

Novartis Institutes for BioMedical Research

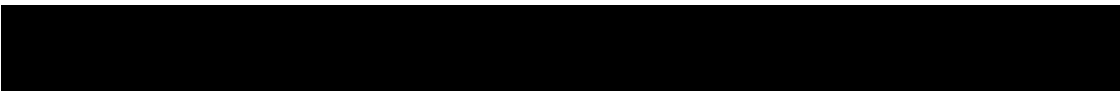
LIK066

Clinical Trial Protocol 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**

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to [Section 9.2](#) of the protocol for SAE criteria and additional requirements. See also page 2 of the SOM for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The contact information are provided in the SOM.

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List of abbreviations

γ -GT	gamma-glutamyl transferase
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
b.i.d.	twice a day
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CK	creatinine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTRD	Clinical Trial Results Database
CV	coefficient of variation
EC	Ethics Committee
ECG	electrocardiogram
EDxx	effective dose xx%
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
h	hour
HIV	Human Immunodeficiency Virus
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LC-	liquid chromatography-mass spectrometry/mass spectrometry

MS/MS

LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
MDRD	Modification of Diet in Renal Disease Study equation
MedDRA	medical dictionary for regulatory activities
MI	myocardial infarction
NCDS	Novartis Clinical Data Standards
NOEL	no observed effect level
p.o.	oral
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
REB	Research Ethics Board
RI	renal impairment
SAE	serious adverse event
SCr	serum creatinine
SD	standard deviation
SGLT	sodium glucose co-transporter
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	type 2 diabetes mellitus
TBL	total bilirubin
UGE	urinary glucose excretion
ULN	upper limit of normal
ULOQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

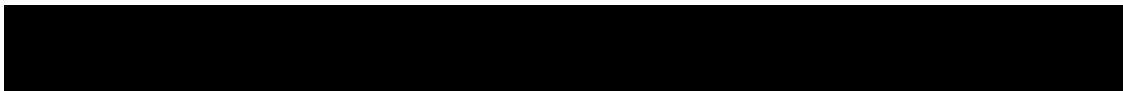
Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUCinf	The area under the plasma concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma [volume / time]
Cmax	The observed maximum plasma concentration following drug administration [mass / volume]
F	Bioavailability of a compound.
T1/2	The terminal elimination half-life [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, treatment, follow-up) which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Screen Failure	A subject who is screened but is not treated
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)


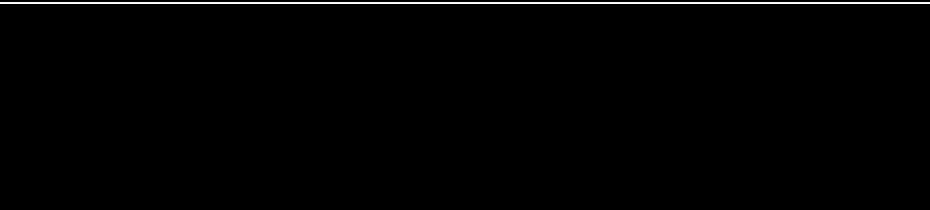
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
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
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, <u>and</u> does not want any further visits or assessments, <u>and</u> does not want any further study related contact, <u>and</u> does not allow analysis of already obtained biologic material



Protocol synopsis

Protocol number	CLIK066B2202
Title	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
Brief title	Study of pharmacodynamics, pharmacokinetics, safety and tolerability of LIK066 in patients with decreased renal function
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Investigational Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is: 1) to determine whether LIK066 displays a similar effect on the urinary glucose excretion in patients with varying degrees of reduced renal function as those with normal renal function, and 2) to assess the pharmacokinetics of LIK066 in patients with varying degrees of renal impairment as compared to those with normal renal function; to support development of LIK066 in patients with renal impairment
Primary Objectives	<ul style="list-style-type: none"> To assess the effect of a 7-day treatment with LIK066 on 24-hour urinary glucose excretion in subjects with decreased renal function compared to those with normal renal function. 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.
Secondary Objective	<ul style="list-style-type: none"> 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.
Study design	<p>An open-label, multiple-dose, parallel-group study in patients with varying degrees of decreased renal function (mild, moderate and severe renal impairment) and subjects with normal renal function. 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.</p> <p>Eligible subjects will be admitted to the study site at Baseline (Day -2). Meal contents including carbohydrates and salt will be standardized from Day -2 to the morning of Day 2, and then from Day 5 to Day 8, [REDACTED]. LIK066 treatment will be administered once daily after an overnight fast, before breakfast from Day 1 to Day 7. Subjects can be domiciled during the study per the investigator discretion. The study assessments will include 24-hour urine collection and blood collections for pharmacokinetic, pharmacodynamics, safety [REDACTED].</p> <p>Study completion evaluations will be performed after the last pharmacokinetic assessment is completed (Day 11), or in the case of early termination, prior to discharge from the study site.</p>

Population	<p>Ten (10) subjects each with mild (eGFR 60-89 ml/min/1.73 m²), Grade A moderate (eGFR 46-59 ml/min/1.73 m²), Grade B moderate (eGFR 30-45 ml/min/1.73 m²), and normal renal function (eGFR ≥90 ml/min/1.73 m²); and up to 10 patients with severe renal impairment (eGFR ≤29 ml/min/1.73 m², not on dialysis) will be enrolled in this study.</p> <p>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 (at least two in each group of patients with moderate renal impairment, and at least one patient in the group of patients with severe renal impairment) have been enrolled. The 10 subjects with normal renal function will be matched to 10 of the enrolled patients with decreased renal function by age, weight, and, if possible, diabetic status.</p>
Key Inclusion criteria	<p>All individuals:</p> <ul style="list-style-type: none">• Male and female subjects age 18 to 78 years, inclusive, with BMI ≤ 50 kg/m² and with controlled health condition as determined by past medical history, physical examination, electrocardiogram, and laboratory tests at screening.• For patients with Type 2 diabetes, HbAc1 < 10% at screening. If treated with antidiabetic medications (other than prohibited medications), patients must be on a stable dose for approximately 6 weeks prior to starting the study treatment and maintain the dose until the end of the study. <p>Patients with decreased renal function:</p> <ul style="list-style-type: none">• Patients must have stable renal disease without evidence of active progression at screening (for the purpose of this study stable renal disease will be defined as no significant change of eGFR for 12 weeks, per the discretion of the investigator upon reviewing the medical history or previous lab assessments).<ul style="list-style-type: none">• Mild renal impairment: eGFR from 60 to 89 ml/min/1.73 m²• Grade A moderate renal impairment: eGFR from 46 to 59 ml/min/1.73 m²• Grade B moderate renal impairment: eGFR from 30 to 45 ml/min/1.73 m²• Severe renal impairment: eGFR of ≤ 29 ml/min/1.73 m², not on dialysis <p>Subjects with normal renal function:</p> <ul style="list-style-type: none">• Normal renal function reflected by an eGFR of ≥90 ml/min/1.73m².• Subjects 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.

Key Exclusion criteria	All individuals: <ul style="list-style-type: none">• Pregnant or nursing (lactating) women. Women of child-bearing potential, unless they are using basic methods of contraception during the study.• Patients with type 1 diabetes, or history of acute diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the 6 months prior to screening.• Evidence of urinary obstruction or difficulty in voiding at screening• Symptomatic genital or urinary tract infection (UTI) in the 4 weeks prior to screening or the presence of active UTI at screening• Any finding during screening assessments (physical examination, vital signs, ECG or clinical lab assessments), surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject, per the investigator's judgment, in case of participation in the study.• Clinically significant GI disorder related to malabsorption or GI surgery that may affect drug or glucose absorption (e.g. swallowing disorder, severe GI motility disorder, chronic diarrhea, glucose/galactose/lactose intolerance)• Use of prohibited medications Patients with decreased renal function: <ul style="list-style-type: none">• Hemoglobin levels <8.0 g/dl at screening Subjects with normal renal function: <ul style="list-style-type: none">• Hemoglobin levels <12.0 g/dl for males, or <11.0 g/dl for females at screening
Study treatment	The investigational drug, LIK066 tablets will be prepared by Novartis. This is an open label nonrandomized study. All subjects will receive LIK066 50 mg once daily before breakfast for 7 days.
Efficacy/PD assessments	<ul style="list-style-type: none">• Urinary glucose excretion
Key safety assessments	<ul style="list-style-type: none">• Physical examination• Body temperature• Hematology• Blood chemistry• Urinalysis• Blood pressure• Pulse rate• ECG evaluation• Adverse events and serious adverse events
	



Data analysis	The primary analyses will assess the effect of reduced renal function on 24-hour urinary glucose excretion (UGE24) and on the PK of LIK066. The change from baseline in UGE24 will be analyzed using an analysis of covariance model with diabetic status, renal impaired group, day, and all associated interactions (where possible) as fixed factors and age, baseline body weight, and baseline fasting plasma glucose as covariates. Each of the log-transformed PK parameters will be analyzed using the same model but without the baseline covariates.
Key words	Decreased renal function. Urinary glucose excretion. Pharmacokinetics



1 Introduction

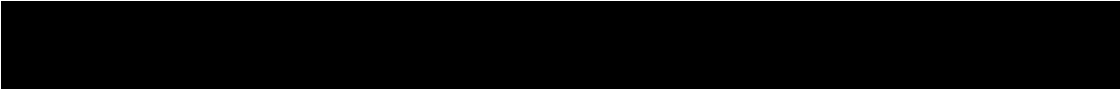
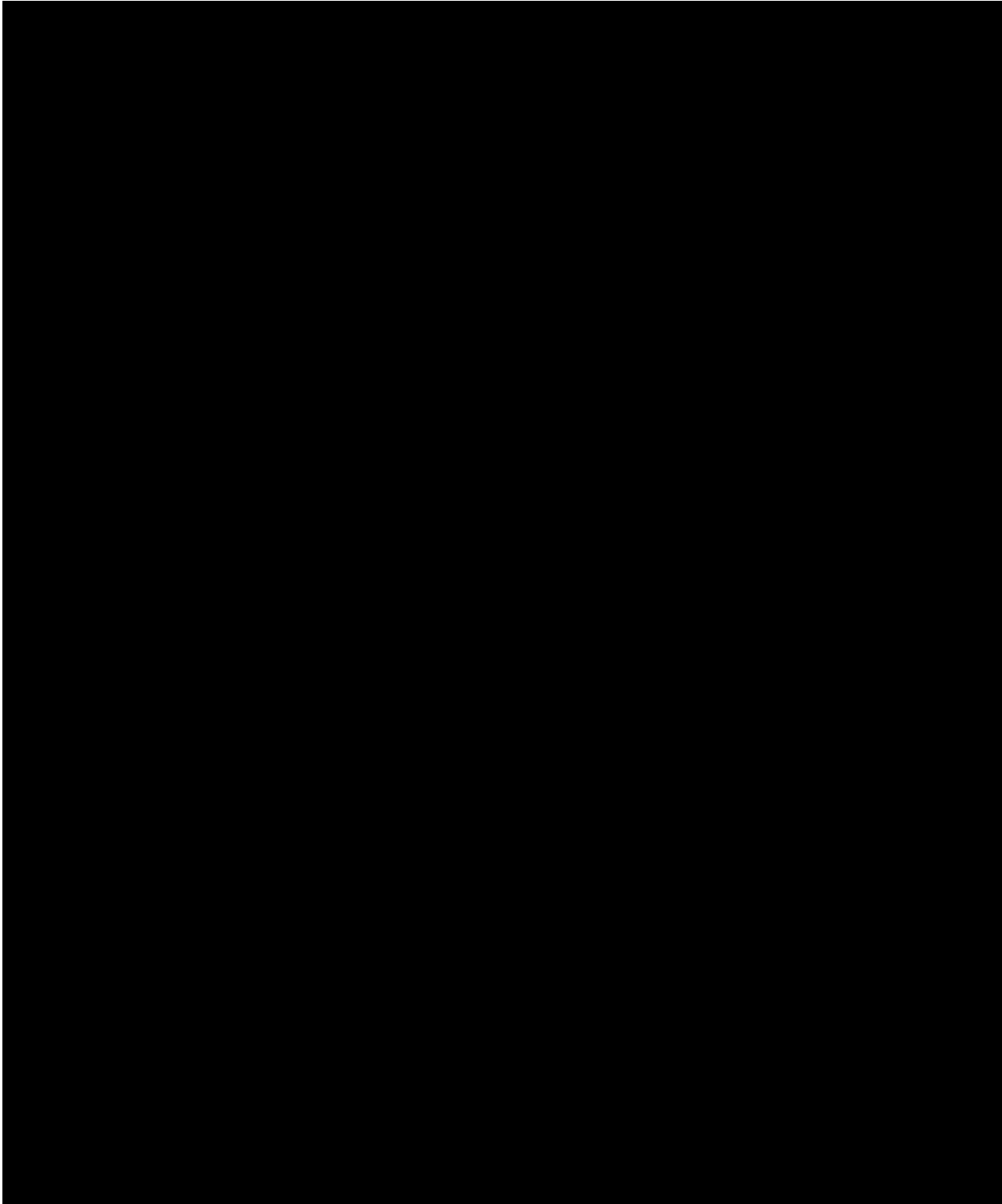
Obesity has become a major global health problem that contributes causally to and exacerbates many serious co-morbidities including hypertension, dyslipidemia, and importantly type 2 diabetes (T2DM). In contrast to the numerous medicines that are available to treat these obesity-related diseases, relatively few agents are available for the treatment of obesity itself that are effective, safe or scalable to the size of the affected population (Morgen and Sorensen 2014). A novel mechanism to lower body weight is via inhibition of the sodium glucose co-transporters 1 and 2 (SGLTs) resulting in inhibition of the glucose absorption in the gut and reabsorption in the kidney (Chao and Henry 2010). In healthy subjects, virtually all of the filtered glucose is reabsorbed into the circulation and no glucose is detected in the urine. SGLT2 located in the segments 1 and 2 of the proximal tubule contributes to ~90% of reabsorption of the filtered glucose (Abdul-Ghani et al 2015). SGLT1 is located in the more distal part of the proximal tubule, segment 3, and contributes to the remaining ~10% of filtered glucose. However, when SGLT2 is inhibited with empagliflozin (a SGLT2 inhibitor), SGLT1 compensates for the reabsorption of filtered glucose and SGLT1 is capable of reabsorbing >40% of filtered glucose load in a mouse model (Abdul-Ghani et al 2015). In addition to expression in the kidney, SGLT1 is also expressed in the small intestine, where it is required for glucose and galactose absorption. Inhibition of enteric SGLT1 results in glucose and galactose malabsorption (Turk et al 1991), which results in calorie wasting and other potential endocrine-based weight loss mechanisms.

