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LIK066

CLIK066B2202 / NCT03131479

An open-label, parallel-group study to assess the effect of LIK066 on urinary glucose excretion, pharmacokinetics, safety and tolerability following multiple dose administration in patients with decreased renal function compared to subjects with normal renal function

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLIK066B2202"*** as well as for the Interim Analysis.

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Study documents available at the time of finalization of this Statistical Analysis Plan include the study protocol v00, the eCRF (Version 7.0), and the Data Management Plan (Version 4.0).

1.3 Study objectives

1.3.1 Primary objectives

- To assess the effect of a 7-day treatment with LIK066 on 24-hour urinary glucose excretion (UGE) in subjects with decreased renal function compared to those with normal renal function
    - 24-hour urinary glucose excretion on Day 7
- To assess the pharmacokinetics of LIK066 on Day 1 and Day 7 in subjects with decreased renal function compared to those with normal renal function.
    - Cmax, Tmax, AUCtau, AUClast, AUCinf, T1/2, CL/F, Vz/F, CLr

1.3.2 Secondary objectives

- To assess the safety and tolerability of a 7-day treatment with LIK066 in subjects with decreased renal function compared to those with normal renal function.
    - Adverse events

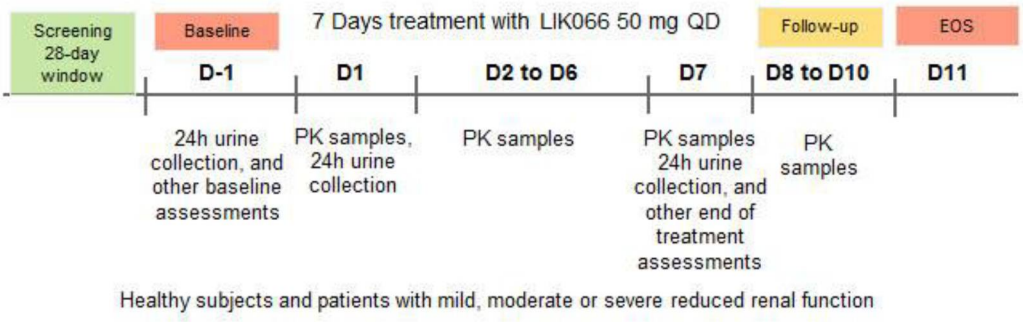
[redacted]

1.4 Study design and treatment

This study employs an open-label, multiple-dose, parallel-group design in patients with varying degrees of decreased renal function (mild, moderate and severe renal impairment) and subjects with normal renal function.

Ten (10) subjects each with mild (eGFR 60-89 ml/min/1.73 m^2), Grade A moderate (eGFR 46-59 ml/min/1.73 m^2), Grade B moderate (eGFR 30-45 ml/min/1.73 m^2), and normal renal function (eGFR≥90 ml/min/1.73 m^2); and up to 10 patients with severe renal impairment (eGFR ≤29 ml/min/1.73 m^2, not on dialysis) will be enrolled.
As it can be seen from Figure 1-1, each subject will participate in a screening period of up to 28 days, one baseline period, one treatment period of 7 days (including domicile and outpatient visits), a follow-up period, and an end-of-study evaluation approximately 96 hours after the last drug administration.

Figure 1-1: Study Design



Patients with varying degrees of decreased renal function will be enrolled first; subjects with normal renal function will be enrolled after approximately 50% of the patients with decreased

renal function have been enrolled. Because body weight and age are covariates in the estimation of eGFR formula, the 10 subjects with normal renal function will be matched to 10 of the enrolled patients with decreased renal function by age (approximately ± 10 years), weight (approximately ± 20%), and, if possible, diabetic status. The enrolled patients will be ranked by age and selected, beginning with the youngest and ending with the oldest, in an increment that yields 10 total patients.

Since this is a non-randomized study, subjects will be assigned to one of the following 5 groups according to their disease status. All subjects will receive LIK066 50 mg qd before breakfast for 7 days.

- Group 1 (n=10, mild renal impairment)
- Group 2 (n=10, moderate renal impairment grade A)
- Group 3 (n=10, moderate renal impairment grade B)
- Group 4 (n= up to 10, severe renal impairment)
- Group 5 (n=10, subjects with normal renal function)

2 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The study FIR template (mock slides) can be found in CREDI in the study RAP folder Cabinets/CREDI Projects/L/LIK066/CREDI Studies/LIK066B2202/Administrative Files (study level)/RAP or RAMP Meeting/.

