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LIK066

Clinical Trial Protocol CLIK066B2203 / NCT03198767

A randomized, open label, two-part, three-period, cross-over study to investigate the effects of carbohydrate in diet and to evaluate supplements on the gastrointestinal tolerability of LIK066 in overweight or obese subjects

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[redacted]

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 Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Drug Safety and Epidemiology (DS&E) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CD-ROM	compact disc – read only memory
CDS	Core Data Sheet (for marketed drugs)
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CO_2	carbon dioxide
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRD	Clinical Trial Results Database
CV	coefficient of variation
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HIV	human immunodeficiency virus

[redacted]

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
LDH	lactate dehydrogenase
LFT	Liver function test
LLN	lower limit of normal
LLQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRSD	maximum recommended starting dose
NCDS	Novartis Clinical Data Standards
o.d.	once a day
p.o.	oral
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
s.c.	subcutaneous
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin

ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization

[redacted]

Pharmacokinetic definitions and symbols

AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) 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]
Clast	The last observed quantifiable concentration [mass / volume]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Tlast	The time point that corresponds to the last measurable concentration [time]
Tmax	The time to reach the maximum concentration after drug administration [time]

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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, randomization, treatment, and follow-up) which applies across all arms of a study.
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"
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
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.

[redacted]

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.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, 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, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 1 (August 2017)

Amendment Rationale:

This Amendment is to provide minor adjustments and clarifications to the protocol.

Changes to the protocol:

- Section 3.6.1: In the protocol, it is defined "Approximately 400 mL of blood is planned to be collected over a period of 8 weeks including the Screening visit, from each subject as part of the study." However, inconsistencies were discovered showing that the total blood volume adds up ~560 mL based on the blood log (defined in the Site Operations Manual). This was due to the collection of banking samples for future use, if warranted by study results. The collection of banking samples are now removed (108mL), consequently, the total blood volume adds up to ~450 mL as originally defined in the protocol.
- Section 3.1, Section 6.1.1, and Section 8 (Table 8-1, footnote 13): The 1 gram tablet formulation of calcium carbonate was changed to liquid formulation (4 mL) due to difficulty in sourcing the tablet formulation.
- [redacted]
- Section 5.2: To ensure consistency, changes were made in the Prohibited Treatment: "a stable regimen for approximately **6 weeks** prior to randomization" to "a stable regimen for approximately **12 weeks** prior to randomization".
- Section 8: To be consistent with the protocol language, the time points (2 and 4 hours) where VAS will be conducted is clarified in the Assessment schedule.
- [redacted]
- Minor corrections and updates were made as needed throughout the document.

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

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

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

[redacted]

Protocol synopsis

Protocol number	LIK066B2203
Title	A randomized, open label, two-part, three-period, cross-over study to investigate the effects of carbohydrate in diet and to evaluate supplements on the gastrointestinal tolerability of LIK066 in overweight or obese subjects
Brief title	Effects of carbohydrate in diet and supplements on the GI tolerability of LIK066
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Investigational drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to 1) to assess whether or not a meal containing low carbohydrate in the form of glucose and galactose is associated with less diarrhea compared to a high carbohydrate meal; 2) to assess the potential effects of supplements such as psyllium or calcium carbonate on alleviating diarrhea.
Primary Objective(s)	• To assess the effects of meals with different carbohydrate content on diarrhea • To assess the effects of supplements (psyllium and calcium carbonate) on diarrhea
Secondary Objectives	To assess the effects of LIK066 and carbohydrate in meal on fecal parameters
Study design	This randomized, open-label, two-part, three-period cross-over design will enroll approximately 24 overweight or obese subjects in each part (A and B) for a total of approximately 48 subjects over the course of the 25 day study. Part A will assess the effects of % carbohydrate (50%, 25% and 0%) in the breakfast meals on diarrhea when LIK066 is administered immediately before the breakfast. Part B of the study will assess the effects of a concomitant treatment with a supplement (calcium carbonate or psyllium) on diarrhea when LIK066 is administered immediately before a breakfast meal with 50% carbohydrate. The study will consist of an up to 24 day screening period, a 3 day baseline/run in period, three periods of treatment of 3 days each with a 5 day washout period in between each treatment period. Study completion will occur 3 days after the last dose of LIK066. The baseline, treatment, and washout periods will be conducted with subjects being domiciled (25 days consecutively). Diarrhea will be captured based on both reduced consistency (stools with Bristol Stool Chart (BSC) score of 6 or 7) and increased frequency (total number of bowel movements, total number of stools with BSC of 6 or 7). Symptoms such as urgency, bloating, flatus and abdominal pain will also be recorded for each bowel movement. The stool assessments include recording of the timing, weight, pH, consistency of stool using BSC according to the Assessment schedule.
Population	Overweight and obese subjects will be enrolled in this study.

[redacted]

Key Inclusion criteria	• Male and female aged 18-65 • Body mass index (BMI) of 25 - 50 kg/m2 • HbA1c < 10% • oral body temperature between 35.0-37.5 °C • sitting systolic blood pressure, 90-139 mm Hg • sitting diastolic blood pressure, 50-89 mm Hg • sitting pulse rate, 40 - 90 bpm
Key Exclusion criteria	• Pre-existing, clinically significant gastrointestinal, liver, cardiovascular, renal (including familial glucosuria) or other chronic medical condition which is considered serious or unstable, other than stable cardiovascular disease, stable adequately treated hypertension, dyslipidemia or other stable chronic disorders • Clinically significant GI disorder related to malabsorption or that may affect drug or glucose absorption • 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) • Pregnant or lactating women • Type I diabetes
Study treatment	• The investigational drug, LIK066 tablets will be prepared by Novartis.
Efficacy/PD assessments	• Diarrhea is the primary endpoint in this study.
Key safety assessments	• Physical examination • Body temperature • Hematology • Blood chemistry • Urinalysis • Blood pressure • Pulse rate • ECG evaluation • Adverse events and serious adverse events
Other assessments	• Stool pH, stool weight, and BSC score • [redacted] • [redacted] • [redacted] • [redacted] • [redacted]

[redacted]

Data analysis	The primary analysis will be performed by study part. The endpoint will be analyzed using a negative binomial mixed effects model with fixed effects of period, treatment, day, the period-by-day interaction, and the treatment-by-day interaction, and a random subject effect. An unstructured covariance matrix will be specified for the repeated observations on a subject within the same period. The least-squares mean and associated 80% CI for the number of diarrhea episodes per day for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model for each day, and summarized by a table and a line chart. Conclusions from the analysis will be based on treatment differences from all 3 days, collectively.
Key words	SGLT1/2, GI tolerability, carbohydrate

[redacted]