LIK066 is a potent dual inhibitor of SGLT1/2, which has been studied in healthy subjects, patients with T2DM, and obese patients with elevated BMI. LIK066 is generally safe and well tolerated in the clinical studies being completed to date. LIK066 has a favorable pharmacokinetic profile (T_{1/2} of 10-16 hours), which allows once daily dosing. LIK066 at 150 mg daily dose (as qd, bid or tid) results in a significant weight loss in obese patients; ~ 6% decrease in body weight was demonstrated after 12 week treatment.

All selective SGLT2 inhibitors being approved in the clinical practice are either not recommended or contraindicated in patients with moderate or severe renal impairment (either eGFR<60; or eGFR<45 mL/min) primarily due to lack of efficacy and certain safety concerns. Dual inhibition of SGLT1 and SGLT2 leads to further caloric wasting of glucose attributed to reduced absorption of glucose from the intestine and enhanced inhibition of glucose reabsorption from the kidneys, which is a major mechanistic differentiation from a selective SGLT2 inhibitor. This study is designed to assess the potential efficacy of LIK066 in patients with moderate or severe chronic kidney disease using 24-hour urinary glucose excretion (UGE₂₄) as the primary surrogate endpoint. The design of this study will also evaluate the PK of LIK066 in patients with reduced renal function. Safety and tolerability of LIK066 at 50 mg qd for 7 days will also be assessed in this patient population with reduced renal function.

1.1 Background

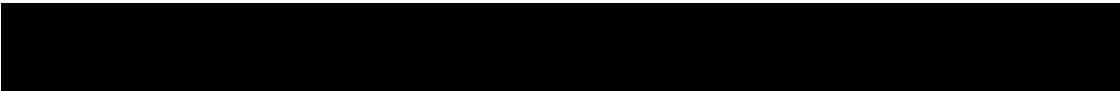
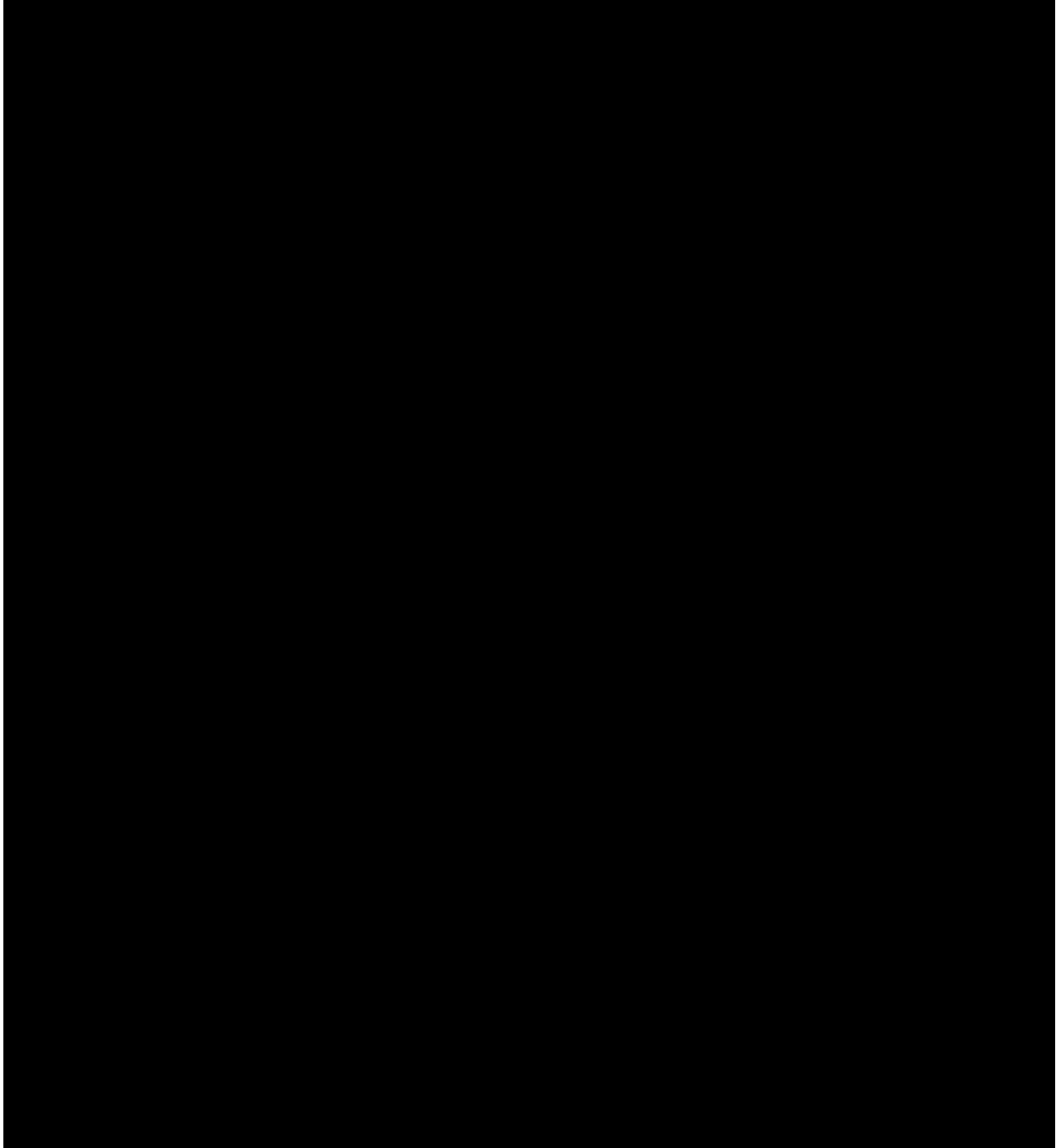
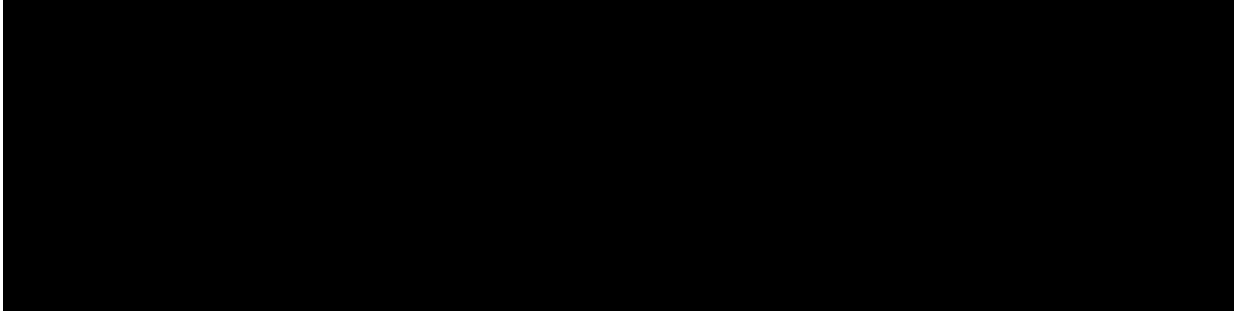
The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

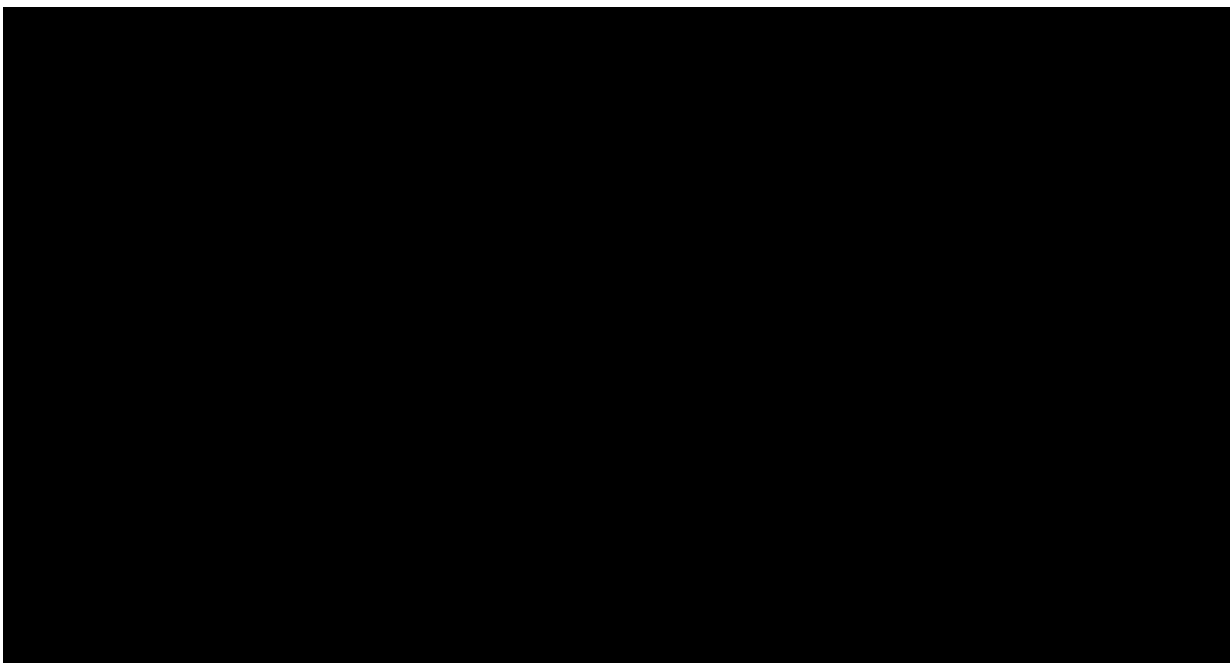


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1.4 Study purpose

The purpose of this study is: 1) to determine whether LIK066 displays a similar effect on the urinary glucose excretion in patients with varying degrees of reduced renal function as those with normal renal function, and 2) to assess the pharmacokinetics of LIK066 in patients with varying degrees of renal impairment as compared to those with normal renal function; to support development of LIK066 in patients with kidney disease.