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as "Key" in the Programming Deliverables Tracker (PDT) output list.

FIR will focus on the following analyses:

- Analysis of populations (if needed)
- Subject disposition
- Demographics and baseline characteristics. Baseline characteristics include, but not limited to:
    - Age, Weight/Height/BMI, Diabetes status, UGE24
- Safety results include, but are not limited to:
    - Number and percentage of subjects with adverse events by body system and preferred term with a breakdown by renal function
- Pharmacokinetic (PK) results for plasma:
    - Arithmetic mean (SD) plasma PK concentration-time plot per renal function (overlaying).
    - Summary statistics for PK parameters.
- Pharmacodynamic (PD) analyses include, but are not limited to:

- Model estimated renal function comparison in UGE24, change from baseline and % change from baseline in UGE24.
- Arithmetic mean (SD) UGE24 plot per renal function (overlaying) over time

3 Interim analyses

An interim analysis may be initiated once approximately half of the enrolled subjects have completed the study. The purpose of the analysis will be to assess the impact of reduced renal function on UGE24 in order to inform development decisions for LIK066. Actions such as early termination of the study should objectives be met, adjustments to the sample size, and/or revisions of the dose may be made.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns. The clinical team may communicate interim results to relevant Novartis teams for information, consulting and/or decision purposes.

4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from PD and PK analysis in case of these protocol deviations:		Exclude subject from PD and PK analysis set
COMD01	*Subject received prohibited concomitant medication*	

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher) from the plasma concentration-time data:

- Primary PK endpoints: Cmax, Tmax, AUCtau, AUClast, T1/2, CL/F
- Secondary PK endpoints: Vz/F and CLr

Additional PK parameters (Racc, T1/2acc, Cmin,ss, Cav,ss, Tlast, Clast etc.) may be calculated or reported as appropriate.

[redacted]

The total amount of LIK066 excreted into urine (Ae0-t) will be used to calculate the renal clearance (CLr) of LIK066 based on both plasma and urine data if the data allows.
Plasma sample will be collected for protein binding analysis in order to determine the unbound fraction of LIK066. Accordingly, unbound PK parameters [AUC,u and Cmax,u] may be calculated.

5.2 Descriptive analyses

LIK066 plasma concentration data will be listed by renal function, diabetic status, subject, and visit/sampling time point. Descriptive statistics will be provided by renal function and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in the summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Each of the PK parameters will be listed by renal function, subject, and day and summarized by renal function and day. Descriptive statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

5.3 Statistical model, assumptions and hypotheses

The natural logarithm of each PK parameter will be analyzed using a MMRM model with diabetic status, renal function group, day, and all associated interactions (where possible) as fixed factors and age as covariate. An unstructured covariance matrix will be used.

For each parameter, the least-square geometric mean will be estimated for each diabetic status by renal function by day combination. In addition, the geometric mean ratio of each renal impaired group to the group with normal renal function and the corresponding two-sided 90%

confidence interval and p-value for the ratio will be extracted for each diabetic status by day combination.

Statistical analysis may be performed to compare the free fraction (fu) across the renal function groups. If statistically significant difference exists in fu across renal function groups, the same analysis (as planned for total parameters) will also be performed to compare the AUC,u and Cmax,u between renal function groups. [redacted]

5.3.1 Graphical presentation of results

Arithmetic mean (SD) and geometric mean (90% CI) plasma concentration-time plots will be produced.

Overlaid individual plasma concentration-time profiles will be generated.

6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the PD data analysis.

6.1 Primary objective

The primary objective of this study is to assess the effect of a 7-day treatment with LIK066 on 24-hour urinary glucose excretion (UGE24) in subjects with decreased renal function compared to those with normal renal function.

6.1.1 Variables

The primary PD endpoint will be UGE24.

6.1.2 Descriptive analyses

UGE24 will be listed and summarized by renal function, day, diabetic status and overall. The change from baseline and % change from baseline in UGE24 will also be listed and summarized. Summary statistics for raw, change from baseline and % change from baseline in UGE24 will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum as appropriate. Arithmetic mean (SD) plot and spaghetti plot of individuals' observed data will be produced by renal function group for overall and for each diabetic status.