1 Introduction

1.1 Background

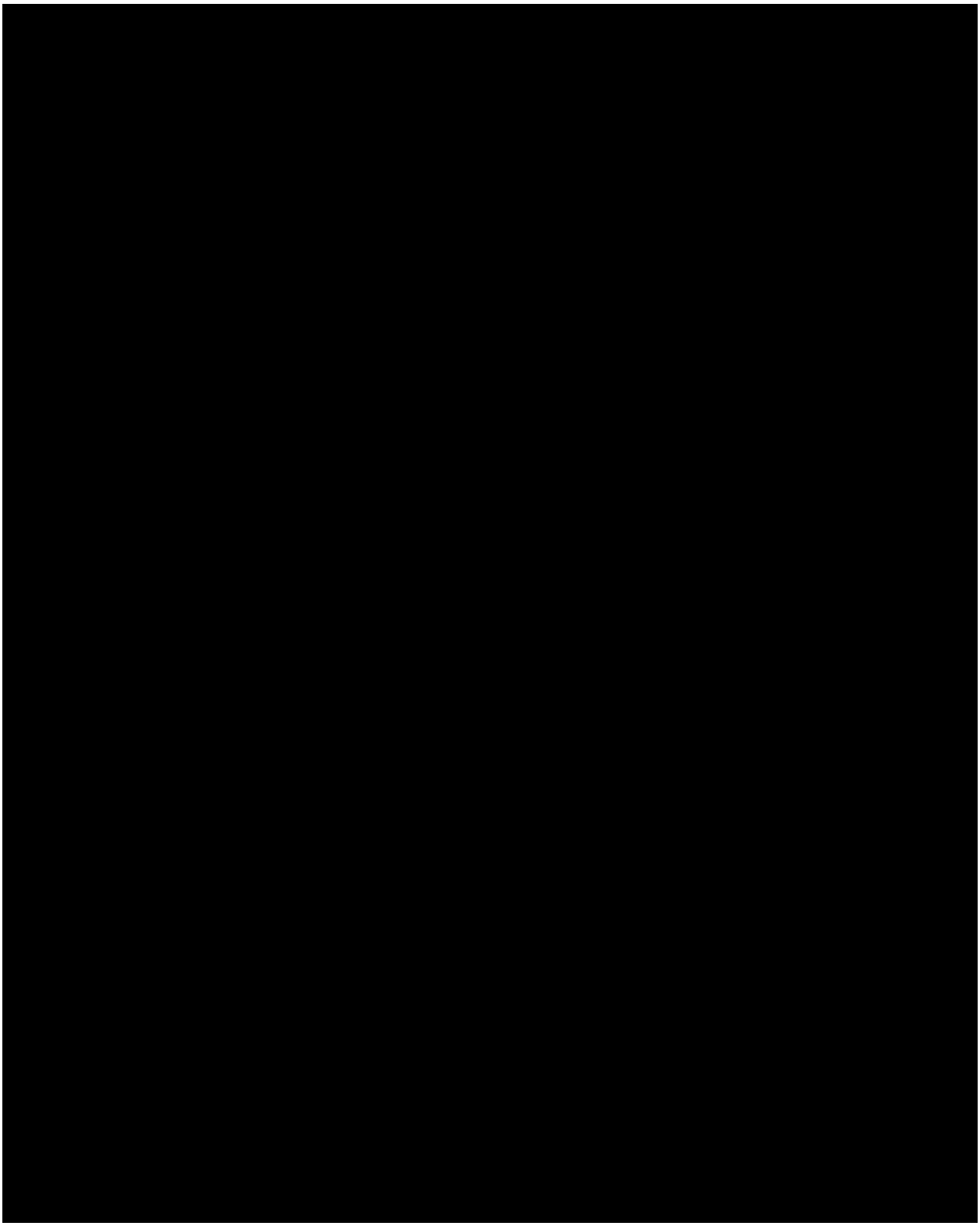
Obesity has become a major global health problem that contributes causally to and exacerbates many serious co-morbidities including hypertension, dyslipidemia, and importantly type 2 diabetes (T2DM). In contrast to the numerous medicines that are available to treat these obesity-related diseases, relatively 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), SGTL1 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; Macha et al 2014). 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 (T1/2 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 and ~ 6% of body weight loss was demonstrated after 12 week treatment.

The most frequent adverse event observed in a 12 week study in obese patients (LIK066X2201) associated with LIK066 was diarrhea. The observed diarrhea adverse event is likely to be related to the complete inhibition of SGLT1 in the gut (Pfister et al 2011). It is known that diarrhea observed in patients with SGLT1 inactivating mutation can be managed with elimination of glucose and galactose from the diet. Therefore, the observed LIK066-induced diarrhea may be managed by recommending a low carbohydrate (especially glucose and galactose) diet when LIK066 is administered. This study is designed to assess the effects of meals with different carbohydrate content and supplements on the incidence of diarrhea associated with LIK066 treatment, and to assess the potential effects of LIK066 on incretin hormones (GLP-1 and PYY) in overweight or obese subjects.

[redacted]

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



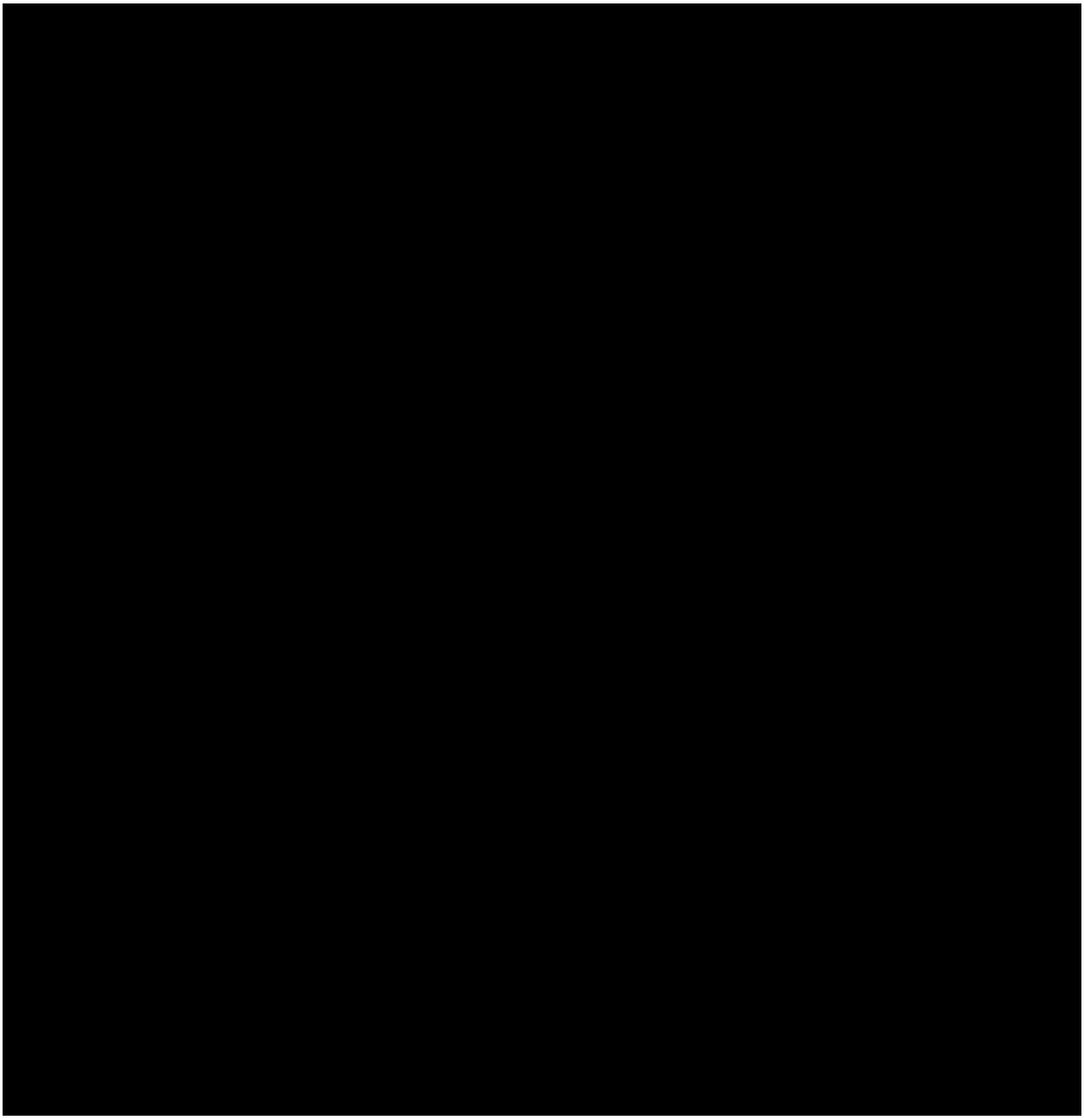
1.3 Clinical data

Four clinical studies have been completed for LIK066: a safety/tolerability/efficacy study in healthy subjects and patients with T2DM, a mechanistic study in patients with T2DM, and a proof-of-concept study in obese patients with normoglycemia or dysglycemia in the US, and an ethnic sensitivity study in healthy Japanese subjects.

1.3.1 Human safety and tolerability data

LIK066 was administered to 72 healthy subjects in the US, 36 healthy subjects in Japan and 41 patients with T2DM and 127 obese patients in the US. Overall, single doses of up to 350 mg and repeated doses of up to 300 mg for 14 days in healthy subjects were generally safe and tolerated. Treatment with LIK066 at 150 mg qd for 12 weeks was also shown to be safe and tolerated. AEs were predominantly diarrhea and related GI AEs after single doses or multiple doses in the higher daily dose groups (≥150 mg as qd, bid or tid). No SAEs, withdrawals from treatment for AEs or significant clinical, laboratory, or ECG abnormalities were related to LIK066 administration.

With the exception of a small increase in urinary specific gravity, BUN and expected glucosuria, there were no consistent differences between LIK066 and placebo treated subjects in the prevalence of any specific laboratory abnormality, the number of subjects observed to have an abnormality, or in the magnitude of specific laboratory abnormalities. In the most recently completed clinical trial (CLIK066X2201) in obese patients, 12 week treatment with LIK066 at 150 mg qd appeared to lead to a minor increase in subjects with urine ketones (urine dipstick) and anion gap, although there were no episodes of clinically meaningful ketoacidosis.