2 Study objectives and endpoints

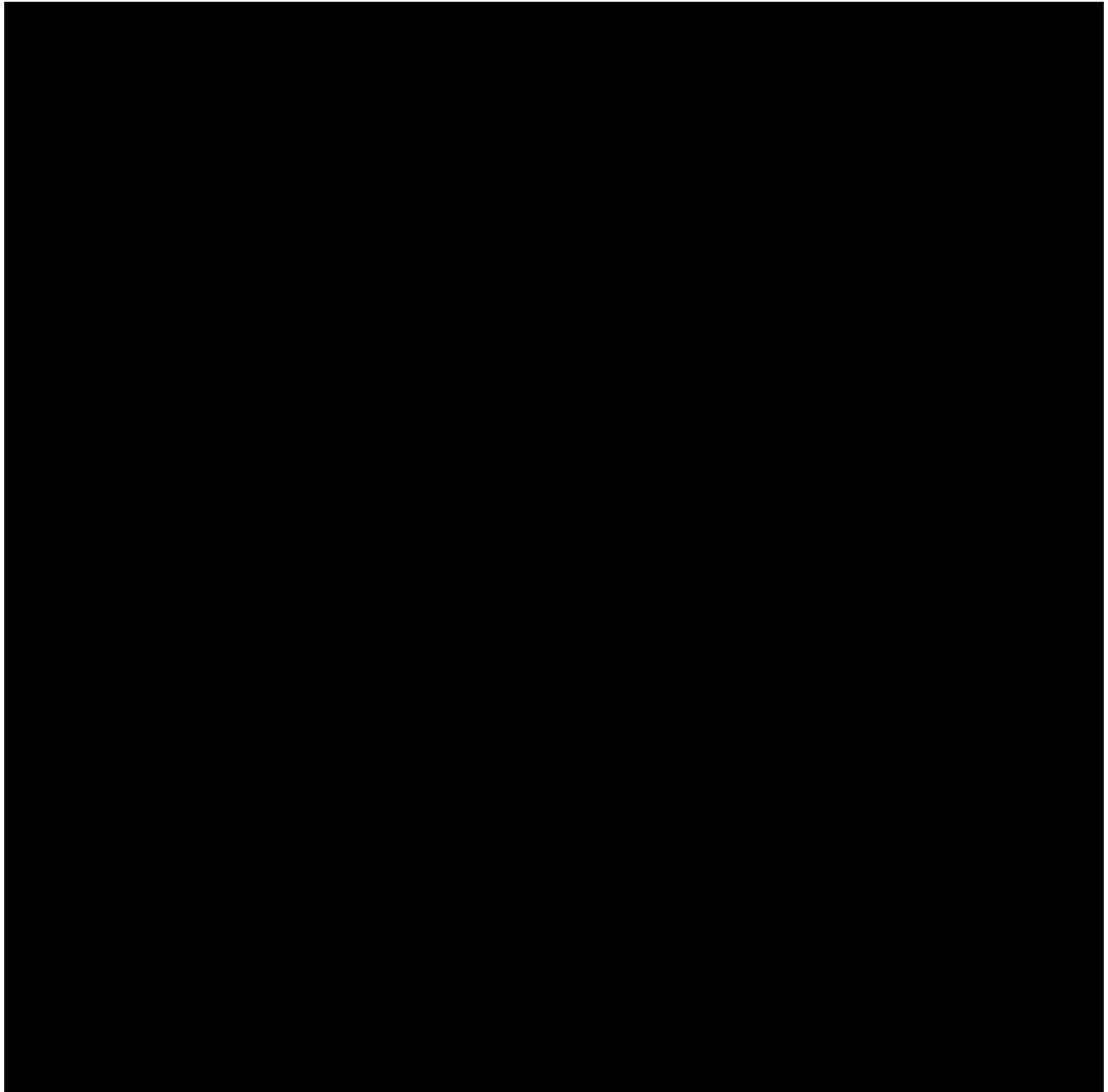
2.1 Primary objectives

<i>Primary objectives</i>	<i>Endpoints related to primary objectives</i>
<ul style="list-style-type: none">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	<ul style="list-style-type: none">24-hour urinary glucose excretion on Day 7
<ul style="list-style-type: none">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	<ul style="list-style-type: none">C_{max}, T_{max}, AUC_{tau}, AUC_{last}, AUC_{inf}, T_{1/2}, CL/F, V_z/F, CL_r



2.2 Secondary objective

<i>Secondary objective</i>	<i>Endpoints related to secondary objective</i>
<ul style="list-style-type: none">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	<ul style="list-style-type: none">Adverse events



3 Investigational plan

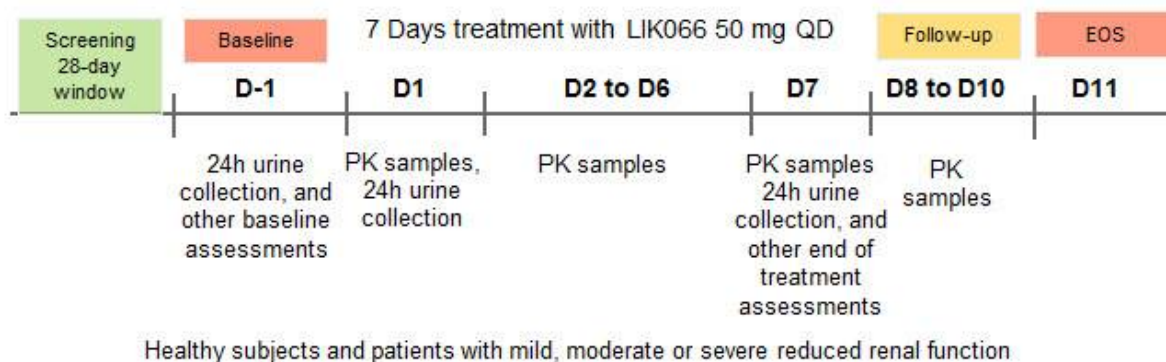
3.1 Study design

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. The most common cause of chronic kidney disease is diabetes, which accounts for roughly 50% of all cases. Approximately 50% of the patients enrolled in each group of the mild, moderate and severe renal impairment are expected to be patients with T2DM.

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.

Ten (10) subjects each with mild (eGFR 60-89 ml/min/1.73 m²), Grade A moderate (eGFR 46-59 ml/min/1.73 m²), Grade B moderate (eGFR 30-45 ml/min/1.73 m²), and normal renal function (eGFR ≥90 ml/min/1.73 m²); and up to 10 patients with severe renal impairment (eGFR ≤29 ml/min/1.73 m², not on dialysis) will be enrolled.

Figure 3-1 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 (at least two in each group of patients with moderate renal impairment, and at least one patient in the group of patients with severe renal impairment) 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 $\pm 20\%$), and, if possible, diabetic status. The 10 patients with decreased renal function on whom the matching will be based will be selected so as to cover as broad age range as possible. 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. Efforts will be made to match the diabetic status, where possible, to ensure representation of both diabetic and non-diabetic populations in the group of subjects with normal renal function.

The renal function (eGFR) will be assessed based on the MDRD equation ([Levey et al 2006](#)) during the screening visit. The MDRD equation (Serum creatinine levels in mg/dl) to be used is as follows:

$$\text{eGFR} = 175 \times \text{Serum Creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.212 \text{ if Black}] \times [0.742 \text{ if Female}]$$

Additional details about the eGFR equations and the standardized creatinine assays will be provided in the SOM.

Each subject will attend Screening visit(s) when the inclusion/exclusion criteria will be assessed. Eligible subjects will be admitted to the study site at Baseline (Day -2), where eligibility for enrollment into the study will be confirmed as needed. All baseline safety evaluation results must be available and reviewed prior to dosing when screening is performed more than 7 days prior to dosing. Each subject will receive once daily LIK066 at 50 mg dose for 7 days. Meal contents including carbohydrates and salt will be standardized from Day -2 to the morning of Day 2, and then from Day 5 to Day 8, [REDACTED]

[REDACTED] Detailed information on meal recommendation is provided in the SOM. Baseline twenty-four hour urine samples will be collected. Study participants must be fasted for approximately 10 hours before Day 1 dosing of LIK066. Standardized breakfast will be provided immediately after the administration of LIK066 in the morning.

Following the first dose on Day 1, subjects will remain domiciled for at least 24 hours for collection of urine and blood samples for urinary glucose excretion, pharmacokinetic, pharmacodynamic and safety assessments. Subjects will either remain domiciled (mandatory for subjects with severe renal impairment) or return in the morning to the study site every day (Day 3 to Day 5) to receive their medication after approximately 10-hour fasting overnight, per the investigator discretion as described in the SOM. A standardized breakfast will be served immediately after administration of LIK066 every day. Subjects will be domiciled from Day 5 and will be fasted for approximately 10 hours before the final dose on the morning of Day 7 at the site. Subjects will remain domiciled up to Day 8 to complete 24-hour collection of urine and blood for urinary glucose excretion, pharmacokinetic, pharmacodynamic and safety assessments after the final dose. Blood and urine samples for pharmacokinetic assessments will be taken on Days 9, 10 and 11 (up to 96 hours post the final dose). Study completion evaluations will be performed after the last pharmacokinetic assessment is completed (Day 11), or in the case of early termination, prior to discharge from the study site.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (blood chemistry, urinalysis, hematology), and adverse event and serious adverse event monitoring. See the assessment schedule for further details.

[REDACTED]

3.2 Rationale of study design

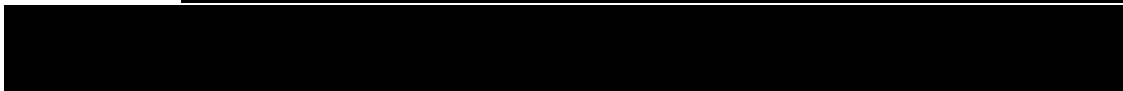
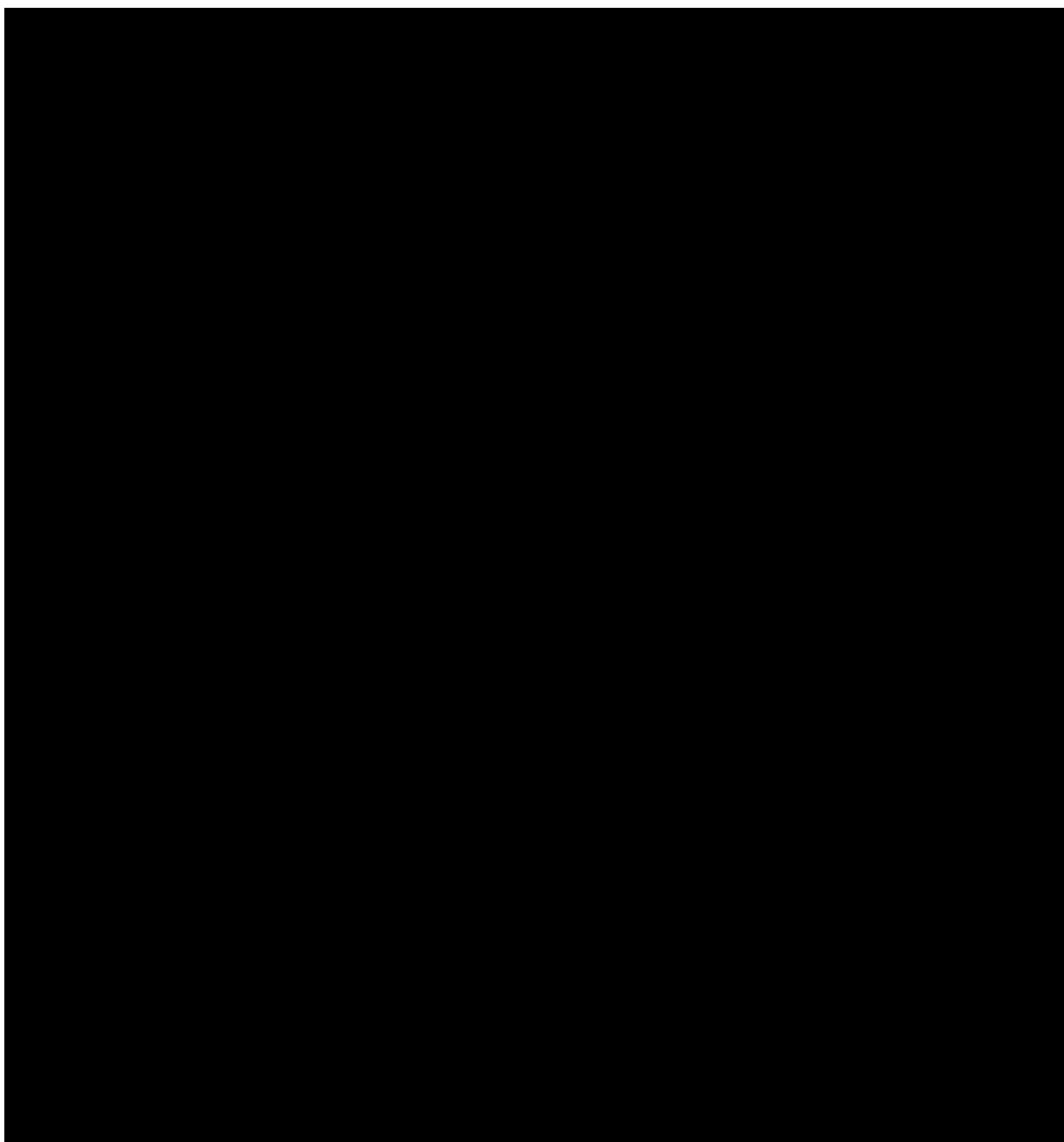
The design of this study addresses the primary objective of assessing the effects of LIK066 on urinary glucose excretion and the pharmacokinetics of LIK066 in subjects with reduced renal function as compared to those with normal renal function. The 24-hour urinary glucose excretion (UGE24) is zero in healthy subjects and ~10 g in patients with T2DM in the absence of a SGLT inhibitor such as LIK066. The UGE24 is ~100 g when LIK066 is given to patients with T2DM, therefore, the diabetic status is expected to have little impact on the assessment of UGE24. In addition, the assessment of UGE24 will be based on the changes corrected by baseline UGE24. The matching of subjects with normal renal function to a subset of the subjects with reduced renal function will be done to minimize bias in the comparison due to confounding factors of age, body weight, and diabetic status. An open-label design without a placebo comparator is appropriate as the primary endpoints, 24-hour urinary glucose excretion and pharmacokinetics, are objective parameters.