Baseline UGE24 is defined to be the measurement collected on Day -1.

6.1.3 Statistical model, assumptions and hypotheses

The primary PD analysis will assess the effect of reduced renal function on UGE24.

The change from baseline in UGE24 will be analyzed using a MMRM with diabetic status, renal function group, day, and all associated interactions (where possible) as fixed factors and age, baseline body weight, and baseline fasting plasma glucose as covariates. Baseline fasting plasma glucose and baseline body weight will be the measurements on Day 1 0-hour. An unstructured covariance matrix will be used.

The least-square mean change from baseline will be estimated for each diabetic status by renal function by day combination. In addition, the mean difference between each renal impaired group and the group with normal renal function (or other least severe group with data) and the corresponding two-sided 90% confidence interval and p-value for the difference will be extracted for each diabetic status by day combination.

Additionally, the change from baseline in UGE24 will be analyzed for the overall group, using a MMRM with diabetic status, renal function group, day, and interaction terms of renal function*day and diabetic*day as fixed factors and age, baseline body weight and baseline fasting plasma glucose as covariates. An unstructured covariate matrix will be used.

6.1.3.1 Model checking procedures

Missing data will be assumed to be missing at random and thus the above analysis will be performed on all available data. There will be no imputation of missing data.

Normal distribution of UGE24 will be examined. In case there is strong deviation from normal distribution, a supportive analysis, similar to the primary UGE analysis, except that natural logarithm of the ratio to baseline in UGE24 will be modeled instead of the change from baseline, and baseline fasting plasma glucose will also be log transformed. For this analysis, the least-square geometric mean will be estimated for each diabetic status by renal function by day combination, in addition to the geometric mean ratio of each renal impaired group to the group with normal renal (or other least severe group with data) function and the corresponding two-sided 90% confidence interval and p-value, separately for each diabetic status by day combination.

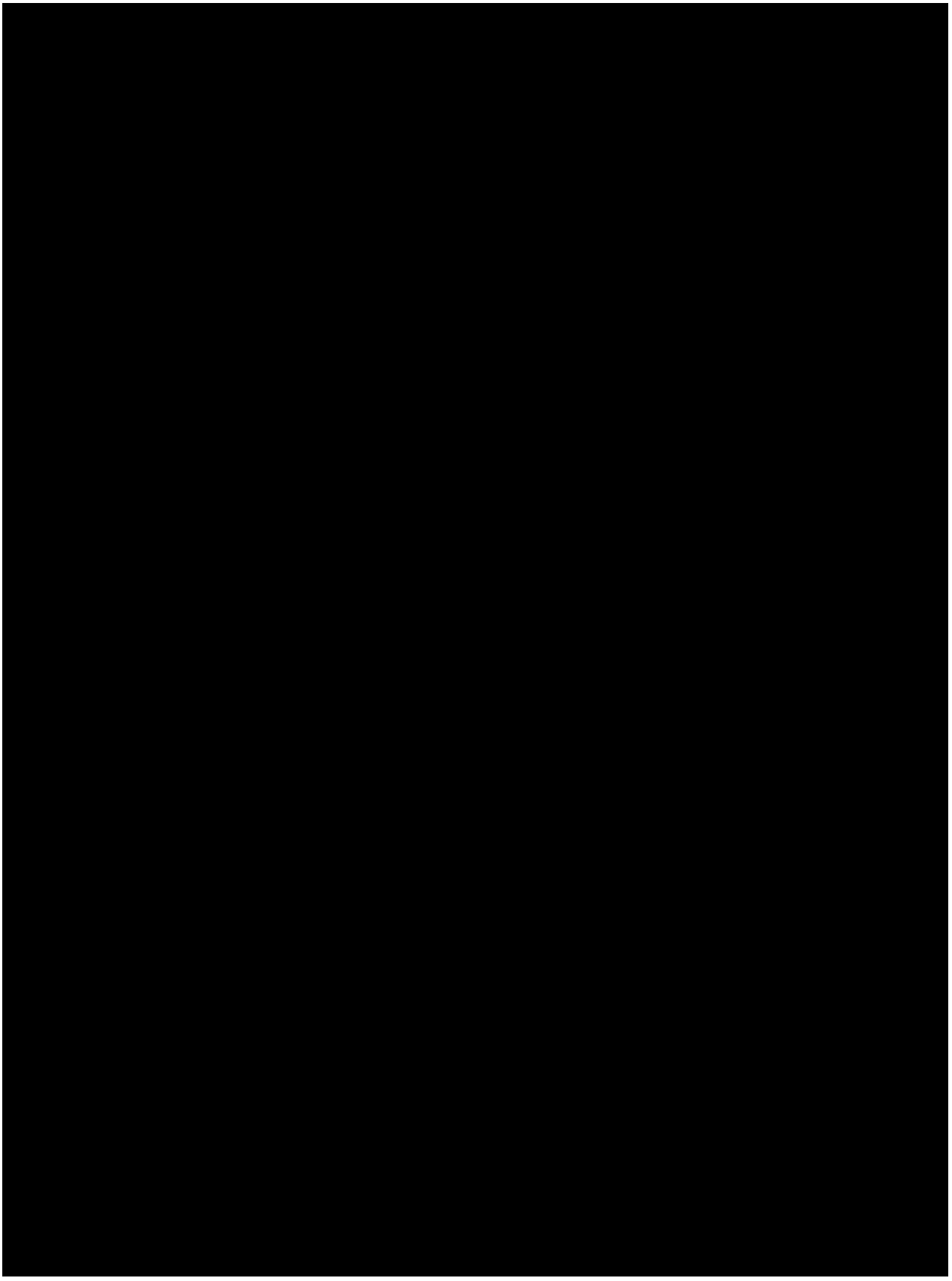
In addition, another supportive analysis similar to the primary UGE analysis, except that baseline UGE24 will be used as a covariate in place of baseline fasting plasma glucose. Baseline UGE24 will be the collection taking place on Day -1. The same model-based quantities described for the primary analysis will be extracted.

