NOVARTIS

Clinical Development

LIK066B

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

Statistical Analysis Plan (SAP)

Author:	Statistician, [redacted]

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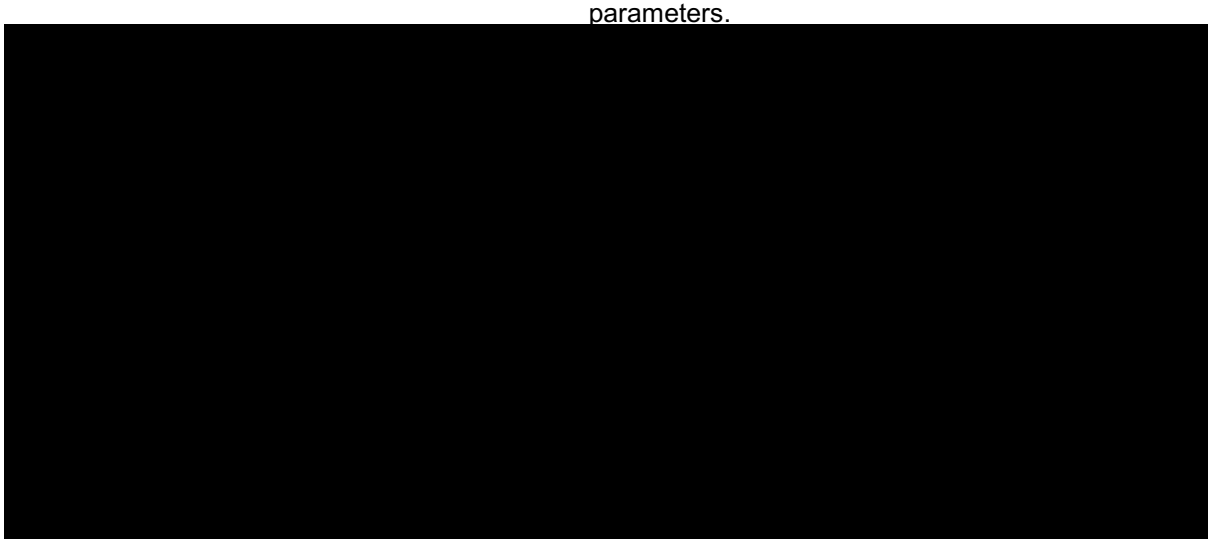
Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
09NOV2017	Prior to FPFV		First Final version	
20JUL2018	Prior to DBL	Alignment with B2201 on definition of baseline	Any measurement, regardless of whether scheduled or not, could be handled as baseline if it occurs at or before visit 201.	2.1.1 General definition
20JUL2018	Prior to DBL	Project-level update on the model-averaging method	The model-averaging is implemented via a parametric bootstrap method.	2.5.1 Primary endpoint
20JUL2018	Prior to DBL	Project-level update on the method for multiple imputation	The imputation model is updated.	2.5.3 Handling of missing balues/consoring/discontinuations
20JUL2018	Prior to DBL	Project-level update on the model-averaging method	The plan for dose-response model based on the best-fit model is cancelled.	2.5.4 Supportive analyses
20JUL2018	Prior to DBL	Revision of display of summary statistics for BW	BW is to be summarized using percent changes for overall population and subgroups. For subgroup summaries, only observed values are to be included.	2.5.4 Supportive analyses

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20JUL2018	Prior to DBL	Clarification on CMH test	It is clarified to use observed values for CMH test for BW responder analysis.	2.7.2 Statistical hypothesis, model, and method of analysis
20JUL2018	Prior to DBL	Update of ANCOVA models for efficacy analysis	The baseline glycemic status is added to ANCOVA models for secondary efficacy endpoints.	2.7.2 Statistical hypothesis, model, and method of analysis
20JUL2018	Prior to DBL	Simplification of subgroup analysis by stratum	ANCOVA models are applied by stratum.	2.7.2 Statistical hypothesis, model, and method of analysis
20JUL2018	Prior to DBL	Change of cut-off value for AE frequecies	Summary of the most frequent AEs includes AEs whose frequencies are >= 5% in 50mg qd arm.	2.8.1.1 Adverse events of special interest / grouping of AEs
20JUL2018	Prior to DBL	Clarification of diarrhea event for analysis of event periods	The number of days with “on-treatment” diarrhea is used for negative binomial regression analysis.	2.8.1.1 Adverse events of special interest / grouping of AEs
20JUL2018	Prior to DBL	Project-level update on analysis plan for hypoglycemic events	It is clarified to summarize “clinically significant” hypoglycemic events. Also it is updated how to use hypoglycemic events in AE summary.	2.8.1.1 Adverse events of special interest / grouping of AEs

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20JUL2018	Prior to DBL	Project-level update on the AE of special interest	"Pre-amputation events" is additionally listed as AE of special interest.	2.8.1.1 Adverse events of special interest / grouping of AEs
20JUL2018	Prior to DBL	Clarification of cut-off values for shift tables	Cut-off values are specified for selected ECG parameters.	2.8.4.1 ECG and cardiac imaging data
				
20JUL2018	Prior to DBL	Documentaton of the change in analysis plan from the protocol	It is clarified which analysis to be changed from the study protocol.	4 Change to protocol specified analysis
20JUL2018	Pror to DBL	To remove confusing information about handling of hypoglycemic event data	No impact	5.2 AEs coding/grading