3.4 Rationale for choice of comparator

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

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.



3.6.1 Blood sample volumes

Approximately up to 200 mL of blood is planned to be collected from each subject over 2-3 weeks during the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, [Section 8.1](#).

A summary blood log is provided in the SOM, together with instructions for all sample collection, processing, storage and shipment information.

See [Section 8.9](#) regarding the potential use of residual samples.

4 Population

4.1 Inclusion criteria

4.1.1 All individuals

Subjects with normal and decreased renal function 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 subjects age 18 to 78 years, inclusive, with controlled health condition as determined by past medical history, physical examination, electrocardiogram, and laboratory tests at screening.
3. For patients with Type 2 diabetes, HbA_{1c} < 10% at screening.
4. If treated with antidiabetic medications (other than prohibited medications), patients must be on a stable dose for approximately 6 weeks prior to starting the study treatment and maintain the dose until the end of the study.
5. Body mass index (BMI) ≤ 50 kg/m² at Screening.
6. Able to communicate well with the Investigator, to understand and comply with the requirements of the study.

4.1.2 Patients with decreased renal function

7. Patients must have stable renal disease at screening without evidence of active progression (for the purpose of this study stable renal disease will be defined as no significant change of eGFR for 12 weeks, per the discretion of the investigator upon reviewing the medical history or previous lab assessments).
 - Mild renal impairment: eGFR from 60 to 89 ml/min/1.73 m²
 - Grade A moderate renal impairment: eGFR from 46 to 59 ml/min/1.73 m²
 - Grade B moderate renal impairment: eGFR from 30 to 45 ml/min/1.73 m²
 - Severe renal impairment: eGFR of ≤ 29 ml/min/1.73 m², not on dialysis
8. Vital signs (after 3 minutes resting measured in the supine position). The Investigator should be guided by the following ranges:
 - oral body temperature between 35.0-37.8 °C
 - systolic blood pressure, 100-180 mm Hg
 - diastolic blood pressure, 50-110 mm Hg
 - pulse rate, 45-100 bpm

Blood pressure and pulse will be taken again in a standing position. After 3 minutes standing, there shall be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure associated with clinical manifestation of symptomatic postural hypotension.

4.1.3 Subjects with normal renal function

9. Except for the medical conditions allowed in the inclusion/exclusion criteria (e.g. diabetes or hypertension), no other significant medical conditions at screening or baseline as determined by medical history and physical examination.
10. Normal renal function reflected by an eGFR of ≥ 90 ml/min/1.73m².
11. Vital signs (after 3 minutes resting measured in the supine position). The Investigator should be guided by the following ranges:
 - oral body temperature between 35.0-37.2°C
 - systolic blood pressure, 100-150 mm Hg
 - diastolic blood pressure, 60-100 mm Hg
 - pulse rate, 45-100 bpm

Blood pressure and pulse will be taken again in a standing position. After 3 minutes standing, there shall be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure associated with clinical manifestation of no symptomatic postural hypotension.

12. Subjects will be matched to 10 of the enrolled patients with decreased renal function by age (approximately ± 10 years), weight (approximately $\pm 20\%$), and, if possible, diabetic status.

4.2 Exclusion criteria

4.2.1 All individuals

Subjects with normal and decreased renal function fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
2. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during the study. Basic contraception methods include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (i.e., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy)), total hysterectomy or tubal ligation at least six weeks before taking study treatment. 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). The vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap. For UK: with spermicidal foam/gel/film/cream/vaginal suppository
- Use of oral, 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 (IUD) or intrauterine system (IUS)

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

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) or tubal ligation (hysterectomy is acceptable) 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.

3. Patients with type 1 diabetes, or history of acute diabetic complications such as ketoacidosis or hyperosmolar state (coma) within the 6 months prior to screening.
4. Evidence of clinically significant abnormal liver function tests for any of the labs at screening, confirmed by a repeat measure within 7 days :
 - ALT, AST, γ -GT, alkaline phosphatase > 3 x ULN.
 - serum bilirubin > 1.5 x ULN.
5. Evidence of urinary obstruction or difficulty in voiding at screening.

6. Symptomatic genital or urinary tract infection (UTI) in the 4 weeks prior to the first study visit or the presence of active UTI at screening.
7. Evidence or medical history of clinically significant ECG abnormalities.
8. Any of the following within 6 months of screening:
 - myocardial infarction (MI)
 - coronary artery bypass surgery, balloon angioplasty, coronary stent(s) *in situ*
 - unstable angina
 - peripheral arterial disease
 - congestive heart failure NYHA class II- IV
9. History of autonomic dysfunction (e.g. history of fainting, clinically significant orthostatic hypotension, clinically significant sinus arrhythmia).
10. Significant blood loss equaling at least one unit of blood (500 ml) or a blood transfusion within 3 months prior to screening.
11. Evidence of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at screening.
12. History of drug or alcohol abuse within the 12 months prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or tests conducted during baseline evaluations.
13. Malignancy including leukemia and lymphoma (not including basal cell skin cancer which has not been adequately treated) within 5 years prior to screening.
14. Any finding during screening assessments (physical examination, vital signs, ECG or clinical lab assessments), surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject, in the investigator's judgment, in case of participation in the study.
15. Patients undergoing any method of dialysis (hemodialysis or peritoneal dialysis).
16. History of hypersensitivity to the study drug, or to drugs of similar chemical classes.
17. Clinically significant GI disorder related to malabsorption or that may affect drug or glucose absorption (e.g. swallowing disorder, severe GI motility disorder, chronic diarrhea, glucose/galactose/lactose intolerance).
18. History of significant gastrointestinal surgery that could affect intestinal glucose absorption (e.g. bariatric surgeries including, Roux en Y gastric bypass, sleeve gastrectomy, Nissen fundoplication).
19. Subjects who experienced ketoacidosis, lactic acidosis, or hyperosmolar coma within 6 months of Screening Visit, or between Screening Visit and Baseline Day -1.

20. Use of prohibited medications:

- Use of SGLT2 or alpha-glucosidase inhibitors within 2 weeks prior to dosing and during the study. If treated with other oral antidiabetic medications, patients must be on a stable regimen for at least 6 weeks prior to starting the study treatment
- Use of potassium-binders within 3 days prior to dosing and during the study
- Treatment with drugs that have a high incidence of diarrhea during the study
- Chronic systemic steroid treatment or systemic steroids for > 7 consecutive days for worsening of an underlying condition within 4 weeks of screening. Use of topical or inhaled steroids is permitted
- Strong inhibitors of CYP3A4/5 including boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole within 7 days prior to the study treatment and during the study
- Strong CYP3A inducers including avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort within 7 days prior to the study treatment and during the study
- General UGT inhibitors including probenecid, valproic acid within 7 days prior to the study treatment and during the study
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of starting the study treatment or longer if required by local regulations. Any other limitation of participation in an investigational trial based on local regulations
- Use of any medications that are contraindicated in patients with renal impairment
- Use of any drugs with known toxicity to a major organ system within the past 3 months (i.e., cytostatic drugs)
- Unless allowed by the study protocol, use of any other prescription drugs, new herbal supplements, within four (4) weeks prior to initial dosing, and/or over-the-counter (OTC) medication, new dietary supplements (vitamins included), within 3 days prior to initial dosing. If needed, acetaminophen or ibuprofen is acceptable for incidental and limited use.

Such medications must be documented in the Concomitant medications / significant non-drug therapies page of the CRF.

4.2.2 Patients with decreased renal function

Patients with decreased renal function fulfilling any of the following criteria are not eligible for inclusion in this study:

21. Hemoglobin levels <8.0 g/dl at screening.

4.2.3 Subjects with normal renal function

Subjects with normal renal function fulfilling any of the following criteria are not eligible for inclusion in this study:

22. Hemoglobin levels <12.0 g/dl for males, or <11.0 g/dl for females at screening.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Please refer to exclusion criteria ([Section 4.2](#)) for details of contraception requirements for the study.

5.2 Prohibited treatment

Please refer to the exclusion criteria ([Section 4.2](#)). Subjects may need to discontinue the study treatment if treated with any of the prohibited medications during the study. Concomitant and prior medications (dose, regimen, indication and treatment duration) must be recorded in the CRF.

5.3 Dietary restrictions and smoking

- █ [REDACTED]
- No alcohol for approximately 24 hours before the study visits until the Study Completion evaluation.
 - No cigarettes/use of nicotine products for 8 hours before certain visits as noted in the SOM.
 - No grapefruit or grapefruit juice is to be consumed for approximately 7 days prior to dosing until 7 days following the last dose.
 - In order to avoid wide variations in urine volumes on UGE and PK collection days, subjects should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals and medication.

While domiciled, patients will follow a standard diet or a diet recommended for patients with kidney disease with the following guidelines.

- Approximately 2,200 calories daily, adjusted by body weight; ~50% from carbohydrates, ~30% from fat and ~20% from protein, with consistent and **within** recommended amounts of sodium, potassium, calcium and phosphorus, and free access to water.
 - Identical meals should be served on days (Baseline: Day -1 to Day 1; Treatment: Day 7 to Day 8) when 24 hour PD endpoints (UGE24, electrolytes and [REDACTED]) are assessed.
- █ [REDACTED]

- No food other than that specified in the protocol and the SOM will be consumed during confinement.

A meal record will confirm timing and consumption of meal. A copy of the diet with content and nutritional information (amount of protein, sodium, carbohydrates, fat and calories for each meal) will be provided to the Sponsor upon request.

5.4 Other restrictions

No strenuous physical exercise (e.g. weight training, aerobics, football) for 3 days before dosing until after Study Completion evaluations.

6 Treatment

6.1 Study treatment

The investigational drug, LIK066 tablets, will be prepared by Novartis and supplied to the Investigator as open labeled bulk medication. No control drugs will be used in this study.