1.3.3 Human pharmacodynamic data

Administration of LIK066 to healthy subjects or obese patients lowered body weight, consistent with a potentially significant anti-obesity effect, and in patients with T2DM, LIK066 lowered average and postprandial glucose levels, thus also demonstrating a significant antidiabetic effect. In obese patients with BMI $\geq$ 35 kg/m^2, treatment with LIK066 150 mg qd for 12 weeks led to significant efficacy on lowering body weight (5.70% reduction). Two weeks of treatment with 75 mg bid or 50 mg tid led to similar effects on body weight loss (2.39 % and 2.38%, respectively). In healthy volunteers, administration of LIK066 dose dependently increased urinary glucose excretion (UGE) to a maximal level of

approximately 80 g/24 hr in HVs after single and multiple oral daily (14 days) dosing. In patients with T2DM, administration of LIK066 (multiple daily doses of 15 mg and single doses of 30, 300 mg) also increased urinary glucose excretion, leading to a placebo-adjusted UGE_{24} of 90-100 g over 24-hours. A single dose administration of LIK066 at 15, 30 and 300 mg was associated with 30%, 31% and 48% reduction in the postprandial glucose levels during an oral glucose tolerance test (OGTT), respectively. In addition, two week average blood glucose levels measured using continuous glucose monitoring (CGM) decreased by 41 mg/dL following treatment with LIK066 15 mg once daily for 2 weeks.

1.4 Study purpose

The most frequent adverse event observed in a 12 week study in obese patients (LIK066X2201) associated with LIK066 was diarrhea. This diarrhea is likely to be related to complete SGLT1 inhibition. It is known that diarrhea related to SGLT1 inactivating mutation can be managed with elimination of glucose and galactose from the diet (Martin et al 1996). Therefore, the observed LIK066-induced diarrhea may be managed by recommending a low carbohydrate diet when taking LIK066. The purpose of this study is to assess the effects of meals with different carbohydrate content and supplements on the incidence of diarrhea associated with LIK066 treatment, [redacted] in overweight or obese subjects.

2 Study objectives and endpoints

The objectives of this study are: 1) to assess whether or not a meal containing low carbohydrate in the form of glucose and galactose is associated with less diarrhea compared to a high carbohydrate meal; 2) to assess the potential effects of supplements such as psyllium or calcium carbonate on alleviating diarrhea.

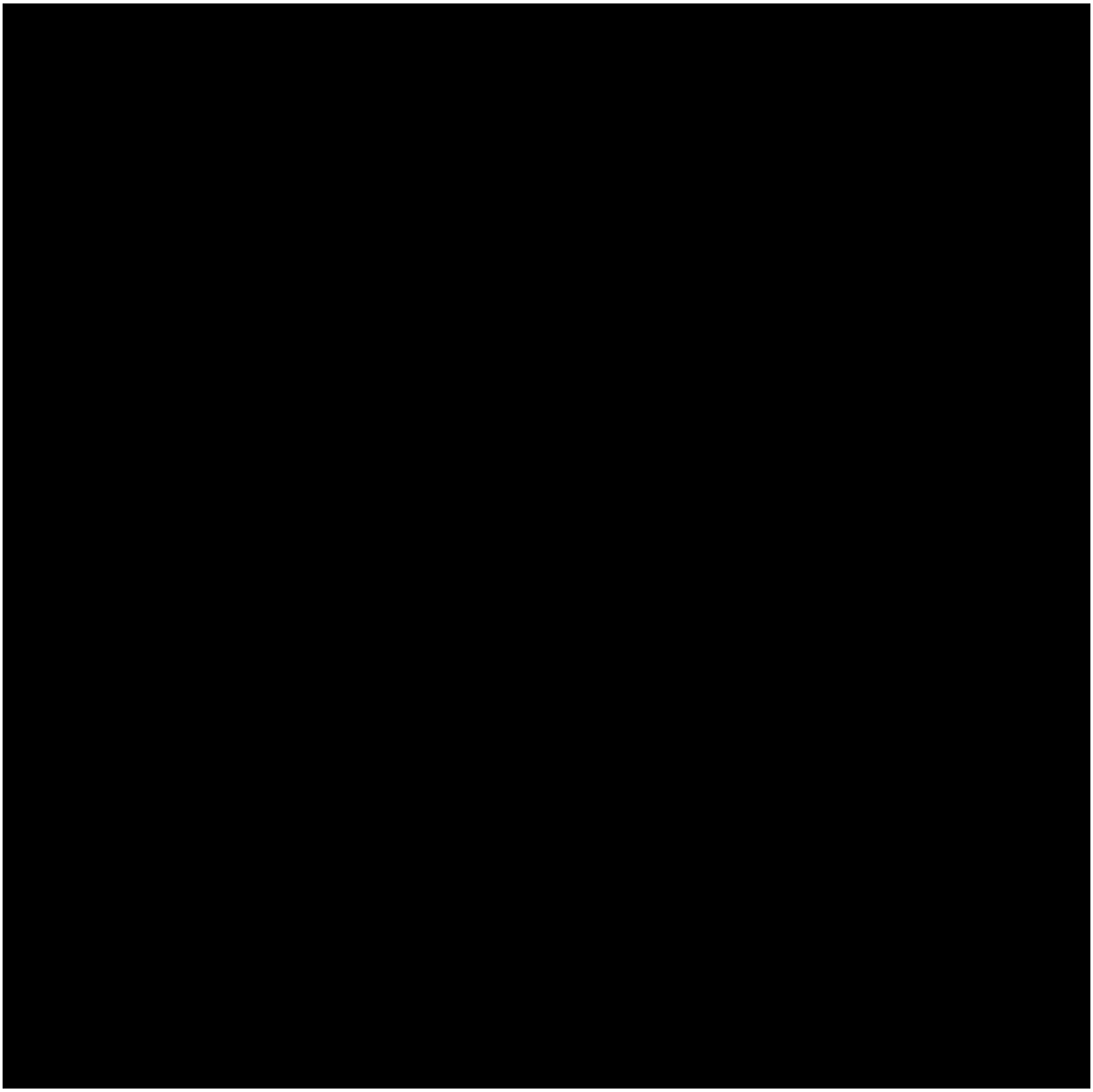
2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To assess the effects of meals with different carbohydrate content on diarrhea	• Diarrhea (consistency and incidence)
• To assess the effects of supplements (psyllium and calcium carbonate) on diarrhea	• Diarrhea (consistency and incidence)

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the effects of LIK066 and carbohydrate in meal on fecal parameters	• Stool samples (timing, assessment of consistency with Bristol stool chart, stool weight, stool pH)

[redacted]



3 Investigational plan

3.1 Study design

This study employs a randomized, open-label, two-part, three-period, cross-over design. This is a non-confirmatory study. Each part of the study will enroll approximately 24 overweight or obese subjects, thus, a total of approximately 48 subjects will be enrolled for the entire study. In each part of the study, each subject will be randomized to one of the 3 treatment sequences shown in Figure 3-1 (Part A) and Figure 3-2 (Part B).

Part A of the study will assess the effects of % carbohydrate (50%, 25% and 0%) in the breakfast meals on diarrhea when LIK066 is administered immediately before the breakfast. Part B of the study will assess the effects of a concomitant treatment with a supplement (calcium carbonate or psyllium) on diarrhea when LIK066 is administered immediately before a breakfast meal with 50% carbohydrate.

The primary endpoint of this study is the diarrhea events. Diarrhea is usually defined by reduced consistency and/or increased frequency of stools. Normal stool frequency ranges from 3 per week to 2 per day. Bristol Stool Chart (BSC) is frequently used as a measure of consistency, and a score of 6 or 7 (pourable or watery stool) is considered abnormal. Diarrhea events will be captured based on both reduced consistency (stools with BSC score of 6 or 7) and increased frequency (total number of bowel movements, total number of stools with BSC of 6 or 7). Symptoms such as urgency, bloating, flatus, and abdominal pain will also be recorded for each bowel movement.

The study will consist of an up to 24 day screening period, a 3 day baseline/run in period, and three periods of treatment of 3 days each with a 5 day washout period in between each treatment period. Study completion will occur 3 days after the last dose of LIK066. The baseline, treatment and washout periods will be conducted with subjects being domiciled for approximately 25 days (see Figure 3-1 and Figure 3-2).

Screening (Day-28 to Day -4)

Potential study subjects will present to the clinical site for a screening visit where eligibility for the study will be evaluated.

Baseline/Run In (Day-3 to Day -1)

Subjects who meet the inclusion/exclusion criteria at screening will be admitted to the clinical site on Day -3. A survey for food preference of each subject will be conducted so that meal menus can be provided to accommodate the usual diet habits of each individual. As diet changes may impact on the bowel movement habits, subjects participating in this study will be encouraged to follow their usual dietary habit whenever possible.

During the baseline period, a standardized breakfast meal (600 calories with 50% carbohydrate, 15% protein and 35% fat) will be served; for lunch and dinner, menu options will be offered so that each subject can follow their usual diet following the standard nutritional guidance.