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20JUL2018	Prior to DBL	To add PD OTH01 to handle erroneous randomization	Any patient would be excluded from PPS if randomised under a CRC's erroneous operation at the site.	5.5 Rule of exclusion criteria of analysis sets
13SEP2018	Prior to DBL	To update the units for eGFR and FPG to SI units	The units in TFLs are updated.	2.3 Patient disposition, demographics and other baseline characteristics
13SEP2018	Prior to DBL	To clarify at which time point for BW to be summarized as baseline data	It becomes clear that screening BW is to be sumamrized.	2.3 Patient disposition, demographics and other baseline characteristics
13SEP2018	Prior to DBL	To add categorized summary on BL eGFR with Japanese coefficients	The plan for BL summary is updated.	2.3 Patient disposition, demographics and other baseline characteristics
13SEP2018	Prior to DBL	To revise ANCOVA models for efficacy variables assessed only at BL and Week 12.	The factors incuded in the ANCOVA models are revised.	2.7.2 Statistical hypothesis, model, and method of analysis 4 Change to the protocol specified analyses
13SEP2018	Prior to DBL	To specify in the footnote for Table 2-4 that by-visit summary will be provided as only efficacy analysis.	For uric acid, urine albumin, and urine alubmin to creatinine ratio by-visit summary statistics will be displayed as efficacy analyses.	2.8.3 Laboratory data

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
[redacted]				

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
BL	Baseline
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
[redacted]	[redacted]
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of this Statistical Analysis Plan, SAP, is to document the analysis plan for reporting in the clinical study report from CLIK066B1201.

1.1 Study design

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

1.1.1 Epoch 2 (run-in)

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

At Visit 101, the subject's volume status must be assessed 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 a 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:

- The dose of SUs for subjects with T2DM 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. To limit the number of subjects with early deterioration of glycemic control who would meet the FPG rescue criteria early after randomization, an FPG randomization criterion is included as an exclusion criteria.

- 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.

1.1.2 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.

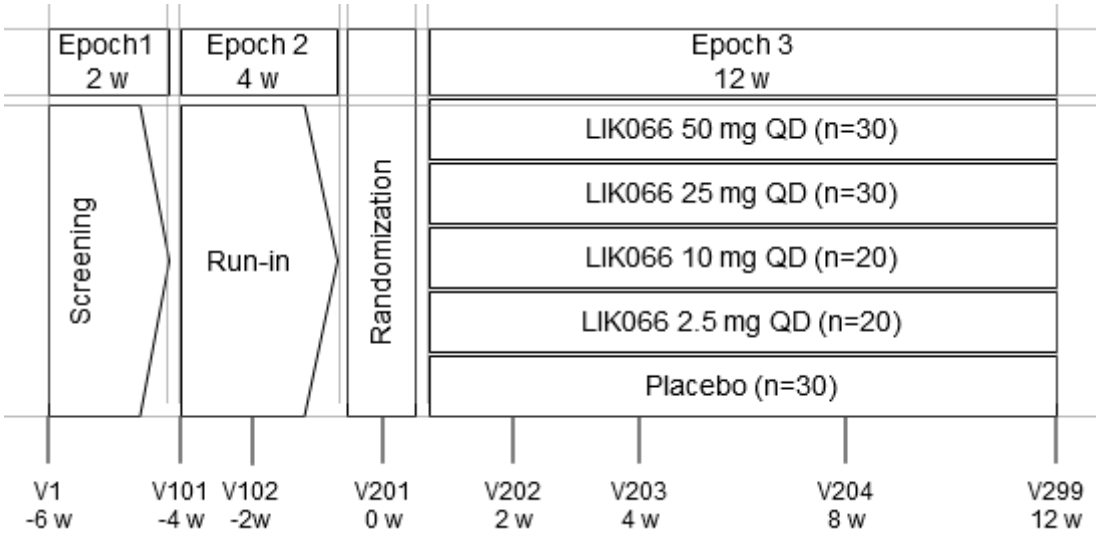
At randomization, subjects will be stratified according to their glycemic status at screening using the following criteria:

- 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. During Epoch 3, subjects will take the study medication.

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.).

Figure 1-1 Study design



The primary analysis time point is Week 12 (Visit 299). There is no interim analysis planned.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
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	**Endpoint(s) for primary objective(s)** Percent change from BL in body weight at Week 12
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).	**Endpoint(s) for secondary objective(s)** Responder rates according to percent change in body weight ≥3%, ≥5%, ≥10% from BL at Week 12
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
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: Waist circumference at umbilical level Hemoglobin A1c (HbA1c) Fasting plasma glucose (FPG)

Objective(s)	Endpoint(s)
	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 creatinine ratio Visceral fat area (VFA) and subcutaneous fat area (SFA) by 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, ECG
To evaluate the pharmacokinetics (PK) of LIK066	PK (trough).
[redacted]	

2 Statistical methods

2.1 Data analysis general information

Novartis will perform the analysis for the study. SAS Version 9.4 or higher will be used to perform all the statistical analyses in the report.

In general, for continuous data, mean, standard deviation, median, lower quartile, upper quartile, minimum, and maximum will be presented. Categorical data will be presented as frequencies and percentages of patients in each category. For categorical variable summaries, an additional category 'Missing' will be presented if there are missing values for that variable. If not otherwise specified, p-values will be presented for two-sided hypothesis testing and two-sided confidence intervals will be displayed; the level of significance will be 5% unless otherwise stated.