Same analysis, for both supportive analysis models, will be repeated for overall diabetic status, without including the interaction of renal function*diabetic status.

6.1.3.2 Graphical presentation of results

A bar chart showing the least-square mean and mean difference from normal renal function (or other least severe group with data) with two-sided 90% CI at each day will be generated for change from baseline in UGE24 by renal function group for each diabetic status. In addition, similar plot will be produced for ratio to baseline in UGE24 based on the ratio to baseline analysis.

The relationship between eGFR and UGE24 will be assessed by scatterplots and linear regression line with both diabetic statuses overlaying, separately by day.



7 Statistical methods for safety and tolerability data

All subjects within the safety analysis set will be included in the safety data analysis.

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, anion gap, urine ketones (dipstick), as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by renal function, diabetic status and subject. Summary statistics will be provided by renal function.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by renal function and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by renal function and subject.

Vital signs

All vital signs data will be listed by renal function, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by renal function and visit/time.

ECG evaluations

All ECG data will be listed by renal function, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by renal function and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by renal function, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by renal function and visit/time.

Adverse events

All information obtained on adverse events will be displayed by renal function and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by renal function. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 1% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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.

Other safety evaluations

Anion gap

From measurements of sodium, chloride, and bicarbonate in serum, the anion gap in mmol/L will be derived as sodium – (chloride + bicarbonate) in mmol/L and will be an additional safety variable.

The anion gap and change from baseline in anion gap will be summarized by diabetic status, renal function, and day. Baseline will be derived from the Day 1 0-hour measurements. Summary statistics will include sample size, mean, standard deviation, minimum, median, and maximum.

For each subject, the maximum post-baseline value and the maximum change from baseline will be extracted and will be summarized by diabetic status and renal function. Summary statistics will include sample size, mean, standard deviation, 90% confidence interval, minimum, median, and maximum.

The frequency of patients with a maximum post-baseline value $< / \geq 11$ will be tabulated by diabetic status and renal function.

[redacted]

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for Pharmacokinetic/Pharmacodynamic interactions

The relationship between UGE24 [redacted] and each of the primary PK parameters may be assessed graphically, in addition to the relationship between eGFR and each of the primary PK parameters. Modelling approach may also be used to explore the PK/PD interactions.

[redacted]