Starting on Day-3 and continuing through the 25 days of domiciling period, stool assessments will take place whenever a subject has a bowel movement (Assessment schedule). Starting from Day -2 at approximately 07.00, a 24-hour stool collection will be done for each subject. During Day -2 through Day 22, daily bowel movements will be monitored and collected, and stored in a refrigerated container and will be assessed by the study staff according to the Bristol Stool Chart and bowel movement record.

[redacted]

The stool assessments include recording of the timing, weight, pH, consistency of stool using Bristol Stool Chart, [redacted] according to the Assessment schedule.

Day -1 Baseline Assessment

Twenty-four (24) hour baseline stool samples will be collected from Day-1 to Day 1 morning (approximately 07.00 to 07.00) for various assessments of fecal parameters according to the Assessment schedule.

[redacted]

On Day -1, at approximately 07.30, a 600 calorie standardized breakfast meal containing 50% carbohydrate, 15% protein, and 35% fat will be served, and subjects will drink 250 mL water immediately before breakfast during treatment periods. The time of drinking water will be defined as time zero for the measurement of baseline PD endpoints. Each subject will consume the designated breakfast within 15 mins. [redacted] Lunch will be served at approximately 13.00 (after completion of the PD sample collection and at least 5 hours from breakfast), and dinner will be served at approximately 18.30. The timing of meals should be harmonized on all days (Day -1, Day 3, Day 11, and Day 19) when PD are measured to minimize the effects of diurnal rhythm.

[redacted]

All other samples and measurements will be taken according to the Assessment schedule.

Part A: Effects of Carbohydrate in the Breakfast Meals

Treatment Period I (Day 1 to Day 3); Period II (Day 9 to Day 11); Period III (Day 17 to Day 19)

Starting on the morning of Day 1 and through Day 3 of each treatment period, each subject will receive LIK066 50 mg qd in the morning immediately before the assigned breakfast meal according to their assigned treatment sequence. All subjects will take 50 mg LIK066 once daily with their assigned breakfast meal containing either 50% carbohydrate, 25% carbohydrate, or no carbohydrate. For lunch and dinner, menu options will be offered so that the participants can follow their usual dietary habits. These menus will be designed in accordance with the current Recommended Dietary Guidelines (United States Department of Agriculture 2015). The estimated calories consumed will be documented for each meal and for each subject. As with the baseline period, 24-hr stool collection will be done and stool assessment will be recorded for every bowel movement of every subject according to the Assessment schedule.

[redacted]

Twenty-four (24) hour stool samples will be collected from Day 3 to Day 4 morning (approximately 07.00 to 07.00) of each treatment period for various assessments of fecal parameters according to the Assessment schedule.

[redacted]arious assessments including UGE24 and electrolytes according to the Assessment schedule.

[redacted] At approximately 07.30, a 600 calorie standardized breakfast meal containing either 50% or 25% or 0% carbohydrate as designated will be served, and LIK066 50 mg will be administered immediately before the breakfast meal. Each subject will consume the designated breakfast within 15 mins. [redacted]

Lunch will be served at approximately 13:00 (after completion of the PD sample collection and at least 5 hours from breakfast), and dinner will be served at approximately 18.30. The timing of meals should be harmonized on all days (Day -1, Day 3, Day 11, and Day 19) when PD are measured to minimize the effects of diurnal rhythm.

All other measurements and blood samples will be taken according to the Assessment schedule.

Washout Period I (Day 4 to Day 8); Period II (Day 12 to Day 16); Period III (Day 20 to Day 22)

Study subjects will also remain domiciled at the clinical site during the washout periods and no LIK066 will be administered. There are no particular restrictions for the meals during the washout time period, and subjects can choose foods according to their eating habits and preference (meal menu to be provided offering varied choices). The estimated calories consumed will be documented for each meal for each subject. As with the run-in and baseline period, all stool samples will be collected and bowel movement assessments will be recorded for every subject.

On Day 22, following the end of study assessments, subjects will be discharged from the clinical site.

During the study, safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring, as recorded in the Assessment schedule. [redacted]

[redacted]

Figure 3-1 Part A: Effects of Carbohydrate in the Breakfast Meals

Screening Period Day-28 to -4	Baseline Day -3 to -1	Sequence	Treatment Period 1 Day 1-3	Washout 5 Days	Treatment Period II Day 9-11	Washout 5 Days	Treatment Period III Day 17-19	Washout EOS Day 20-22
	Run-In	1 (n=8)	50% CHO		25% CHO		0% CHO	
	Run-In	2 (n=8)	25% CHO		0% CHO		50% CHO	
	Run-In	3 (n=8)	0% CHO		50% CHO		25% CHO	

CHO = % carbohydrate content in the standardized breakfast meal

LIK066 50mg QD will be given in the morning immediately before the breakfast meal

Part B: Effects of Supplements (Psyllium and Calcium carbonate)

The same Assessment Schedule will apply to Part B of the study as described for Part A. Each subject will consume one of the three supplement treatment options (6 g psyllium, 1g calcium carbonate (to be provided in a 4mL liquid, sugar free formulation), or no supplement) according to the randomization assignment immediately after administration of 50 mg LIK066, and before having the standardized breakfast meal, containing 50% carbohydrate (Figure 3-2). All supplement products will be the sugar free version.

Treatment Period I (Day 1 to Day 3); Period II (Day 9 to Day 11); Period III (Day 17 to Day 19)

Starting on the morning of Day 1 and through Day 3 of each treatment period, each subject will receive LIK066 50 mg qd in the morning, and then consume the designated supplements (6 g psyllium or 1g calcium carbonate or no supplement) according to their randomization assignment sequence. Immediately after administration of LIK066 50 mg and the supplement, a 600 calorie breakfast meal containing 50% carbohydrate will be served. For lunch and dinner, menu options will be offered for the participants to choose following their usual dietary habits. These menus will be designed in accordance with the current Recommended Dietary Guidelines. The estimated calories consumed will be documented for each meal and for each subject. As with the baseline period, all stools will be collected and assessment will be recorded for every bowel movement of every subject according to the Assessment schedule.

Twenty-four (24) hour stool samples will be collected from Day 3 to Day 4 morning (approximately 07.00 to 07.00) of each treatment period for various assessments of fecal parameters according to the Assessment schedule.

[redacted]

[redacted]

[redacted]

On Day 3 of each treatment period, at approximately 07.30 in the morning, each subject will take LIK066 50 mg and then consume the supplement (6 g psyllium or 1g calcium carbonate or no supplement) as designated immediately before the breakfast. A 600 calorie breakfast meal containing 50% carbohydrate will be served and each subject will consume the breakfast within 15 mins. [redacted] Lunch will be served at approximately 13.00 (after completion of the PD sample collection and at least 5 hours from breakfast), and dinner will be served at approximately 18.30. The timing of meals should be harmonized on all days (Day -1, Day 3, Day 11, and Day 19) when PD are measured to minimize the diurnal rhythm.

[redacted]

All other samples and measurements will be taken according to the Assessment schedule.

Washout Period I (Day 4 to Day 8); Period II (Day 14 to Day 16); Period III (Day 20 to Day 22)

Study subjects will remain at the clinical site from the Day 4 through Day 8 of each treatment period for a washout period. During this time, no LIK066 will be administered. As with the run-in and baseline period, stool samples will be collected and bowel movement assessments will be recorded for every subject.

On Day 22, following the end of study assessments, subjects will be discharged from the clinical site.

During the study, safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring, as recorded in the Assessment schedule. [redacted]

Figure 3-2 Part B: Effects of Supplements in the Breakfast Meals*

Screening Period Day-28 to -4	Baseline Day -3 to -1	Sequence	Treatment Period 1 Day 1-3	Washout 5 Days	Treatment Period II Day 9-11	Washout 5 Days	Treatment Period III Day 17-19	Washout EOS Day 20-22
	Run-In	I (n=8)	NS		Psyllium		CC	
	Run-In	II (n=8)	Psyllium		CC		NS	
	Run-In	III (n=8)	CC		NS		Psyllium	

*CHO = % carbohydrate content in the standardized breakfast meal (50%) for all groups

LIK066 (50 mg QD) and supplement will be administered immediately before the breakfast meal

NS = No supplement

CC = Calcium Carbonate (1 gram)

Psyllium = 6 grams

[redacted]

3.2 Rationale of study design

This is a mechanistic study to investigate the effect of percentage carbohydrate in the breakfast meal on the LIK066-induced diarrhea and potential treatments with a supplement in overweight or obese subjects. The study will use a randomized, open-label, two-part, three-period, cross-over design in each part of the study.