There is no analysis cut-off date for the study.

The strattification factor, glycemic status, will be included as a factor in an ANCOVA model for each analysis wherever applicable and feasible.

Details in key statisical methodology will be reported in CSR Appendix 16.1.9.

2.1.1 General definitions

Baseline (Week 0) for the randomized treatment period will be defined as the last measurement before or at the randomization visit.

The first day of administration of randomized study treatment (first dose) is defined as Day 1 for the study. If the date of first administration is missing, then randomization date will be used as Day 1.

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

The treatment groups presented are:

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

2.2 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.

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

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

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

The **per-protocol set** (PPS) is a subset of the FAS. It consists of all randomized subjects in the FAS who have been exposed to study medication for at least 11 weeks, and have no major protocol deviations affecting the primary endpoint analysis.

Exposure to study medication for at least 11 weeks means that the overall duration of exposure is equal to or longer than 77 days, counted from start of randomized medication to the last intake.

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

2.2.1 Subgroup of interest

Subgroups of interest include:

- Baseline glycemic status (dysglycemic, and T2DM)
- Age (<65, ≥65)
- Sex (Male, Female)
- BMI (<27, ≥27; <30, ≥30; <35, ≥35)

Table 2-1 Specification of subgroups

Subgroup	Method of derivation	Disposition/ Background & Demographics / Exposure	Efficacy	Safety
Baseline glycemic status (dysglycemic, and T2DM)	Screening	X	X	X
Age groups: (<65, ≥65 years)	Screening (derived)		X	X
Sex (Male/Female)	Screening	X	X	X
BMI (<27, ≥27; <30, ≥30; <35, ≥35)	Baseline for body weight, and screening for height		X	

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

2.3 Patient disposition, demographics and other baseline characteristics

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

Continuous variables:

- Age
- Height
- Weight at screening
- Body mass index (BMI)
- Waist circumference (cm)
- Baseline VFA (cm^2)
- Baseline SFA (cm^2)
- Smoking pack years
- Baseline pulse (bpm)
- Baseline systolic blood pressure (mmHg)
- Baseline diastolic blood pressure (mmHg)
- Baseline HbA1c (%)
- Baseline FPG (mmol/L)
- Baseline eGFR MDRD (mL/min)
- Baseline eGFR MDRD with a Japanese coefficient (mL/min)

Categorical variables

- Age category (< 65, ≥ 65)
- Gender
- Subjects of child bearing status (females only)
- Race
- Smoking status at baseline
- Alcohol history (0, 1, 2, >=3 drinks/day)
- BMI (<27, ≥27; <30, ≥30; <35, ≥35)
- Baseline glycemic status (dysglycemic, and T2DM)
- Baseline VFA category (<150 cm^2, ≥150 cm^2)

- Baseline HbA1c category (<6.5, ≥6.5 - < 8%, ≥8%)
- Baseline eGFR MDRD category (<60, ≥60 mL/min)

Baseline eGFR MDRD category with a Japanese coefficient (<60, ≥60 mL/min)

BMI will be calculated using the following formula:

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

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

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

The protocol solicited medical history events will be summarized by event type, event status (yes, no, unknown), and treatment.

2.3.1 Patient disposition

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

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

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

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

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

2.4.1 Study treatment / compliance

The duration of double-blind treatment exposure in Epoch 3 will be summarized by treatment group both descriptively in days (mean, standard deviation, minimum, Q1, median, Q3, and maximum) and by duration category in weeks (≤2, >2-4, >4-8, >8-12, and >12) for the SAF.

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

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

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

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

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

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

Duration of treatment interruption will also be summarized as appropriate.

2.4.2 Prior, concomitant and post therapies

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

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

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

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

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

- Metformin + AGI
- DPP-4i + TZD

- Other

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

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

Table 2-2 Prohibited medication for reporting

Prohibited Medication	Drug code
Empagliflozin	07271601
Clarithromycin	00984601
Telithromycin	01548701
Itraconazole	00780701
Ketoconazole	00532501
Voriconazole	01510101
Posaconazole	01762801
Probenecid	00045101
Valproic Acid	00228501
Mefenamic Acid	00044201

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary analysis variable is the percent change in body weight (kg) from BL at Week 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 2.5.3.