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

6.2 Treatment arms

This is an open label nonrandomized study. Subjects will be assigned to one of the following 5 treatment arms 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)

6.3 Treatment assignment

The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. Treatment numbers will be assigned in ascending, sequential order to eligible subjects according to the disease status as described in the SOM. The investigator will enter the treatment number on the (e)CRF.

If a subject requires a replacement, the replacement subject will be assigned a treatment number corresponding to the original number (e.g. Subject 6103 would replace Subject 5103). Any additional subjects enrolled will use sequential subject numbering.

6.4 Treatment blinding

This is an open label non-randomized study.

6.5 Treating the subject

LIK066 will be administered to the subject orally at the investigator site. See the SOM for further details

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

For patients who are unable to tolerate the protocol-specified dosing scheme, treatment should be discontinued. These changes must be recorded on the Dosage Administration Record CRF.

6.7 Emergency breaking of assigned treatment code

Not applicable as this is an open label study.

6.8 Treatment exposure and compliance

Study medication will be given at the site by study personal during domiciling or patients will return to the investigator site on a daily basis during the study. PK parameters (measures of treatment exposure) will be determined in all patients treated with LIK066, ensuring treatment exposure and compliance.

6.9 Recommended treatment of adverse events

Based on prior clinical experience with LIK066, which was administered to more than 200 subjects at doses up to 350 mg single dose or up to 150 mg for 12 weeks, LIK066-related AEs can be managed by clinical monitoring including vital signs and blood tests. If diarrhea occurs, it can be treated with oral rehydration therapy if needed. More aggressive treatment, if required, will be performed at the discretion and direction of the investigator, with timely communication with the sponsor. Stopping rules ([Section 7.4](#)) will be applied as appropriate. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

This is not a therapeutic study. Rescue medication use is not allowed.

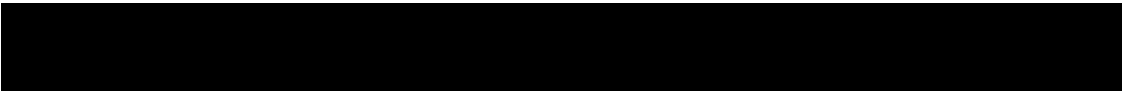
Use of medications other than the study drug during the study must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.11 Concomitant treatment

Patients with T2DM on antidiabetic medications (other than prohibited medications) are allowed to participate in the study if they are on a stable dose for at least 6 weeks prior to dosing and maintain the dose until the end of the study.

Antihypertensive, dyslipidemia and GERD medications are allowed but patients must be on a stable regimen for 3 months or more prior to dosing and maintain the dose until the end of the study.

Aspirin and antianginal medications (other than ranolazine) are allowed.



The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before enrolling a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy
- Use of prohibited treatments.

Study treatment of individual subject will be placed on hold and, based on full review of the clinical data and discussion with the investigator, discontinuation of study treatment may occur when that subject experiences:

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- Clinically significant urinary tract or genitourinary infections, at the discretion of the investigator and consult with the sponsor if deemed necessary.
- Clinically symptomatic hypoglycemia confirmed by repeated blood glucose levels (<56 mg/dL).
- Ketoacidosis (symptoms of ketoacidosis include nausea, vomiting, abdominal pain, unusual tiredness and trouble breathing).
- 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.
- Any hospitalization, or other SAE, that is suspected to be related to the study treatment.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments indicated by an asterisk (*) in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact. This contact should preferably be done according to the study visit schedule.

7.3 Withdrawal of informed consent

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 subject:

- 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 subject's decision to withdraw his/her consent and record this information.

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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 subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

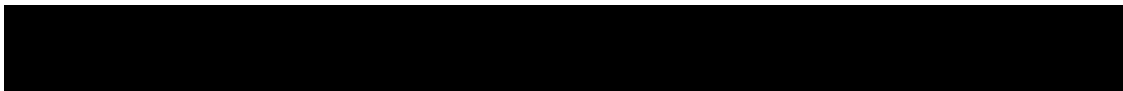
For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered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

7.5 Study Stopping rules

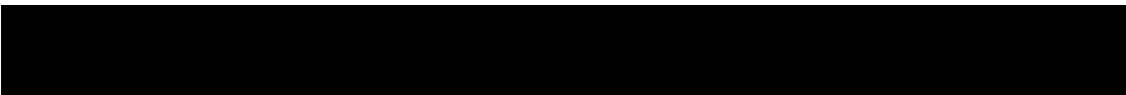
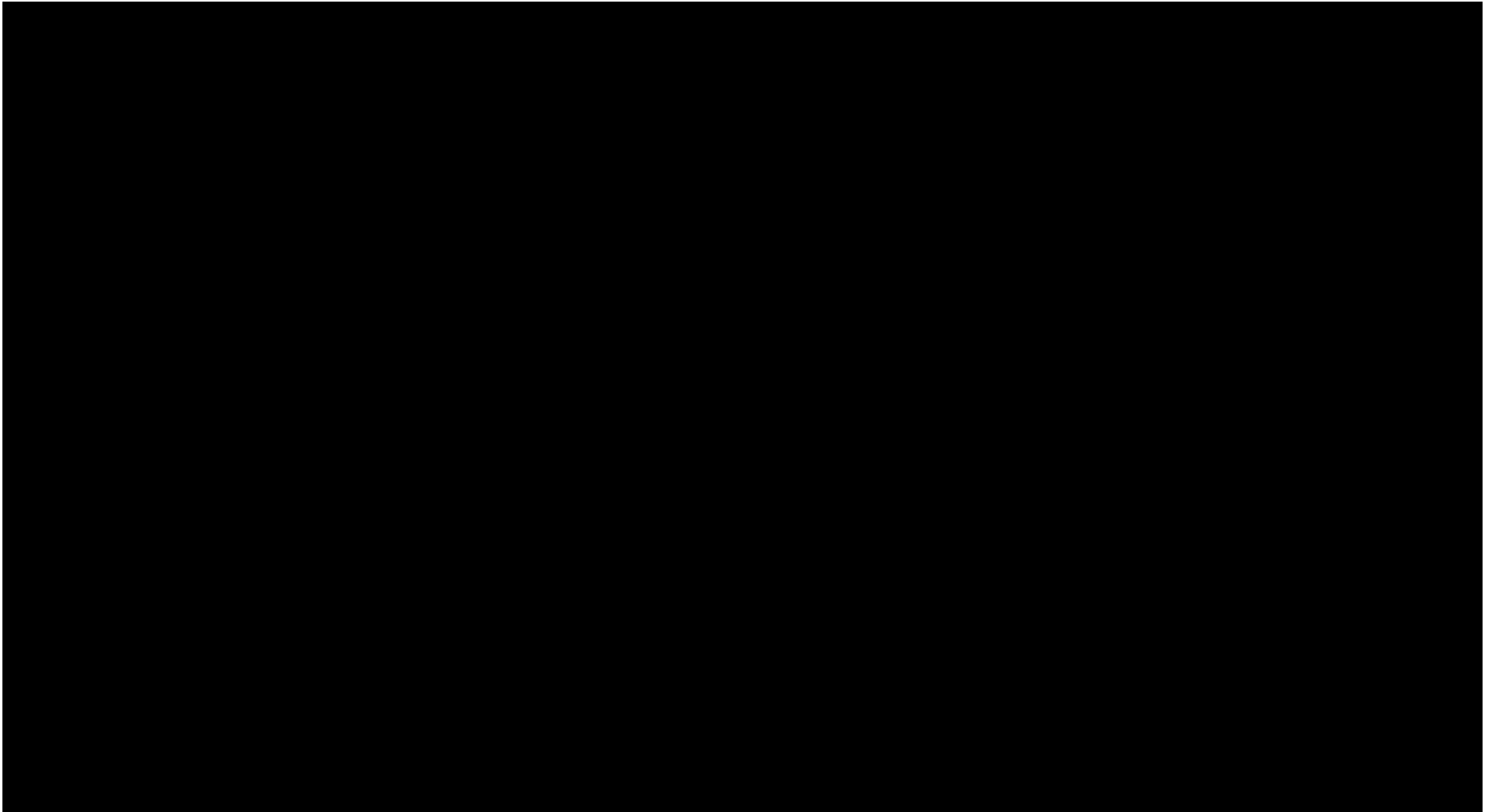
The principal investigator and the sponsor will continually review adverse events and laboratory findings throughout the study. The study will be placed on hold and based on full review of the clinical data and discussion with the investigator may be halted if the principal investigator and the sponsor consider that the number and/or severity of adverse events justify discontinuation of the study; including cumulative cases of clinically significant diarrhea, urinary tract infections, severe adverse events, clinically significant laboratory changes suspected to be related to the study drug, or serious adverse events suspected to be related to the study drug.

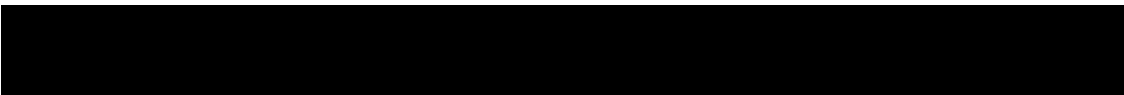
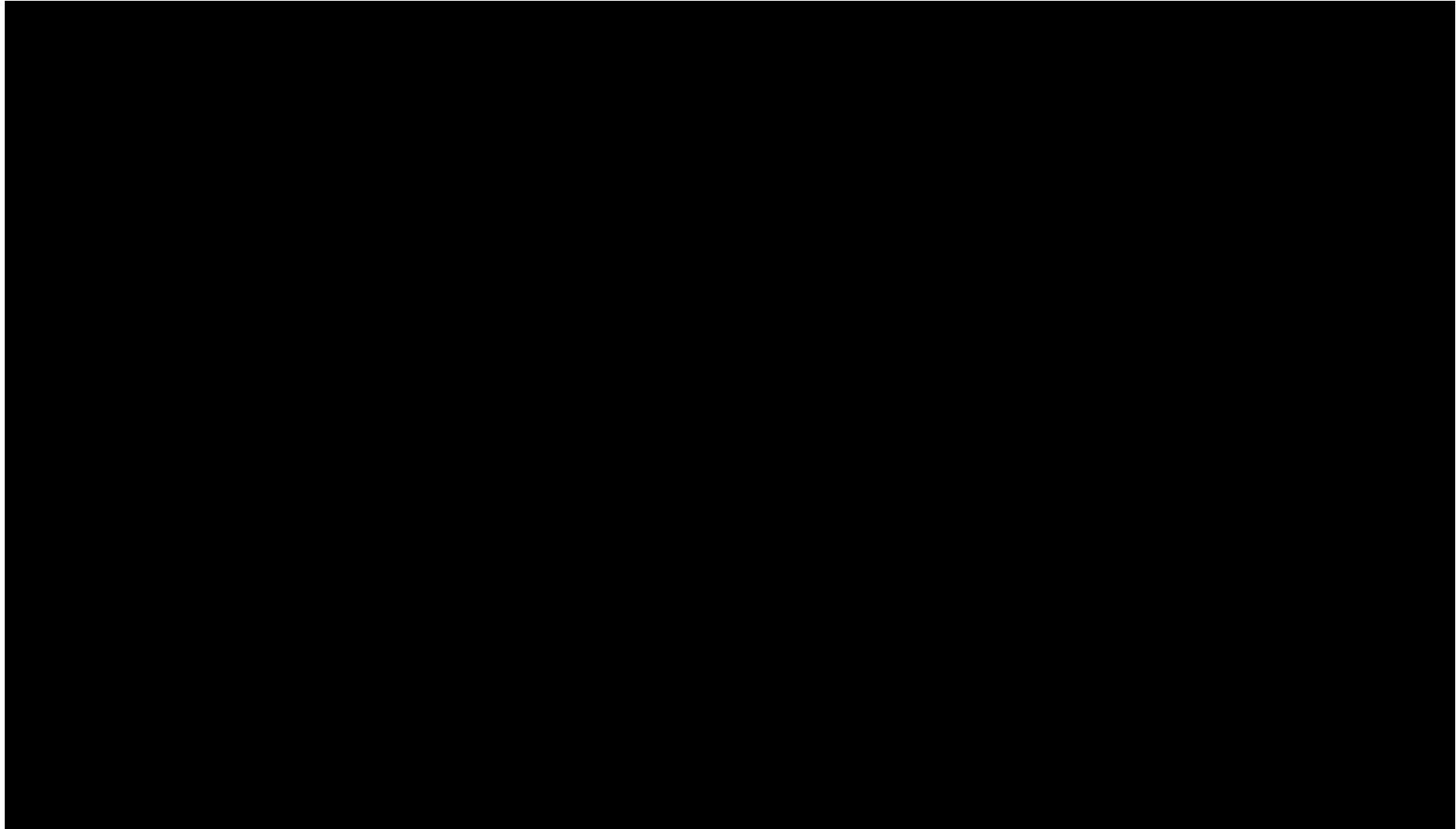
7.6 Early study termination by the sponsor