- An open label design is considered appropriate because all the primary and secondary endpoints assessed in this study are objective measures in nature. A crossover design is ideal as comparisons among treatment groups are based on within-subject differences which are associated with less variability than between-subject differences. The main objective is to assess whether or not the diarrhea adverse event can be alleviated by reducing or removing carbohydrate containing glucose and galactose in the meal or by concomitant administration of supplements, therefore, placebo control is not needed.
- The design of two parts (Part A and Part B) with 3 treatment periods, cross-over design is preferred because a single part, six treatment periods cross-over design requires longer duration of domiciling which may lead to operational complexity such as difficulty in recruitment and higher drop-out rates. The two parts, three periods design is also preferred from statistical perspective because it yields the most statistically efficient design for addressing the clinical questions.
- A five day washout period is considered sufficient based on the fact that limited diarrhea episodes were observed on the following day after the last dose of 50 mg qd (one out of 40 patients showed diarrhea on day 15 after 14 day dosing in LIK066X2201).
- A standardized breakfast meal (together with menu options for lunch and dinner) enables each subject to choose the diets following their usual eating habits during the run-in will normalize the bowel movement habit of each subject under similar meal conditions for the purpose of comparison during the treatment periods.
- The overweight or obese subjects in this study will closely represent the patient population for LIK066, which is being developed as a pharmacotherapy for obesity.

Therefore, the study design is considered adequate and appropriate to address the primary objectives, the stool consistency and incidence of diarrhea associated with LIK066 treatment, which are endpoints that can be measured objectively.

[redacted]

[redacted]

[redacted]

3.4 Rationale for choice of comparator

Not applicable.

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis is not planned, but may be conducted before all subjects complete the study if deemed necessary. Depending on the progress of the trial, the analysis may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development strategy in general, or in case of any safety concerns.

3.6 Risks and benefits

There is no anticipated therapeutic benefit expected for subjects participating in this study. The risk to participants in this trial will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring during the treatment periods, and stopping rules outlined in Section 7.5.

Risks of LIK066 administration in human subjects may include the development of gastrointestinal adverse reactions, postural hypotension due to volume depletion, ketoacidosis, urinary tract infection, genitourinary infection, renal and hepatic toxicity, and changes in calcium homeostasis with subsequent effects on bones, hyperglycemia and hypoglycemia.

Doses of LIK066 proposed in this study have been tested and deemed safe in healthy subjects, patients with T2DM and obese patients. Subjects should be closely monitored and treated according to the standard of care if deemed necessary by the principle investigator. LIK066 is considered an aneugen at extremely high doses. With the doses and treatment duration proposed in this study, more than 10-fold exposure multiple is maintained relative to the threshold NOEL exposure for aneugenicity. LIK066 is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans when administered at the highest planned clinical dose of 150 mg. Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study (Section 4.2). If there is any question that the subject will not reliably comply, they should not be entered in the study.

The supplements used in this study are generally well tolerated and widely used as the OTC supplements. Potential risks associated with psyllium are bloating and flatulence, and those associated with calcium carbonate are constipation, gas and burping.

Blood samples will be collected frequently during the study either via venipuncture or cannula. 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. Risks associated with blood collection include pain, swelling and/or bruising at the insertion site of the needle. Although rare, localized clot formation, infections and nerve damage may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

There may be unknown risks to LIK066 which may be serious and unforeseen.

[redacted]

3.6.1 Blood sample volumes

Approximately 450 mL of blood is planned to be collected over a period of 8 weeks including the Screening visit, from each subject as part of 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 Site Operations Manual, 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

The study population will consist of male and female overweight or obese subjects.

A total of approximately 48 patients will be enrolled in the study and randomized. At least 36 subjects are expected to complete the study.

The investigator must ensure that all subjects meet the subsequent eligibility criteria at screening. No additional criteria should be applied by the investigator to ensure that the study population is representative of all eligible subjects. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the documentation at the study site.

Deviation from any entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Overweight or Obese Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects age 18 to 65 years, with stable health condition as determined by past medical history, physical examination, electrocardiogram, and laboratory tests at screening.
3. Subjects with a body mass index (BMI) of 25 - 50 kg/m^2 at screening
4. HbA_{1c} < 10% at screening. If treated with antidiabetic medications (other than prohibited medications), subjects must be on a stable dose for 12 weeks prior to randomization and maintain the dose until the end of the study.
5. Able to communicate well with the Investigator, to understand and comply with the requirements of the study.

[redacted]

6. At screening and baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position after the subject has rested for at least three (3) minutes, and again when required after three (3) minutes in the standing position Investigators can be guided by the following ranges:

   oral body temperature between 35.0-37.5 °C
   sitting systolic blood pressure, 90-139 mm Hg
   sitting diastolic blood pressure, 50-89 mm Hg
   sitting pulse rate, 40 - 90 bpm

   If vital signs are out-of-range, the Investigator may obtain two additional readings**,** so that up to three (3) consecutive assessments are made, each after at least 30 minutes (one hour is recommended), and with the subject seated quietly during the five (5) minutes preceding the assessment. ***At least the last reading must be within the ranges provided above in order for the subject to qualify.***

   When blood pressure and pulse will be taken again 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 and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension.

   All blood pressure measurements at other time-points should be assessed with the subject seated, unless stated otherwise in the protocol design, and utilizing the same arm for each determination.

4.2 Exclusion criteria

Overweight or Obese Subjects fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Pre-existing, clinically significant gastrointestinal, liver, cardiovascular, renal (including familial glucosuria) or other chronic medical condition which is considered serious or unstable, other than stable cardiovascular disease, stable adequately treated hypertension, dyslipidemia or other stable chronic disorders
2. 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)
3. 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)
4. History of hypersensitivity to the study drugs, or to drugs of similar chemical classes.
5. 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
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of study treatment.

[redacted]

Basic contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation (hysterectomy is acceptable) 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 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) 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.
- 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

7. 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
8. Evidence of significant diabetic complications such as symptomatic neuropathy, severe diabetic retinopathy, diabetic nephropathy, diabetic gastroparesis or enteropathy
9. Use of prohibited medications, refer to Section 5.2.
10. Evidence of clinically significant renal or liver disease/injury including:
    - eGFR less than 60 mL/min/1.73m^2 at screening.
    - Patients with macroalbuminuria as determined by spot urine albumin:creatinine ratio >300 mg/g at screening.

    Abnormal liver function tests at screening:
    - ALT, AST, GGT, alkaline phosphatase > 2 x ULN.
    - serum bilirubin > 1.5 x ULN
11. Evidence of urinary obstruction or difficulty in voiding at screening
12. Symptomatic genital or urinary tract infection in the 4 weeks prior to first study visit
13. Any uncontrolled endocrinopathy including thyroid disease. Patients with an underlying endocrinopathy should be on stable treatment for 3 months prior to screening
14. Evidence or medical history of clinically significant ECG abnormalities

[redacted]

15. Any of the following within 6 months of screening:
    - Acute coronary syndrome (ACS)
    - coronary artery bypass surgery, balloon angioplasty, coronary stent(s) *in situ*
    - peripheral arterial disease
    - congestive heart failure NYHA class I- IV
16. History of autonomic dysfunction (e.g. history of fainting, clinically significant orthostatic hypotension, clinically significant sinus arrhythmia).
17. Significant blood loss equaling at least one unit of blood (500 ml) or a blood transfusion within 3 months prior to screening
18. Evidence of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test at screening
19. History of drug or alcohol abuse within the 12 months prior to initial dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or tests conducted during baseline evaluations
20. Malignancy including leukemia and lymphoma (not including basal cell skin cancer) within 5 years prior to screening
21. Any finding during screening assessments (physical examination, vital signs, 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.
22. Subjects who experienced ketoacidosis, lactic acidosis, or hyperosmolar coma within 6 months of Screening Visit, or between Screening Visit and Baseline Day -1.
    No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

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

Except for medication which may be required to treat adverse events, no medication including OTCs other than study drugs will be allowed from the first dosing until all of the Study Completion evaluations have been conducted. If needed, acetaminophen or ibuprofen is acceptable for incidental and limited use. Aspirin, antihypertensive, dyslipidemia, COPD and GERD medications including PPIs are allowed but subjects must be on a stable regimen for 12 weeks or more prior to randomization (Section 6.10).

[redacted]

The following medications are prohibited during the study:

- Antidiabetic drugs including injectable antidiabetic medications (such as insulin and GLP-1 agonists), SGLT and alpha-glucosidase inhibitors are NOT allowed during the study. Patients must be on a stable regimen for approximately 12 weeks prior to randomization if treated with other oral antidiabetic medications.
- Treatment with drugs that affect gastric motility (e.g. erythromycin)
- Treatment with drugs that have a high incidence of diarrhea
- Drugs which act primarily in the GI tract (e.g. Orlistat, acarbose)
- 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
- Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations
- 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.