2.5.2 Statistical hypothesis, model, 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:

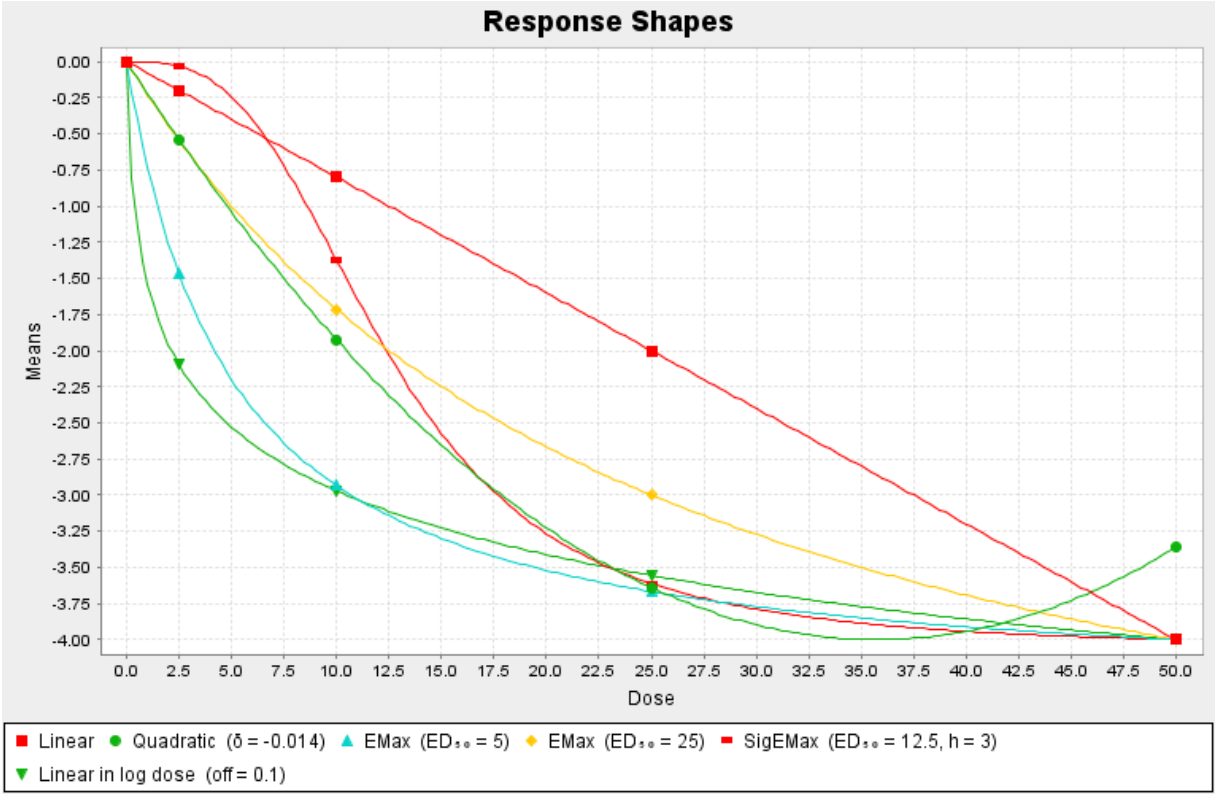
- H_0: There is no dose-response relationship for LIK066 (i.e. the dose response relationship is flat).
- H_1: There is a dose-response relationship for LIK066 (i.e. as dose increases, the percent weight decreases).

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 2-1:

- 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

Figure 2-1 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 2.5.3. In order to account for the imputation uncertainty, this ANCOVA model will be repeated for each imputed dataset, which results in a set of least squares (LS) mean estimates for all dose groups 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_{01} 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) $\geq C_{0.025}$.

Model averaging to obtain the dose responses

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

1. The parametric bootstrap procedure will draw a sample of mean percent changes in body weight from baseline to Week 12 for all doses (including placebo) from a multivariate normal distribution, with mean and covariance matrix was determined using Rubin's rule, as described earlier. This sample corresponds to the mean response for each dose (including placebo).
2. Model selection will be performed as follows: dose-response models as depicted in Figure 2-1 will be fit to this bootstrap sample. The best model will be selected on basis of the gAIC criterion.
3. The dose response estimate will be calculated for each dose group, including placebo, using this model. The difference in estimated dose response between each dose and placebo will also be calculated. The target doses of interest in each dosing regimen will be calculated based on this model as well.
4. The above procedure (steps 1-3) will be repeated 5,000 times. The mean dose-response estimates by dose group and mean differences of dose-response estimates between each LIK dose and placebo, the target doses of interest, as well as their 95% confidence intervals will be calculated based on the quantiles (median, 2.5^{th} and 97.5^{th} percentiles) of these multiple sets of dose-response and target dose estimates generated in step 3.

2.5.3 Handling of missing values/censoring/discontinuations

Missing data for the primary endpoint will be imputed using a multiple imputation approach that assumes that the missingness mechanism can be retrieved from observed data (missing at random; MAR). The imputation model will be fitted within each treatment and stratum, using MCMC method, based on the longitudinal sequence of body weight data collected at each visit up to and including Week 12. .

2.5.4 Supportive analyses

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

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 percent changes from BL to the post-BL visits. Also summary statistics will be presented using observed values only by visit, treatment, and subgroup of interest: baseline glycemic status, age group, gender, and BMI category.

Figures will be produced to visually show the raw and the imputed mean percent changes by visit over 12 weeks of Epoch 3 for each treatment group, for all subjects and by strata separately.

2.6 Analysis of the key secondary objective

There is no key secondary objective for the study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

- Responder rates based on percent decrease in body weight from BL at Week 12 ≥ 3%, ≥ 5%, or ≥ 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
- Change from BL at Week 12 in FPG
- Change from BL at Week 12 in SBP and DBP
- Percent 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)
- Change from BL at Week 12 in $\log_{10}$-transformed 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)

2.7.2 Statistical hypothesis, model, and method of analysis

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 2.5.3. 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 $\geq 3\%$, $\geq 5\%$ or $\geq 10\%$) will be summarized by treatment for all subjects and by glycemic stratification factor. Cochran-Mantel-Haenszel-test will be performed to compare each dose to the placebo using observed values.

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 2.5.2 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

Other efficacy secondary endpoints are analyzed using ANCOVA models.

