10.4 Publication of study protocol and results

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

10.5 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Global Development Quality Audit, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

11 Protocol adherence

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

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

11.1 Protocol amendments

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

[redacted]

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Rosenstock J and Ferrannini E (2015) Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care; 38:1638-42.

References are available upon request.

[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

Vital signs range deviations are defined as per Table 13-1.

Table 13-1 Vital signs notable range deviations

Vital sign		Notable abnormalities
Pulse (beats/min)		either ≥ 120 + increase ≥ 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.

[redacted]

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

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 × ULN < ALT / AST ≤ 5 × ULN • 1.5 × ULN < TBL ≤ 2 × ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

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

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

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	• Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

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