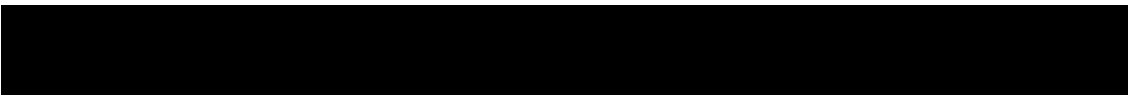
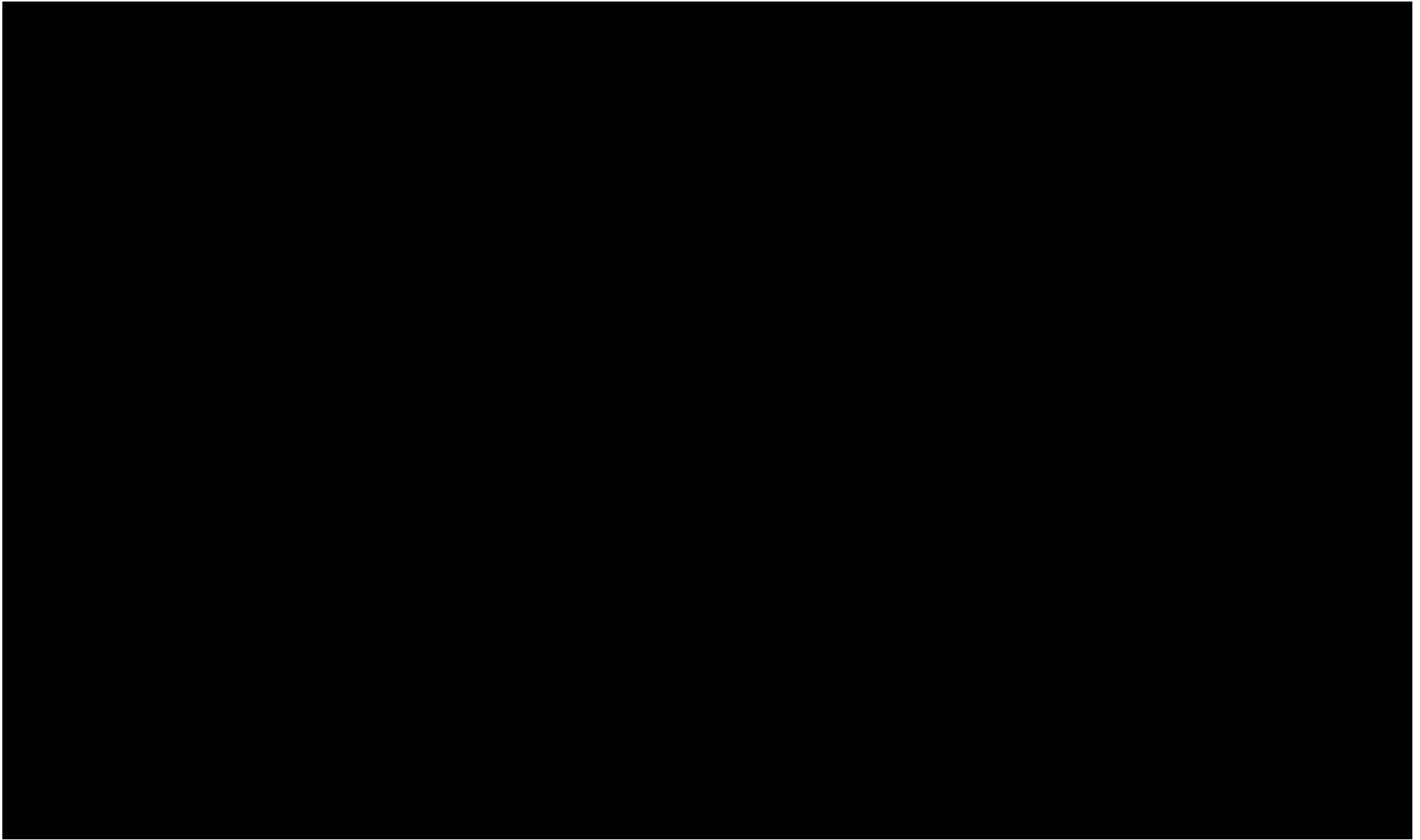
The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

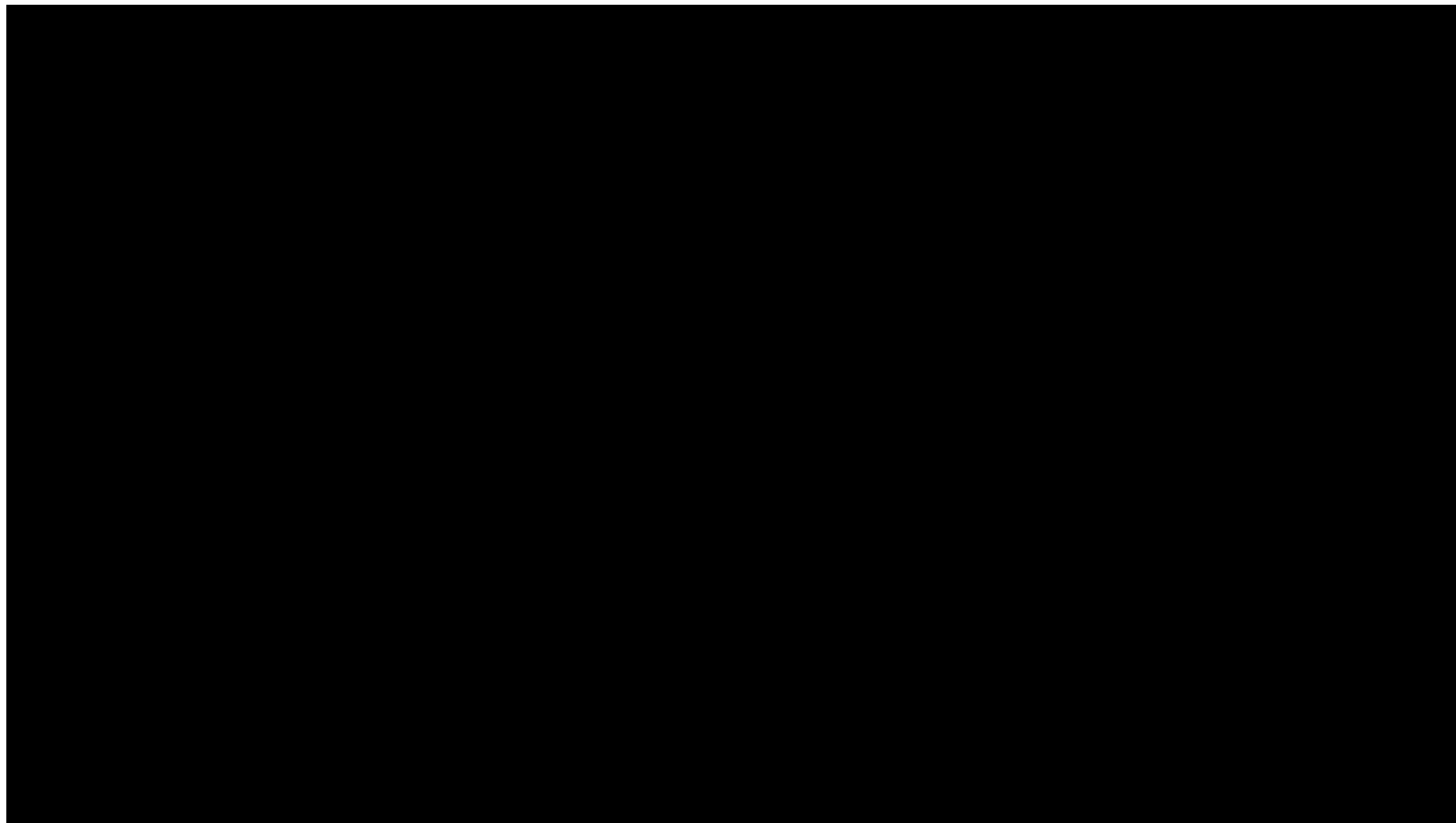


8 Procedures and assessments









8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug 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 then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

[REDACTED]

[REDACTED]

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

8.3 Subject screening

In general it is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms should be recorded.

Patients will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates), hepatitis B and C and HIV as noted in the [Assessment schedule](#). Results will be available as Source data and will not be recorded within the eCRF.

[REDACTED]

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.5 Efficacy / Pharmacodynamics

Urinary glucose excretion (UGE) is the primary pharmacodynamic (PD) endpoint in this study. PD samples will be obtained and evaluated in all subjects. PD samples will be collected at the time points defined in the Assessment schedule, [Section 8.1](#). Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment Schedule ([Section 8.1](#)) detailing when each assessment is to be performed.

Physical examination

Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]²)

Laboratory evaluations

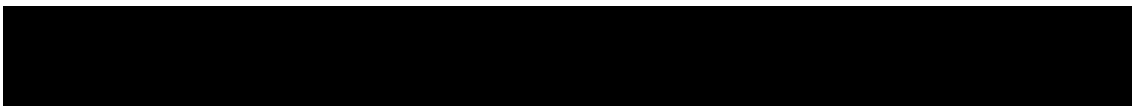
Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

Clinical chemistry

Albumin, alkaline phosphatase, AST, ALT, total bilirubin, bicarbonate/CO₂, chloride, creatinine, CK, γ -GT, glucose, LDH, inorganic phosphorus, lipase, amylase, calcium, magnesium, potassium, sodium, cholesterol (including total cholesterol, HDL-C and LDL-C), triglycerides, total protein, BUN and uric acid.

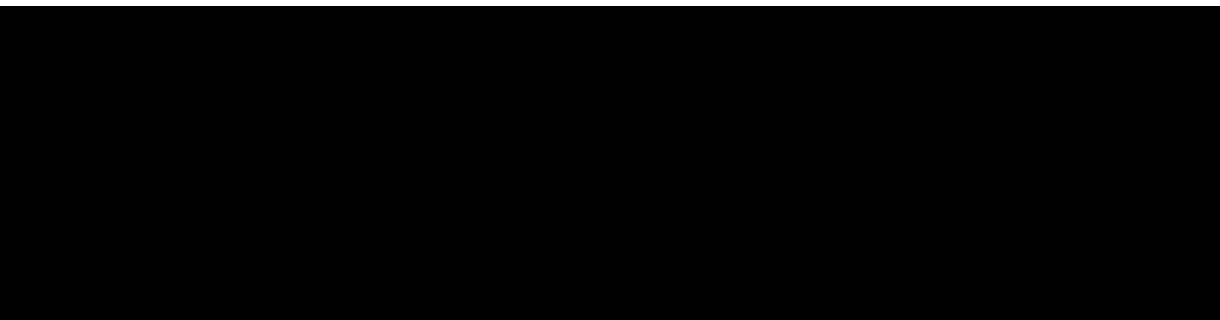


If the total bilirubin concentration is increased above 2 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.



Electrocardiogram (ECG)

PR interval, QRS duration, heart rate, RR, QT, QTc.