- For changes from BL at Week 12 in HbA1c, FPG, lipid parameters, fat area parameters, uric acid, urine albumin, urine albumin to creatinine ratio, and log10-transformed hsCRP, an ANCOVA model will be applied for individual variables, including treatment and baseline glycemic status as fixed effect factors, and baseline as a covariate.
- For changes from BL at Week 12 in other variables, a repeated measure ANCOVA model will be applied with treatment, visit, baseline glycemic status, and treatment by visit interaction as fixed-effect factors and baseline as a covariate, and an unstructured covariance matrix among visits common between treatments.

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 presented.

In addition, ANCOVA analyses will be applied by baseline glycemic status.

- For changes from BL at Week 12 in HbA1c, FPG, lipid parameters, fat area parameters, urine albumin, urine albumin to creatinine ratio, and log10-transformed hsCRP, an ANCOVA model will be applied for individual variables, including treatment as a fixed effect factor, and baseline as a covariate.
- For changes from BL at Week 12 in other variables, a repeated measure ANCOVA model will be applied with treatment, visit, and treatment by visit interaction as fixed-effect factors and baseline as a covariate, and an unstructured covariance matrix among visits common between treatments.

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.

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.

2.7.3 Handling of missing values/censoring/discontinuations

Missing body weight at Week 12 will be imputed using the multiple imputation method as described in Section 2.5.3.

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

2.8 Safety analyses

All safety analyses will be based on SAF.

2.8.1 Adverse events (AEs)

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.

Treatment emergent AEs will be summarized. The number and percentage of subjects having AEs will be summarized by system organ class, preferred term, and treatment group. Unless otherwise specified, primary system organ will be sorted alphabetically and, within each primary system organ class, the preferred terms will be sorted in descending order of frequency in the LIK066 50 mg qd arm. If a patient reported more than one AE with the same preferred term, the AE will be counted only once. If a patient reported more than one AE within the same primary system organ class, the patient will be counted only once at the system organ class level. The number and percentage of subjects having AEs will be summarized by system organ class, preferred term, treatment group, and subgroups of interest (baseline glycemic status, age group and sex) as well.

The most frequent AEs (>=5% in LIK066 50mg qd arm group) will be presented by preferred term in descending order of frequency in the LIK066 50 mg qd arm.

AEs will also be presented by greatest severity. If a patient reported more than one AE with the same preferred term, the highest severity will be presented. All AEs will be summarized by highest severity, primary system organ class, preferred term, and treatment. If a patient reported more than one AE within the same primary system organ class, only one AE will be counted for that patient at the highest severity level in the total row for each primary system organ class. Missing severity will be assumed to be severe in the summary table.

AEs suspected to be related to study drug, serious AEs, fatal AEs, and AEs leading to study drug discontinuation, study drug interruption will be summarized by presenting number and

percentage of patients with an event by primary system organ class, preferred term, and treatment.

All AEs in the database will be listed. The listings will include those AEs reported during the run-in epoch, and AEs reported after study discontinuation for those who discontinue the study prior to Week 12.

Legal requirement for AE reporting

For the legal requirements of ClinicalTrials.gov, two required tables on treatment emergent AEs which are not SAEs with an incidence greater than 2% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by system organ class, preferred term, and 5 randomized treatment arms on the SAF for overall study duration.

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

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

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

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

2.8.1.1 Adverse events of special interest / grouping of AEs

AEs of special interest, such as risks defined in the development safety profiling plan (DSPP), or topics of interest regarding signal detection or routine analysis, are defined in the electronic case retrieval sheet (eCRS) that is stored in GPS.

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

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

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

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

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

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

Diarrhea events of special interest

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

- Number of days for one diarrhea incidence = AE end date – AE start date +1.
- Number of days with diarrhea events for a patient = sum of days on diarrhea over all incidences that occurred in Epoch 3.

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

In addition, the number of days with diarrhea while on-treatment will be analyzed via a negative binomial regression model. The model will include the number of days with diarrhea as a response variable, treatment, baseline glycemic status as factors, and log(duration of exposure in days) as an offset variable.

Ketoacidosis events of special interest

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

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

Hypoglycemic events of special interest

There are two categories of clinically significant hypoglycemic events:

Table 2-3 Criteria for hypoglycaemia events

Category	Criteria
Severe hypoglycaemia	An event, requiring assistance of another person (third party assistance) to actively administer carbohydrate, glucagon, or other corrective actions, confirmed or not by a blood glucose measurement
Other clinically significant hypoglycaemia	Plasma glucose < 3.0 mmol/l (54 mg/dl) with or without typical symptoms of hypoglycaemia, and which is handled by the subject himself/herself.

Hypoglycemic events entered into the study Hypoglycemic event eCRF will be included in all of the AE summaries in Section 2.8.1. Hypoglycemia classification is included in the Appendix Table 5-1.

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

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

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

- Third party assistance recieved (Yes, No)
- Medical assistance received (Yes, No)

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

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

2.8.2 Deaths

Any deaths up to and including Week 12 will be included in a separate able by treatment group summarizing fatal events.

Deaths will also be listed by treatment groups.

2.8.3 Laboratory data

Table 2-4 displays laboratory parameters analyzed for reporting.