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 are allowed on the study.
- No grapefruit or grapefruit juice is to be consumed for approximately 7 days prior to dosing until 7 days following the last dose.

[redacted]

[redacted]

While domiciled, subjects will be provided a standardized breakfast meal according to their randomization assignment below for Part A and B:

Part A: Effects of carbohydrate in the breakfast meal

- The breakfast meal will contain 600 calories providing 50% carbohydrate, 15% protein and 35% fat. This meal will be served at approximately 07.30, immediately after LIK066 administration. The breakfast meal should be consumed within 15 mins.
- The breakfast meals during each treatment period will include the following and according to the randomization assignment:
  - 600 calories - 50% carbohydrate, 15% protein, and 35% fat
  - 600 calories - 25% carbohydrate, 40% protein, and 35% fat
  - 600 calories - 0% carbohydrate, 65% protein, and 35% fat

Part B: Effects of supplements

- All breakfast meals in Part B treatment periods will include approximately 600 calories containing 50% carbohydrate, 15% protein, and 35% fat, and served at approximately 07.30 immediately after administration of LIK066, then the designated supplements (psyllium, calcium carbonate or no supplement) according to randomization.

In both study parts and during each treatment period, lunch will be served at approximately 13.00 (after completion of the PD sample collection and at least 5 hours from breakfast), and dinner will be served at approximately 18.30. The timing of meals should be harmonized on all days (Day -1, Day 3, Day 11, and Day 19) when PD are measured to minimize the effects of diurnal rhythm. A snack may be served at approximately 20.00 if needed.

Lunch and dinner meals will be provided as a menu option, and study participants can choose from the menu based on their usual eating habits.

Further details on the specified meals and potential meal menu options will be provided in the SOM.

A meal record will confirm timing and consumption of meal. A copy of the diet with content and nutritional information (e.g., 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 evaluation.
- During the domiciled period, study participants are encouraged to maintain usual activity level in the study site (e.g., light to moderate walking) to minimize altered bowel habits associated with inactivity.

[redacted]

6 Treatment

6.1 Study treatment

The investigational drug, LIK066, 50 mg tablets, will be prepared by Novartis and supplied to the Investigator as open labeled bulk medication. Supplements (Sugar Free version) including psyllium and calcium carbonate will be sourced by the Site.

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 Site Operations Manual.

6.1.1 Investigational treatment and control drugs

	Formulation	Unit Dose	Packaging	Provided by
LIK066	Tablet	50 mg	Open-label, bulk, blister-pack	Novartis
Psyllium	Powder	6 grams	Over the counter	Sourced by site
Calcium carbonate	Liquid	1 gram (4 mL equivalent sugar free formulation)	Over the counter	Sourced by site

6.1.2 Additional study treatment

No additional treatment beyond the investigational drug LIK066 and the supplements (psyllium and calcium carbonate) are included in this trial.

6.2 Treatment arms

Study treatments are defined as:

- A: Daily dose of 50 mg LIK066+50% carbohydrate
- B: Daily dose of 50 mg LIK066+25% carbohydrate
- C: Daily dose of 50 mg LIK066+0% carbohydrate
- D: Daily dose of 50 mg LIK066+50% carbohydrate+ 6 g psyllium
- E: Daily dose of 50 mg LIK066+50% carbohydrate+1g calcium carbonate (1 g calcium carbonate in 4mL liquid sugar-free formulation)

  In each part of the study, subjects will be randomized to one of the following 3 treatment sequences in the ratio of 1:1:1.

[redacted]

Table 6-1 Definition of treatment sequences

Part A Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
Part B Sequence	**Period 1**	**Period 2**	**Period 3**
4	A	D	E
5	D	E	A
6	E	A	D

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of [redacted] and [redacted] in Part A and Part B, respectively.

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Replacement randomization numbers will be in the range of [redacted] for Part A and [redacted] for Part B. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g. Subject [redacted] would replace Subject [redacted]). Any additional subjects enrolled will use sequential subject numbering.

The table below details the general details of the numbering of the subjects once randomized to treatment:

Table 6-2 Randomization assignment numbering

Cohort	Randomization numbers	Replacement randomization numbers
Part A (n=24)	[redacted]	[redacted]
Part B (n=24)	[redacted]	[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased. Treatment allocation cards will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

There will be no stratification of randomization. Block randomization will be used to generate the treatment allocation cards.

[redacted]

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treating the subject

LIK066 50 mg will be administered to the subject orally by the study personnel at the investigator site. See the Site Operations Manual for further details.

6.5 Permitted dose adjustments and interruptions of study treatment

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

For subjects 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.

6.6 Emergency breaking of assigned treatment code

This is an open label, non-placebo control study; therefore emergency code breaks are not applicable.

6.7 Treatment exposure and compliance

Study medication will be given at the site by study personnel as subjects will be domiciled during the entire study treatment periods.

[redacted]

6.8 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.

6.9 Rescue medication

This is not a therapeutic study; therefore, rescue medication use is not applicable.

[redacted]

6.10 Concomitant treatment

Except for medication which may be required to treat adverse events, no medication including OTCs other than study drugs will be allowed from the first dosing until all of the Study Completion evaluations have been conducted. If needed, acetaminophen or ibuprofen is acceptable for incidental and limited use. Aspirin, antihypertensive, dyslipidemia, COPD and GERD medications are allowed but subjects must be on a stable regimen for 12 weeks or more prior to randomization.

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 randomizing 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.

All subjects should have a safety follow-up call conducted 30 days after last visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. If unable to contact the subject, documentation of attempts should be recorded in the source documentation.

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.

[redacted]

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 discontinued when that subject experiences:

- Clinically significant diarrhea, suspected to be related to the study drug, that may put the subject at risk at the discretion of the investigator and in consultation with the sponsor
- Clinically significant symptomatic orthostasis confirmed by repeated orthostatic blood pressure changes (more than a 20 mmHg drop in systolic or 10 mmHg drop in diastolic blood pressure and increase in heart rate >20 bpm (compared to the sitting results) when blood pressure and pulse are taken after at least 3 minutes standing)
- Clinically significant urinary tract or genitourinary infections, at the discretion of the investigator and in consultation 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) confirmed by blood pH and ketones bodies in both plasma and urine.
- 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, the 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 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.

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 event 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.

[redacted]

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

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

Table 8-1 Assessment Schedule

Epoch	Screening	Run In						Treatment Period 1										Treatment Period 2				
Visit Name	Screening	Baseline/Run-in						Treatment					Washout					Treatment				
Visit Numbers[1]	1	101	102	199				201	202	203			204	205	206	207	299	301	302	303		
Study Day(s)	-28 to -4	-3	-2	-1				1	2	3			4	5	6	7	8	9	10	11		
Time (post-dose)	-	-	-	Predose: 0 H	0.5h	2h	4h	-	-	Predose: 0 H	2h	4h	-	-	-	-	-	-	-	Predose: 0 H	2h	4h
Informed consent	X																					
Inclusion / Exclusion criteria	S	S[2]																				
Medical history/current medical conditions	X	X																				
Demography	X																					
Physical Examination	S			S						S										S		
Hepatitis and HIV Screen	S																					
Alcohol Test, Drug Screen, and Cotinine Test	S	S																				
Electrocardiogram (ECG)	X			X						X										X		
Pregnancy test	X[3]	X[4]																				
Vital Signs[5]	X			X						X										X		
Body Weight	X			X						X										X		

[redacted]

Epoch	Screening	Run In						Treatment Period 1										Treatment Period 2				
Visit Name	Screening	Baseline/Run-in						Treatment					Washout					Treatment				
Visit Numbers[1]	1	101	102	199				201	202	203			204	205	206	207	299	301	302	303		
Study Day(s)	-28 to -4	-3	-2	-1				1	2	3			4	5	6	7	8	9	10	11		
Time (post-dose)	-	-	-	Predose: 0 H	0.5h	2h	4h	-	-	Predose: 0 H	2h	4h	-	-	-	-	-	-	-	Predose: 0 H	2h	4h
Body Height	X																					
Hematology	X			X						X										X		
Clinical Chemistry	X			X						X										X		
Urinalysis	X			X						X										X		
[redacted]																						
24 hour stool collection[9]			X							X										X		
Bowel movements[10]		X	X	X				X	X	X			X	X	X	X	X	X	X	X		
[redacted]																						
Meal[11]		X[12]	X	X				X	X	X								X	X	X		
Supplements[13]								X	X	X								X	X	X		
Dose administration[14]		X	X	X				X	X	X								X	X	X		
[redacted]																						
Concomitant medications	X	X																X				
Serious Adverse Events		As Required																				
Adverse Events		As Required																				
[redacted]																						