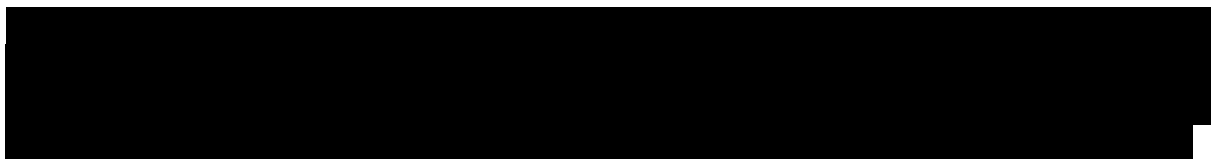
The Fridericia QT correction formula (QTcF) should be used for clinical decisions

8.7 Pharmacokinetics

PK samples will be obtained and evaluated in all subjects. PK samples will be collected at the timepoints defined in the Assessment schedule, [Section 8.1](#). Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment. See [Section 8.9](#) regarding the potential use of residual samples.

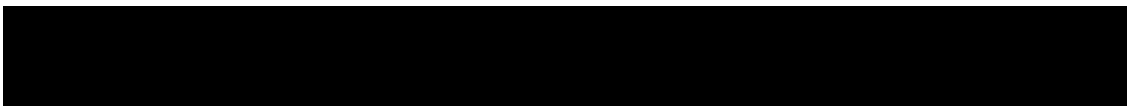
Plasma samples will be assayed for LIK066 concentrations by Novartis or a designated CRO using validated liquid chromatography-tandem mass spectrometry assays (LC-MS/MS). The method will have an LLOQ of at least 5 ng/mL for LIK066.

Concentrations will be expressed in mass per volume units and will refer to LIK066 plasma concentrations.



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

C_{max}, T_{max}, AUC_{last}, AUC_{tau}, AUC_{inf}, T_{1/2}, CL/F, V_z/F, as relevant, from the plasma concentration-time data.



Additional PK parameters (R_{acc} , $T_{1/2acc}$, $C_{min,ss}$, $C_{av,ss}$, T_{last} , C_{last} etc.) may be calculated or reported as appropriate. The linear trapezoidal rule will be used for AUC calculation.

The total amount of LIK066 excreted into urine (A_{e0-t}) will be used to calculate the renal clearance (CL_r) 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 C_{max,u}] may be calculated.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., 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 study treatment are also considered an adverse event irrespective if a clinical event has occurred. See [Section 9.5](#) for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, 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 should 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 patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in [Appendix 1](#) and [Appendix 2](#), respectively.

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

1. 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
2. its relationship to the study treatment
 - Yes or
 - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see [Section 9.2](#) for definition of SAE) and which seriousness criteria have been met
5. 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
 - hospitalization/prolonged hospitalization (see [Section 9.2](#) for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject'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.

9.2 Serious adverse event reporting

9.2.1 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
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the existing condition, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that has not worsened since the start of study drug
 - 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 subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject 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 subject 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 (see 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 subject 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO&PS) as per [Section 9.2.2](#).

9.2.2 SAE reporting

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

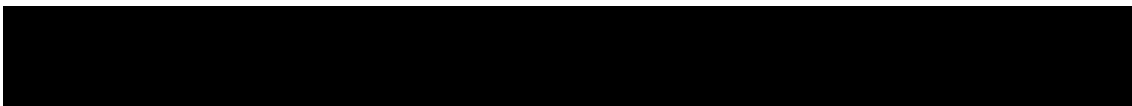
Note: SAEs reported by subjects deemed to be screen failures are only collected from time sign ICF until when subject is deemed a screen failure, with appropriate information also captured in the CRFs as specified in the SOM.

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.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated and whether the subject continued or withdrew from study participation. 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.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the study treatment a Chief Medical Office and Patient Safety 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.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: **SAEs must be reported to Novartis within 24 hours** of the investigator learning of its occurrence/receiving follow-up information.



9.3 Liver safety monitoring

To ensure subject 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.

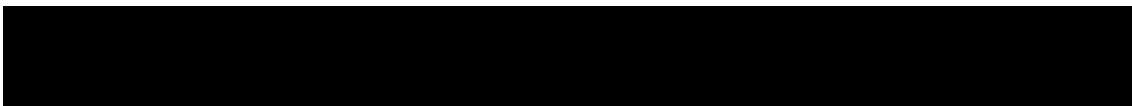
Please refer to [Table 15-1-Appendix 1](#) for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in [Table 15-1-Appendix 1](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 15-2-Appendix 1](#).

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γ -GT) to confirm elevation within 48-72 hours.
These liver chemistry repeats should be performed using the local laboratory used by the site. Repeat laboratory test results must be reported as appropriate via an electronic data transfer (if applicable).
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to [Section 7.2](#) (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
 - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γ -GT. If total bilirubin is elevated $> 2 \times$ ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
 - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
 - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
 - Exclusion of underlying liver disease, as specified in [Table 15-3](#).
 - Imaging such as abdominal US, CT or MRI, as appropriate
 - Obtaining a history of exposure to environmental chemical agents.
 - Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.



9.4 Renal safety monitoring

Renal events are defined as one of the following:

- Confirmed (after ≥ 24 h) increase in serum creatinine of ≥ 25 % compared to baseline during normal hydration status, and deemed as a new onset renal events in patients with reduced renal function at the discretion of investigator(s)
- A doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR).
- New onset ($\geq 1+$) proteinuria or hematuria

Every renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in [Section 16-Appendix 2](#).

9.7 Monitoring 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 discontinued as per [Section 7.2](#) and appropriate measures must be taken to correct the acidosis and monitor glucose levels according to standard of care.

Every case of ketoacidosis must be reported to the Ketoacidosis Adjudication Committee (see [Section 10.5](#)).

9.8 Reporting Medication errors including misuse/abuse

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Chief Medical Office and Patient Safety department if the treatment error is associated with an SAE.

For more information on AE and SAE definition and reporting requirements, please see [Section 9.1](#) and [Section 9.2](#), respectively.

9.9 Pregnancy reporting

To ensure subject 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 Chief Medical Office and Patient Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

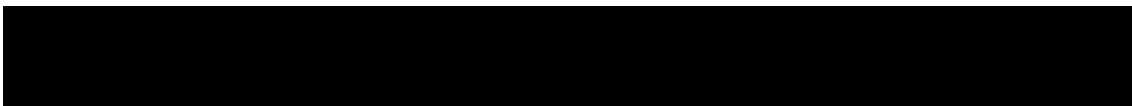
Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

9.10 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.



10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject 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 subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

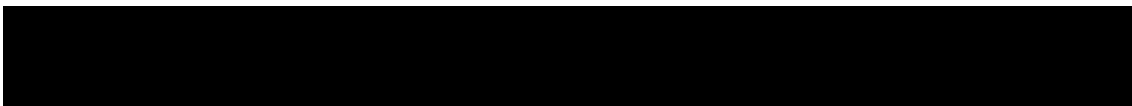
The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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 subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Validation checks for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. 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 subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and [Assessment schedule](#) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.



10.3 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 via the EDC system. 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 who 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. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory results will be sent electronically to Novartis (or a designated CRO).

The occurrence of any 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 made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

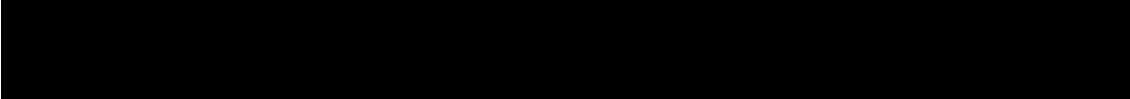


10.4 Data Monitoring Committee

Not applicable.

10.5 Adjudication Committee

An Adjudication Committee will be established to assess suspected cases of ketoacidosis as described in the SOM.



11 Data analysis

11.1 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 with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by renal function (mild impairment, Grade A moderate impairment, Grade B moderate impairment, severe impairment, or normal) 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.

11.3 Treatments

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

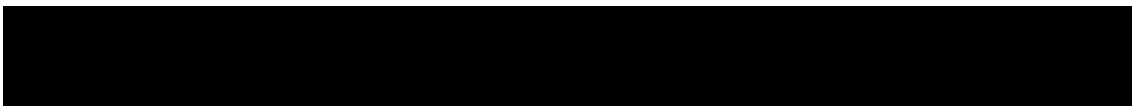
11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary PD endpoint will be UGE24.

The primary PK endpoints will be the C_{max}, T_{max}, AUC_{tau}, AUC_{last}, AUC_{inf}, T_{1/2}, CL/F of LIK066.

The secondary PK endpoints will be V_z/F and CL_r of LIK066.



11.4.2 Statistical model, hypothesis, and method of analysis

The primary analyses will assess the effect of reduced renal function on UGE24 and on the PK of LIK066.

UGE24

The change from baseline in UGE24 will be analyzed using an analysis of covariance (ANCOVA) model with diabetic status, renal impaired 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 and the corresponding two-sided 90% confidence interval and p-value for the difference will be extracted for each diabetic status by day combination.

UGE24 will be summarized by diabetic status, renal function, and day. The change from baseline and % change from baseline will also be summarized.

The relationship between eGFR and UGE24 will be assessed graphically, separately by day.

PK

Each of the log-transformed PK parameters (C_{max} , AUC_{tau} , AUC_{last} , AUC_{inf} as applicable) will be analyzed using the same model described above for UGE24 but without the baseline covariates. 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 (expressed as a percent relative difference) 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 (f_u) across the treatment groups. If statistically significant difference exists in f_u across treatment groups, the same analysis (as planned for total parameters) will also be performed to compare the AUC_{u} and $C_{max,u}$ between treatment groups.

The summary of PK parameters is described below in [Section 11.4.4](#).

11.4.3 Handling of missing values/censoring/discontinuations

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as “zero” and will be treated as zero for calculation of PK parameters. No other imputation of missing values will be performed.

11.4.4 Summary statistics of pharmacokinetics

LIK066 plasma concentration data will be listed by renal function, 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 T_{max} where median, minimum, and maximum will be presented.

11.4.5 Sensitivity analyses

Two sensitivity analyses of UGE24 may be performed:

(1) a similar analysis as the primary UGE analysis, except that natural logarithm of the ratio to baseline in UGE24 will be modeled instead of the change from baseline. 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 function (expressed as a percent relative difference) and the corresponding two-sided 90% confidence interval and p-value, separately for each diabetic status by day combination.

(2) the same analysis described for 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.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

See [Section 11.4.2](#).

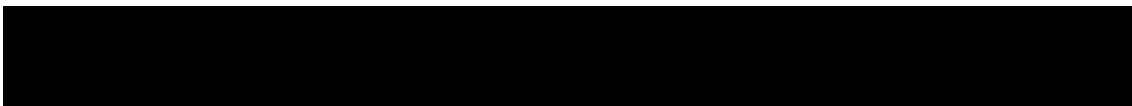
11.5.2 Safety

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

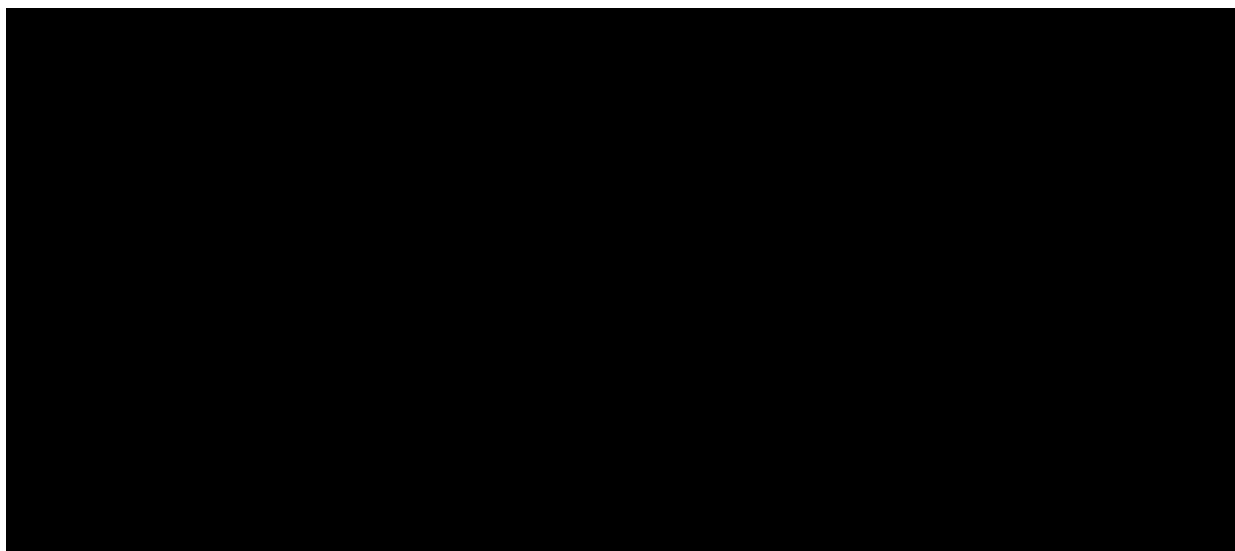
All information obtained on adverse events will be displayed by renal function and subject.