Table 2-4 Laboratory data

Category	Parameter(s)
Hematology	RBC (total), WBC (total), platelet count (direct), hemoglobin, hematocrit, basophils (absolute, %), eosinophils (absolute, %), lymphocytes (absolute, %), monocytes (absolute, %), neutrophils (absolute, %)
Biochemistry	ALT, albumin, alkaline phosphatase (ALP), AST, bicarbonates, bilirubin (direct, total), blood urea nitrogen (BUN), calcium (total), chloride, creatinine, cystatin C, eGFR (MDRD, MDRD with the Japanese coefficient), magnesium, phosphates, potassium, protein (total), sodium, uric acid*, γ-GT, amylase, lipase
Urinalysis	pH, specific gravity, protein, glucose, ketones, nitrites, blood, leucocytes, urine albumin*, urine albumin to creatinine ratio (spot urine)*

*: By-visit summary statistics for the parameter is provided only as efficacy analysis.

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, as well as for the maximum change from BL. In addition, shift tables will be provided for all parameters with available ranges to compare a subject's BL laboratory evaluation relative to the most extreme post-BL value. For the shift tables, normal ranges as well as specifically defined clinically notable/abnormality limits, if available – will be used.

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

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

Table 2-5 Clinically notable laboratory abnormalities for selected tests

Parameter	Criteria (based on a percent change from baseline or change from baseline)
Hematology	
RBC (total)	>50% increase, >20% decrease
WBC (total)	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
Clinical chemistry	
ALT	>150% increase
AST	>150% increase
BUN	≥50% increase
Creatinine	≥50% increase
Total bilirubin	>100% increase
ALP	>100% increase
Sodium	>5% increase, >150 mmol/L, <130 mmol/L
Potassium	absolute values < 3.0 mmol/L, > 5.9 mmol/L
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease, hyper > 2.6 mmol/L
Uric acid	>50% increase
Plasma glucose	>50% increase
Plasma glucose	< 3.0 mmol/L (54 mg/dL)

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

The following quantitative variables will be summarized:

- QT_cF duration (msec)
- Heart rate (beats/min)
- PR duration (msec)
- RR duration (msec)
- QRS duration (msec)

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

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

- $QT_cF > 500$ msec
- $QT_cF > 480$ msec
- $QT_cF > 450$ msec

- QT_cF increases from baseline ≥ 30 msec
- QT_cF increases from baseline ≥ 60 msec
- PR > 200 and ≤ 220 msec
- PR > 220 msec
- PR increases from baseline > 25% and to a value > 200 msec
- QRS > 110 and ≤ 120 msec
- QRS > 120 msec
- QRS changes from baseline > 25 % and to a value > 110 msec
- Heart rate > 100 beats/min

Heart rate < 50 beats/min

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

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

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

2.8.4.2 Vital signs

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

The number and percentage of patients with newly occurring or worsening notable values, including notable change from baseline will be summarized by vital sign parameter at each assessment time point by treatment group. Notable absolute values and notable changes from baseline for each vital sign parameter are defined in Table 2-6.

Table 2-6 Vital signs notable range deviations

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

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

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

2.8.5 Liver events

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

The laboratory parameters for liver function will be shown in the laboratory standard tables as discussed in Section 2.8.3. In addition, summary tables will be provided on the number and percentage of subjects who meet the liver toxicity criteria post baseline by Week 12 displayed in Table 2-7.

Listings of patients with clinically notable LFT values will be provided.

Table 2-7 Criteria for evaluating liver toxicity

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

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

2.8.6 Renal events

The overall frequency of events and percentage of patients with renal events during the treatment period will be provided for the Week 12 analysis. Furthermore, the frequency and percentage of patients with renal events during Epoch 3 will be provided by treatment and the first identified criterion. The frequency of patients with renal events and percentage will be provided for clinical signs and symptoms by the treatment. The criteria for renal events are displayed in Table 2-8.

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

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

Table 2-8 Specific renal alert criteria

Criteria	Action required
Serum event	
Serum creatinine increase 25 – 49 % compared to BL	Confirm 25 % increase after 24-48h Follow up within 2-5 days
Acute kidney injury: serum creatinine increase ≥50 % compared to BL	Follow up within 24-48h if possible Consider study treatment interruption Consider subject hospitalization /specialized treatment
Urine event	
New dipstick proteinuria ≥ 1+ 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 to 48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR

2.9 Pharmacokinetic endpoints

PK trough sampling will be performed in all subjects at visit 299.