[redacted]

Epoch	Screening	Run In						Treatment Period 1											Treatment Period 2				
Visit Name	Screening	Baseline/Run-in						Treatment					Washout						Treatment				
Visit Numbers[1]	1	101	102	199				201	202	203			204	205	206	207	299		301	302	303		
Study Day(s)	-28 to -4	-3	-2	-1				1	2	3			4	5	6	7	8		9	10	11		
Time (post-dose)	-	-	-	Predose: 0 H	0.5h	2h	4h	-	-	Predose: 0 H	2h	4h	-	-	-	-	-		-	-	Predose: 0 H	2h	4h
[redacted]																							
Subjects domiciled		Domiciled																					
Study completion information																							
Comments	As Required																						
Safety Follow up Call																							

[redacted]

Epoch	Treatment Period 2					Treatment Period 3							End of Study
Visit Name	Washout					Treatment					Washout		EOS
Visit Numbers[1]	304	305	306	307	399	401	402	403			404	499	599
Study Day(s)	12	13	14	15	16	17	18	19			20	21	22
Time (post-dose)	-	-	-	-	-	-	-	Predose: 0 H	2h	4h	-	-	-
Informed consent													
Inclusion / Exclusion criteria													
Medical history/current medical conditions													
Demography													
Physical Examination								S					S
Hepatitis and HIV Screen													
Alcohol Test, Drug Screen, and Cotinine Test													
Electrocardiogram (ECG)								X					X
Pregnancy test													X
Vital Signs[5]								X					X
Body Weight								X					X
Body Height													
Hematology								X					X
Clinical Chemistry								X					X
Urinalysis								X					X
[redacted]													
24 hour stool collection[9]								X					X
Bowel movements[10]	X	X	X	X	X	X	X	X					X
[redacted]													
Meal[11]						X	X	X					

[redacted]

Epoch	Treatment Period 2					Treatment Period 3							End of Study
Visit Name	Washout					Treatment					Washout		EOS
Visit Numbers[1]	304	305	306	307	399	401	402	403			404	499	599
Study Day(s)	12	13	14	15	16	17	18	19			20	21	22
Time (post-dose)	-	-	-	-	-	-	-	Predose: 0 H	2h	4h	-	-	-
Supplements[13]						X	X	X					
Dose administration[14]						X	X	X					
[redacted]													
Concomitant medications	X												
Serious Adverse Events	As Required												
Adverse Events	As Required												
[redacted]													
Subjects domiciled	Domiciled					X	Domiciled				X	X	X
Study completion information													X
Comments	As Required												
Safety Follow up Call													X[19]

[redacted]

S – to be collected only as Source data

[1] Visit structure given for internal programming purpose only
[2] Review of inclusion and exclusion criteria and current medical conditions is required before baseline evaluation
[3] Serum pregnancy test at Screening and EOS
[4] Urine pregnancy test
[5] pulse, blood pressure, temperature
[redacted]
[9] 24-hour Stool collection: stool pH, [redacted]
[10] To collect time, mass, and symptoms such as urgency, bloating; the Bristol Stool Chart will be used to document the consistency of the stool at each bowel movement
[11] PART A: Standardized breakfast meal contains 600 calories of either 50% CHO, 15% Protein, 35% Fat OR 25% CHO, 40% Protein, 35% Fat OR 0% CHO, 65% Protein, 35% Fat; all breakfast meals will be taken immediately after dosing with 50 mg LIK066 once daily
[12] Standardized breakfast meal to be given Day -1 through Day -3 (600 calories: 50% CHO; 15% Protein, 35% fat).
[13] PART B: All standardized breakfast meals (600 calories) will contain 50% CHO, 15% Protein, and 35% Fat and will be given immediately after LIK066 50 mg qd; the supplements given include either Psyllium 6 grams qd OR calcium carbonate 1 gram to be provided in a 4mL sugar free liquid formulation
[14] 50 mg LIK066
[redacted]
[19] A follow up call is required 30 days after EOS to check for SAEs

[redacted]

Details for highly repetitive assessments

[redacted]

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 review the Investigators proposed informed consent form to ensure it complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. Any further 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]

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 Site Operations Manual.

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 should be recorded rather than symptoms.

Subjects 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 Table 8-1 (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

Diarrhea is the primary endpoint in this study. PD parameters including glucose, insulin, glucagon and incretin hormones will be 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 Site Operations Manual regarding sample collection, numbering, processing and shipment.

8.5.1 Patient-Reported Outcome

[redacted]

8.5.1.3 Bowel movements

All bowel movements in this study will be captured in a stool diary and CRF that will include timing, weight, and symptoms such as urgency, bloating, flatus, and abdominal pain. In addition, the Bristol Stool Chart will be used to assess the stool consistency to determine the categorization of diarrhea.

[redacted]

[redacted]

8.6 Safety

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

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.

8.6.1 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

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

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

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.2 Vital Signs

- Body temperature
- Blood pressure (BP) systolic and diastolic
- Pulse Rate

8.6.3 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials (e.g., neutrophils, basophils, eosinophils, monocytes, and lymphocytes), erythrocyte sedimentation rate, and platelet count will be measured.

8.6.4 Physical Examination

See Site Operations Manual for details.

[redacted]

8.6.5 Clinical Chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.6 Urinalysis

Dipstick measurements for specific gravity, ketones, albumin, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

8.6.7 Body Height

Height will be measured.

8.6.8 Body Weight

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

[redacted]

[redacted]

[redacted]

[redacted]

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.

[redacted]

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 subjects 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.

[redacted]

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:
  - 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 Drug Safety & Epidemiology (DS&E) 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/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] 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.

[redacted]

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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

Follow the detailed instructions outlined in the Site Operations Manual 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 γGT) 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), or entered on the appropriate unscheduled local laboratory CRF.

[redacted]

- 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 gGT. If total bilirubin is elevated > 2 x 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 ≥ 24h) increase in serum creatinine of ≥ 25 % compared to baseline during normal hydration status, and deemed as a new onset renal events in subjects 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 (≥1+) proteinuria or hematuria

Every renal laboratory trigger or 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.

9.5 Reporting Medication errors including misuse/abuse

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

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

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

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 Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 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 Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

[redacted]

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.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 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.

9.8 Monitoring hypoglycemia

Because hypoglycemia is a potential risk of LIK066 treatment, glucose levels will be measured when a subject experiences a clinically symptomatic hypoglycemia. If a confirmed glucose level is <56 mg/dL by repeated measurement, study treatment will be discontinued and the patient will be treated by the clinical staff according to standard of care for hypoglycemia.

During the course of the study, if any patient experiences symptoms of hypoglycemia (shakiness, nervousness, hunger, nausea, palpitations, dizziness, or confusion), they will be instructed to seek immediate medical evaluation and treatment.

9.9 Monitoring orthostatic hypotension

Because orthostatic hypotension is a potential risk of LIK066 treatment, orthostatic blood pressure readings will be recorded throughout the study as shown in the Assessment schedule.

Any patient with clinically significant symptomatic orthostasis (more than 20 mmHg drop in systolic or 10 mmHg drop in diastolic blood pressure and increase in heart rate >20 bpm) will have the study treatment placed on hold. In addition, individuals with orthostasis will be treated with volume replacement according to standard of care (refer to Section 7.2 (Discontinuation of study treatment).

9.10 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 (Discontinuation of study treatment) 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).

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. Automatic validation programs check 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 Site Operations Manual 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.

[redacted]

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 or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or CRO working on behalf of Novartis 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 samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed locally and the 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 the treatment codes will be unblinded 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 for monitoring ketoacidosis will be established to assess suspected cases of ketoacidosis as described in the SOM.

11 Data analysis

All data analyses will be performed by study part.

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.

[redacted]

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 treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

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

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment sequence and subject.

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary endpoint will be the number of episodes of diarrhea per day. It is defined as the total number of stools with a BSC score of 6 or 7 per day.

11.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will be performed by study part. The daily number of diarrhea will be analyzed using a negative binomial mixed effects model with fixed effects of period, treatment, day, the period-by-day interaction, and the treatment-by-day interaction, and a random subject effect. An unstructured covariance matrix will be specified for the repeated observations on a subject within the same period. The least-squares mean and associated 80% CI for the number of diarrhea episodes per day for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model for each day, and summarized by a table and a line chart. Conclusions from the analysis will be based on treatment differences from all 3 days, collectively.

[redacted]

11.4.3 Handling of missing values/censoring/discontinuations

The primary analysis will be performed on all available data. There will be no imputation of missing data.