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.

Anion gap

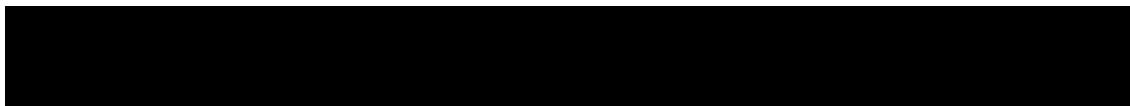
From measurements of sodium, chloride, and bicarbonate in serum, the anion gap will be derived as sodium – (chloride + bicarbonate) and will be an additional safety variable. The anion gap and change from baseline in anion gap will be summarized by diabetic status, renal function, and day.

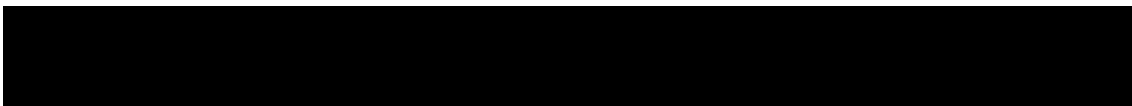
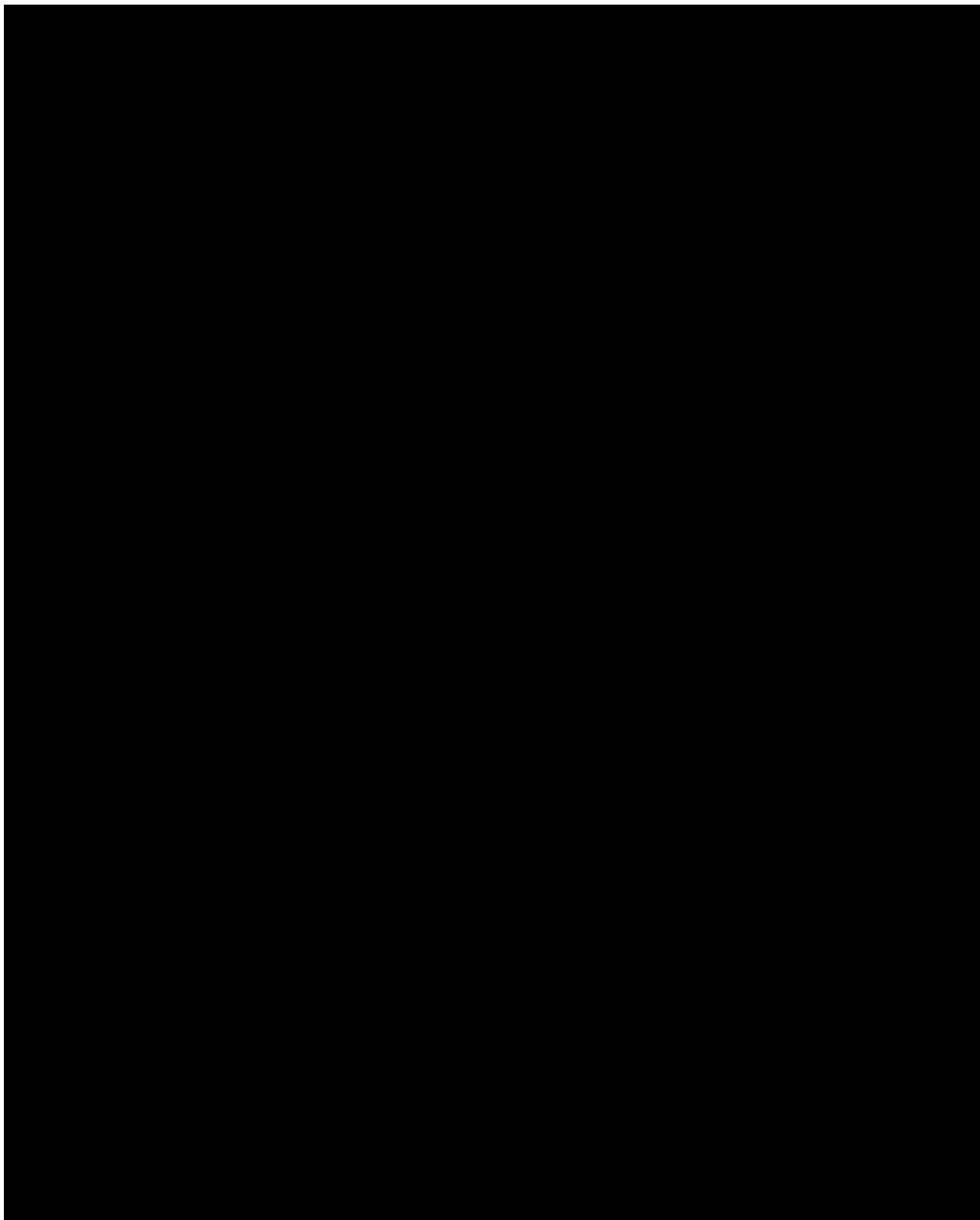
For each subject, the maximum post-baseline value and the maximum change from baseline will be extracted and will be summarized by diabetic status and renal function.



11.5.3 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.





11.7 Sample size calculation

The sample size was chosen to provide adequate precision around the estimated mean difference in change from baseline UGE24 between a renal impaired group and the group of normal controls.

After 7 days of treatment of LIK066 15 mg once daily in patients with type-2 diabetes in the first-in-human study LIK066X2101, the mean and standard deviation of the change from baseline in UGE24 was approximately 98 g and 24 g respectively. If we observe similar variability in this study, with 10 enrolled subjects in the mild and moderate renal impaired groups and in the group of normal controls and at least 8 completers in each of these groups, a two-sided 90% CI for the difference of means will extend no more than 22.7 g from the observed difference. As an example, in the renal impairment study for the SGLT2 inhibitor empagliflozin (Macha et al 2014), the observed difference between the moderate impaired group and the normal controls was 42 g, representing a 43% decrease in UGE24. If we see a similar reduction in our study, the CI for the difference would extend to no more than 19.3 g to 64.7 g. We consider this as adequate precision for the estimation of the difference in change from baseline UGE24 between the groups.

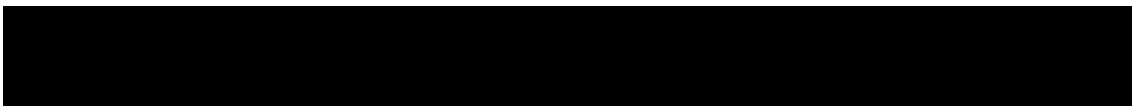
The sample size also provides adequate precision for a comparison of the primary PK variables between groups. After a single dose of LIK066 50 mg in healthy volunteers in LIK066X2101, the coefficient of variation of the C_{max} of LIK066 was approximately 22%. Assuming similar variability in this study, with at least 8 completers in each group, a two-sided 90% CI for the ratio of means will have a lower bound that extends to no less than 0.81 times the observed ratio and an upper bound to no more than 1.23 times the observed ratio. We consider this as adequate precision for the estimation of the ratio of C_{max} between the groups.

11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

Refer to [Section 3.5](#). Statistical details of the interim analysis will be described in the Statistical Analysis Plan (SAP).



12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 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 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.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

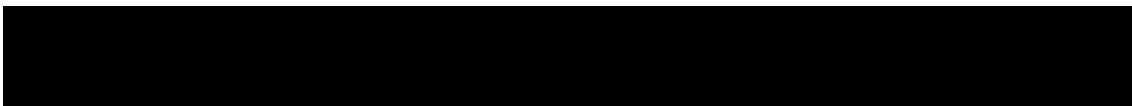
12.3 Publication of study protocol and results

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.

13 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 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.

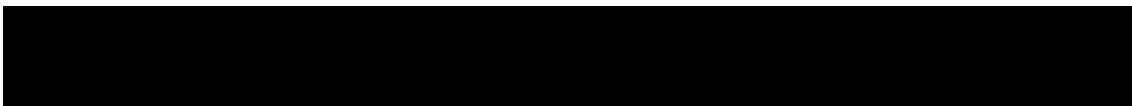


13.1 Protocol Amendments

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in [Section 9](#) (Safety Monitoring) must be followed and the Study Lead informed.



14 References

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Chao EC, Henry RR (2010) SGLT2 inhibition--a novel strategy for diabetes treatment. *Nat Rev Drug Discov* p. 551-9.

Levey AS, Coresh J, Greene T, et al (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann. Intern. Med.* p. 247-54.

Macha S, Mattheus M, Halabi A, et al (2014) Pharmacokinetics, pharmacodynamics and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in subjects with renal impairment. *Diabetes Obes Metab* p. 215-22.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	<ul style="list-style-type: none"> ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
New onset ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
New onset ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	<ul style="list-style-type: none"> ALT or AST > 8 × ULN 5 × ULN < ALT/AST ≤ 8 × ULN 3 × ULN < ALT/AST ≤ 5 × ULN
Isolated ALP elevation	<ul style="list-style-type: none"> ALP > 2 × ULN (in the absence of known bone pathology)
Others	<ul style="list-style-type: none"> Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

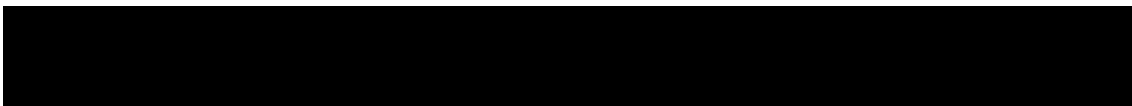
Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case	
New onset ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> Discontinue the study treatment immediately Hospitalize, if clinically appropriate
New onset ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> Establish causality
Isolated ALT or AST elevation > 8 × ULN	<ul style="list-style-type: none"> Complete CRFs per liver event guidance
Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	<ul style="list-style-type: none"> If confirmed, consider interruption or discontinuation of study drug If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	<ul style="list-style-type: none"> Repeat liver chemistry tests within 48-72 hours If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality Complete CRFs per liver event guidance

Criteria	Actions required
Any AE potentially indicative of liver toxicity	<ul style="list-style-type: none"> • Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	<ul style="list-style-type: none"> • IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	<ul style="list-style-type: none"> • IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	<ul style="list-style-type: none"> • ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	<ul style="list-style-type: none"> • Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	<ul style="list-style-type: none"> • Ultrasound or MRI
Hypoxic/ischemic hepatopathy	<ul style="list-style-type: none"> • Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	<ul style="list-style-type: none"> • Ultrasound or MRI, ERCP as appropriate.
Wilson disease	<ul style="list-style-type: none"> • Caeruloplasmin
Hemochromatosis	<ul style="list-style-type: none"> • Ferritin, transferrin
Alpha-1-antitrypsin deficiency	<ul style="list-style-type: none"> • Alpha-1-antitrypsin



16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	<ul style="list-style-type: none"> Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase > 50%	<ul style="list-style-type: none"> Consider causes and possible interventions Repeat assessment within 24-48h if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase \geq 2-fold or new onset dipstick proteinuria \geq 1+ or Albumin-creatinine ratio (ACR) \geq 30 mg/g or \geq 3 mg/mmol; or Protein-creatinine ratio (PCR) \geq 150 mg/g or >15 mg/mmol	<ul style="list-style-type: none"> Consider causes and possible interventions Assess serum albumin & serum protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New hematuria on dipstick	<p>Assess & document:</p> <ul style="list-style-type: none"> Urine sediment microscopy Assess sCr and urine albumin-creatinine ratio Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis



Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load.	<ul style="list-style-type: none">• Urine dipstick and sediment microscopy• Blood pressure and body weight• Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid• Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	<ul style="list-style-type: none">• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or <ul style="list-style-type: none">• Event stabilization: sCr level with $\pm 10\%$ variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm 50\%$ variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

*Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.