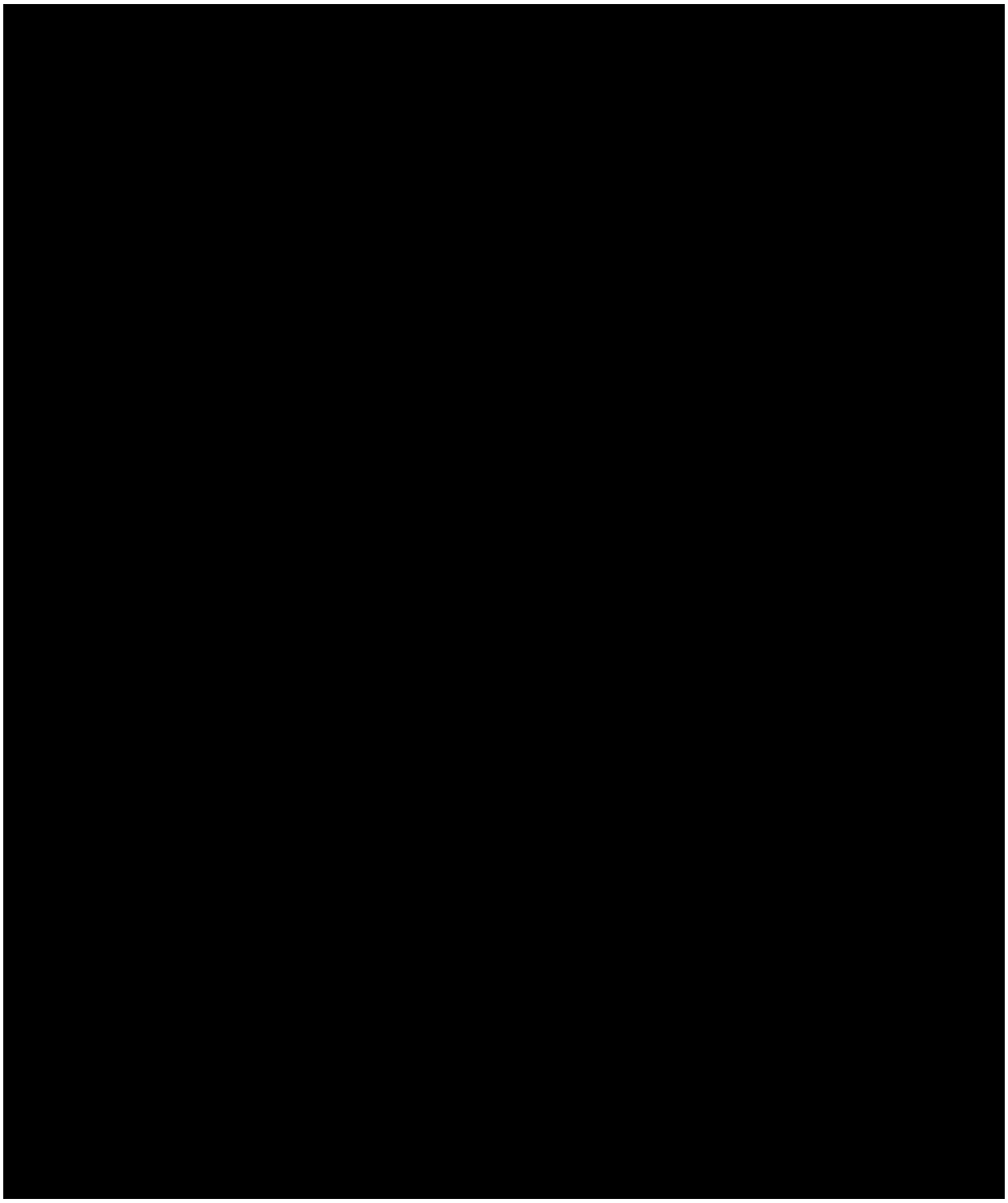
Plasma concentration of LIK066 will be summarized by treatment. Descriptive statistics includes n, mean, standard deviation, minimum, median, maximum, coefficient of variation (%) for arithmetic mean, geometric mean, and coefficient of variation (%) for geometric mean.

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

Individual LIK066 plasma concentration data will be listed by treatment, subject, and visit.

2.10 PD and PK/PD analyses

Not applicable.



2.13 Other Exploratory analyses

Not applicable.

2.14 Interim analysis

Not applicable.

3 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.

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 3-2 summarizes the average power and the lowest power across the candidate dose-response shapes in Figure 2-1, 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 3-1 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 2.5.2. The quadratic model has the lowest power.

4 Change to protocol specified analyses

Per project-level change, the summary on baseline anti-diabetic medications is changed to be provided by baseline glycemic status.

Per project-level change, the procedures for modeling dose-response relationship are changed as follows:

- Modeling via the best-fit model is cancelled.
- The model-averaging method is changed.

For efficacy secondary endpoints other than responder in body weight, ANCOVA models are changed depending on their scheduled post-baseline measurement time points

- For endpoints measured *only* at Week 12, the ANCOVA model is changed to the one including treatment and baseline glycemic status as fixed effect factors, and baseline as a covariate. Such endpoints include HbA1c, FPG, lipid parameters, fat area parameters, urine albumin, urine albumin to creatinine ratio, and log10-transformed hsCRP.
- For other endpoints, baseline status is added to the repeated measure ANCOVA model.

In addition, the models for subgroup analysis are changed to apply the same model by baseline glycemic status.

- For endpoints measured *only* at Week 12, the ANCOVA model for subgroup analysis is changed to the one including treatment as a fixed effect factor, and baseline as a covariate.
- For other endpoints, the repeated measure ANCOVA model is changed to the one including treatment, visit, and treatment by visit interaction as fixed-effect factors and baseline as a covariate.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Any partial dates will be imputed as the earlier day of

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

5.1.2 AE date imputation

AE end date imputation

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

AE start date imputation

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

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

After finding the AE start reference date:

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

c. If ‘month’ is equal to or greater than the treatment start ‘month’, the AE start date will be set to the later of (01MONYYYY, AE start reference date+1).