11.4.4 Sensitivity analyses

As a sensitivity analysis, the interaction between treatment and day will be assessed, and if non-significant, the results from the 3 days will be averaged and corresponding model-based quantities extracted.

Covariates such as baseline number of diarrhea may be included in the model when appropriate.

The model assumption of negative binomial distribution will be examined, especially if over-dispersion (i.e. variance>mean) exists. If the data doesn't fit negative binomial distribution or over-dispersion doesn't exist, other models such as Poisson regression will be explored.

The model assumption of no first-order carry-over effect may be evaluated by incorporating first-order carry-over effects into the above statistical model, and performing a type 3 test for the first-order carry-over effect.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The three-day total number of episodes of diarrhea per period will be summarized by treatment, and analyzed using a negative binomial model with fixed effects of subject, period and diet. The least-squares mean and associated 80% CI for the three-day total number of diarrhea episodes per period for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model, and summarized by a table and a line chart.

The model assumption of no first-order carry-over effect and the negative-binomial distribution may be evaluated in a similar fashion as the primary endpoint.

Other secondary endpoints include average consistency with Bristol stool chart, average stool pH, average stool weight over each 24 hour collection period. They will be summarized by treatment, and analyzed by a linear mixed model with fixed effects of subject, period, treatment, and baseline measurement. The least-squares mean and associated 80% CI for each treatment, and the estimated mean difference between each treatment, the p-value, and corresponding two-sided 80% CI, will be extracted from the model, and summarized by a table and a line chart.

[redacted]

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics for both observed values and change from baseline will be provided by treatment and visit.

ECG evaluations

All ECG data will be listed by treatment sequence, subject and visit/time, abnormalities will be flagged. Summary statistics for both observed values and change from baseline will be provided by treatment and visit.

Clinical laboratory evaluations

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

Adverse events

All information obtained on adverse events will be displayed by treatment sequence and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. An adverse event starting in one period/epoch and continuing into the next period/epoch is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period/epoch is only counted once towards the total of this body system and treatment.

Other safety evaluations

Immunogenicity

Not applicable.

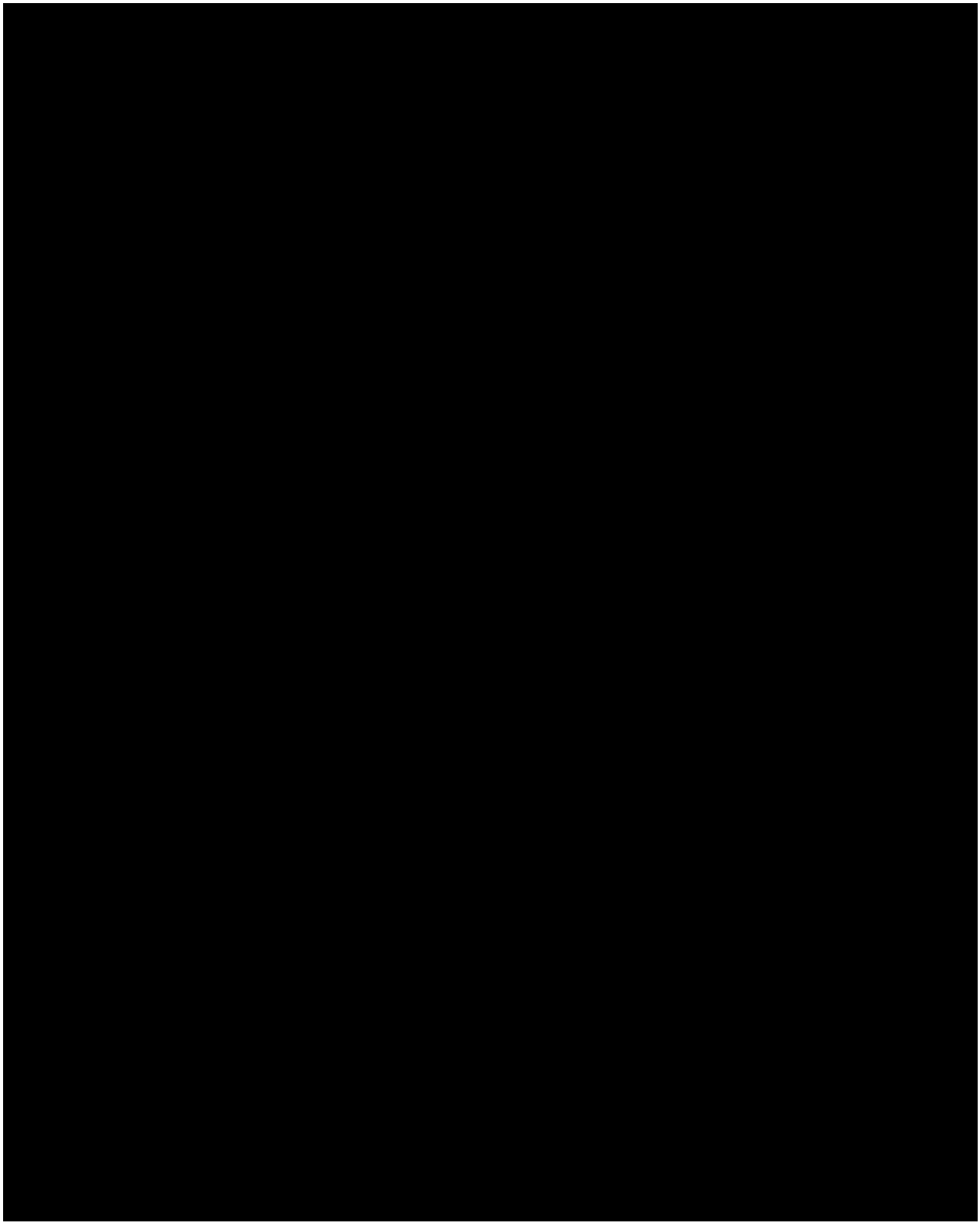
11.5.3 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.4 Other assessments

Not applicable.

[redacted]



11.7 Sample size calculation

The sample size justification for this study is based on internal data from Part 2 of the LIK066 obesity PoC study (LIK066X2201) on the 50 mg tid treatment regimen.

For patients on the 50 mg tid regimen, a mean (range) of 3.5 (0-12), 4.8 (0-18), and 3.9 (0-18) daily episodes of diarrhea were observed for Days 1, 2 and 3, respectively, of which 3.2 episodes occurred between the 1st and 2nd dose on Day 1. If the true effect of the low carb diet or of the supplements is a reduction in the number of episodes per day from a mean of 3 episodes per day on the high carb diet to 1.5 episodes per day, or from a mean of 5 episodes per day to 3 per day, then 5 subjects per sequence per study part (30 subjects total) with complete data will provide 80% power to detect the reduction. Assuming a drop-out rate of 37.5%, 8 subjects per sequence (48 total subjects) should be enrolled.

These results are based on 1000 simulated trials. For each simulated trial, the number of daily diarrhea episodes was generated from a Poisson distribution, where period-specific means, adjusted by the treatment effect, share a common gamma-distributed random subject effect in order to reflect a correlation between observations from the same subject. Only a single observation per-period for each subject was generated, reflecting one day of treatment. Each trial was analyzed using the GLIMMIX procedure in SAS, using a negative binomial model with fixed effects of treatment and period and normally distributed random subject effects, and assuming no carryover effects from one period to the next.

Two plausible scenarios for the variability of the number of daily diarrhea episodes were considered: (1) assuming the variability is as was observed in LIK066X2201, reflected by a dispersion parameter in the negative binomial model of 2.4, and (2) assuming the endpoint is less variable, reflected by a dispersion parameter of 1. In both scenarios, the power for detecting the reductions is at least 80%. Simulations were also performed under two additional scenarios where non-zero period effects were assumed (a sequential increase/decrease of 0.1 in the log scale), and these also demonstrated sufficient power with 5 completers per sequence.

11.8 Power for analysis of key secondary variables

Power for key secondary variables doesn't apply since there will be no formal hypothesis testing for the secondary variables.

11.9 Interim analyses

Refer to Section 3.5.

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.

[redacted]

14 References

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Martín MG, Turk E, Lostao MP, et al (1996) Defects in Na+/glucose cotransporter (SGLT1) trafficking and function cause glucose-galactose malabsorption. Nat. Genet. p. 216-20.

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[redacted]

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

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST £ 8 x ULN • 3 x ULN < ALT/AST £ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• 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 ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• 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)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• 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
Any AE potentially indicative of liver toxicity	• 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	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

[redacted]

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	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• 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 ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• 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 onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • 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.)

[redacted]

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. 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.	• 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:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* 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.

[redacted]