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

5.1.3 Concomitant medication date imputation

CM end date imputation

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

CM start date imputation

1. If ‘year’ is missing, the start date will be set to one day prior to treatment start date.
2. If ‘year’ is less than treatment start ‘year’, the CM started before treatment. Therefore:
   a. If ‘month’ is missing, the start date will be set to 01JULYYYY.
   b. If ‘month’ is non-missing, the start date will be set to 15MONYYYY.
3. If ‘year’ is greater than treatment start ‘year’, the CM started after treatment. Therefore
   a. If ‘month’ is missing, the start date will be set to 01JANYYYY.
   b. If ‘month’ is non-missing, the start date will be set to 01MONYYYY.
4. If ‘year’ is equal to the treatment start date ‘year’
   a. If ‘month’ is missing or equal to the treatment start ‘month’, then the start date will be set to one day prior treatment start date.
   b. If ‘month’ is less than the treatment start ‘month’, the start date will be set to 15MONYYYY.
   c. If ‘month’ is greater than the treatment start ‘month’, the start date will be set to 01MONYYYY.

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

5.1.3.1 Prior therapies date imputation

See Section 5.1.3.

5.1.3.2 Post therapies date imputation

See Section 5.1.3.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

AEs will be coded according to MedDRA dictionary. The MedDRA version used for reporting will be described in the footnotes. Missing severity will be assumed to be severe in the summary table.

Hypoglycemia classification is presented in Table 5-1.

Table 5-1 Hypoglycemia classification

Category	Definition	Criteria as specified in the Hypo eCRF
Severe hypoglycemia	An event, requiring assistance of another person (third party assistance) to actively administer carbohydrate, glucagon, or other corrective actions, confirmed or not by a BG measurement	An event with answer = 'YES' for any one of the two questions: Was third party assistance required? Was medical assistance received?
Other clinically significant hypoglycemia	Plasma glucose < 3.0 mmol/l (54 mg/dl)* with or without typical symptoms of hypoglycaemia, and which is handled by the subject himself/herself.	An event with answer = 'YES' to the question 'Glucose measurement taken' and the plasma glucose < 3.0 mmol/l (54 mg/dl), and answer = NO to both questions: Was third party assistance required? Was medical assistance received?

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

5.3 Laboratory parameters derivations

5.3.1 Japanese coefficient for eGFR

The Japanese coefficient for the MDRD equation is 0.808. Thererfore, eGFR with Japanese coefficient, say eGFR-J, is defined as:

$$\text{eGFR-J} = (\text{source eGFR}) \times 0.808,$$

where "source" eGFR is the one calculated by the central laboratory.

5.4 Statistical models

5.4.1 Primary analysis

See Section 2.5.2.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

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

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	No written informed consent obtained	Excluded from ENR, RUN, RAN, FAS, SAF, and PPS
TRT19	Withdrawal of the consent without discontinuation of study drug	Data collected after withdrawal of IC, excluded from FAS and SAF
TRT34	Mis-randomization	Excluded from FAS and PPS
INCL03	BMI outside range or missing	Excluded from PPS
INCL04	FPG and HbA1c not within range or missing	Excluded from PPS
INCL05	Waist circumference outside range or missing	Excluded from PPS
INCL06	VFA outside range or missing	Excluded from PPS
EXCL04	Use of prohibited medications	Excluded from PPS
EXCL05	History of malignancy	Excluded from PPS
EXCL06	Pregnant or nursing	Excluded from PPS
EXCL08	Use of pharmacologically active weight-loss medications	Excluded from PPS
EXCL10	Bariatric surgery	Excluded from PPS
EXCL20	Substances or alcohol abuse	Excluded from PPS
TRT06	Study treatment adjusted	Excluded from PPS
TRT11	Study treatment unmasked and subject not discontinued from the study	Excluded from PPS
TRT15	Use of prohibited medication and not discontinued from the study	Excluded from PPS
TRT22	Use of another investigational drug	Excluded from PPS
TRT35	Study medication taken after the morning meal	Excluded from PPS
TRT28	Misdispensed medication and taken by subject	Excluded from PPS
OTH01	Mis-randomization	Excluded from PPS

Table 5-3 Subject Classification

Analysis Set	PD ID that cause subjects to be excluded	Non-PD criteria that cause subjects to be excluded
ENR	INCL01	Not having informed consent; Not having screening epoch disposition page
RUN	INCL01	Not in ENR; Not having run-in epoch disposition page
RAN	INCL01	Not randomized
FAS	INCL01, TRT19, TRT34	Not in RAN;
PPS	INCL01, INCL03, INCL04, INCL05, INCL06, EXCL04, EXCL05, EXCL06, EXCL08, EXCL10, EXCL20, TRT06, TRT11, TRT15, TRT22, TRT35, TRT 28, TRT34, and OTH01	Not in FAS; Overall exposure on DB medication < 10 weeks *unless premature discontinuation due to adverse events*
SAF	INCL01, TRT19	No double-blind study drug taken

5.6 Anti-diabetic medications search criteria

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

Table 5-4 Search criteria for anti-diabetic medications by type

Category	Type	ATC code or drug code
Insulin	All insulin A10A	A10A (all insulin), and within this group: A10AB, A10AC, A10AD, A10AE and A10AF
OADs – used as single pills	Metformin	A10BA Biguanides
	SU	A10BB Sulfonylureas A10BC Sulfonamides (heterocyclic)
	AGIs	A10BF Alpha glucosidase inhibitors
	TZDs	A10BG Thiazolidinediones
	DPP-4i	A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors
	GLP-1 analogues	A10BJ Glucagon-like peptide-1 (GLP-1) analogues
	SGLT2i	A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors
Combinations of OADs		See the slide attached below.
Other		A10BX Other
Category	Type	ATC code or drug code

Classification of non-insulin drugs

6 Reference

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