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LIK066

Clinical Trial Protocol CLIK066X2204

A 12-week randomized, patient and investigator blinded, placebo-controlled, parallel group study to investigate the efficacy of LIK066 in obese patients with non-alcoholic steatohepatitis (NASH)

Document type:	Amended Protocol Version
EUDRACT number:	2017-002046-71
Version number:	v03 (Clean)
Clinical Trial Phase:	Phase II
Release date:	29-August-2019

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form 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 Chief Medical Office and Patient Safety (CMO&PS) **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
ALP	alkaline phosphatase
ALT	alanine aminotransferase
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AST	aspartate aminotransferase
b.i.d	twice a day
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CPK	creatine kinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	coefficient of variation
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
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IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL1b	Interleukin 1 beta
INR	International Normalized Ratio
IRB	Institutional Review Board

IRT	Interactive Response Technology
LDH	lactate dehydrogenase
LFT	Liver function test
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MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
p.o.	oral
PD	pharmacodynamic(s)
PDFF	Proton Density Fat Fraction
PK	pharmacokinetic(s)
qd	once a day
RBC	red blood cell(s)
SAE	serious adverse event
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SGLT	Sodium glucose co-transporter
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
t.i.d	thrice a day
T2DM	Type 2 Diabetes Mellitus
TBL	total bilirubin
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ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

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]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Tmax	The time to reach the maximum concentration after drug administration [time]

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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of 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, follow-up) which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
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

Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
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
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
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 occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol Synopsis

Protocol number	CLIK066X2204
Full Title	A 12-week randomized, patient and investigator blinded, placebo-controlled, parallel group study to investigate the efficacy of LIK066 in obese patients with non-alcoholic steatohepatitis (NASH)
Brief title	Study to assess efficacy of LIK066 in obese patients with non-alcoholic steatohepatitis (NASH)
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the effects of LIK066 on liver function tests (LFT) and a variety of metabolic and inflammation biomarkers in patients with phenotypic non-alcoholic steatohepatitis (NASH) after 12 weeks of treatment. Data from this study will be used to support further development of LIK066 in the treatment of patients with NASH.
Primary Objective(s)	• To determine the effect of LIK066 on Liver Function test (circulating ALT) after 12 weeks of treatment
Secondary Objectives	• To determine the effect of LIK066 on intrahepatic lipid as measured by percent liver fat by MRI after 12 weeks of treatment • To determine the effect of LIK066 on total body weight after 12 weeks of treatment • To determine the effect of LIK066 on non-invasive markers of liver fibrosis after 12 weeks of treatment • To determine the safety and tolerability of LIK066 as measured by adverse events and safety laboratory tests • To evaluate the pharmacokinetics (Cmax, Tmax and AUClast) of LIK066 in NASH patients • To determine the effect of LIK066 on circulating aspartate aminotransferase (AST) after 12 weeks of treatment.
Study design	This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study in patients with NASH. The study will consist of a screening period up to 28 days, baseline period up to 14 days, treatment period of 12 weeks followed up by a study completion evaluation approximately 28 days after the final drug administration. Finally, there will be a safety follow up phone call 30 days after the last visit.

Population	The study population will be comprised of male and female adult overweight or obese patients with EITHER histologic evidence of NASH on liver biopsy within 2 years prior to randomization and elevated ALT OR phenotypic diagnosis of NASH based on elevated ALT, elevated BMI and diagnosis of Type 2 diabetes (T2D) by HbA1c
Key Inclusion criteria	Presence of NASH as demonstrated by ONE of the following: **EITHER** Histologic confirmed NASH based on liver biopsy obtained 2 years or less before randomization with a , fibrosis level of F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases **AND** ALT ≥ 50 IU/L (males) or ≥ 35 IU/L (females) at screening **OR** Phenotypic diagnosis of NASH based on presence of ALL THREE of the following at screening: • ALT ≥ 50 IU/L (males) or ≥ 35 IU/L (females) **AND** • BMI ≥ 27 kg/m2 (in patients with a self-identified race other than Asian) or ≥23 kg/m2 (in patients with a self-identified Asian race) **AND** • Diagnosis of Type 2 diabetes mellitus by HbA1C: ≥ 6.5% and ≤ 10%
Key Exclusion criteria	• Use of GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide; SGLT-2 inhibitors such as canagliflozin, empagliflozin or dapagliflozin; Thiazolidinediones (TZDs) such as pioglitazone; FXR agonists such as obeticholic acid (OCA) and any pharmacologically active weight-loss medications such as lorcaserin prior to 6 weeks of screening visit and up to end of study visit • eGFR ≤ 45ml/min/1.73m^2 based on MDRD equation • Patients on treatment with the following medicines **unless** they are on a constant dose for ≥3 months before randomization: anti-diabetic medications, insulin (if ≥25% change in dose), beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 400 IU/day; doses > 800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control • Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) • Presence of cirrhosis on liver biopsy or clinical diagnosis of cirrhosis • Type I diabetes and uncontrolled diabetes defined as HbA_{1c} > 10 % within 60 days prior to enrollment. • Patients with contraindications to MRI imaging

	• For those patients that have had a previous liver biopsy: Significant weight loss (>15%) or change in clinical status (in the opinion of the investigator) since the diagnostic liver biopsy to screening • History or presence of other concomitant liver diseases • Clinical evidence of hepatic decompensation or severe liver impairment. • History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline. • History of inflammatory bowel disease. • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study • History of ketoacidosis, lactic acidosis, or hyperosmolar coma OR if occurring between Screening Visit and Randomization Visit. • History of lower limb amputation (including toe amputation) OR if occurring between Screening Visit and Randomization Visit. • Any history of and/or suspected Fournier's gangrene
Study treatment	Study treatments are defined as: • 50 mg LIK066 tablets • 10 mg LIK066 tablet • Matching placebo tablets Initially, patients will be randomly assigned to one of the following two treatments in a ratio of 2:1: A: LIK066 150 mg B: Matching placebo A third, 30 mg qd arm (C) will be initiated after 33 patients have been enrolled in the initial two arm portion of the study. The randomization will change to a 2:4:1 ratio (150 mg: 30 mg: placebo) to maintain a 2:2:1 ratio across the three arms (150 mg:30 mg: placebo) at study end.
Pharmacokinetic assessments	• Cmax • Tmax • AUClast
Efficacy/PD assessments	• Circulating alanine aminotransferase (ALT) • Circulating aspartate aminotrasferase (AST) • Proton Density liver fat fraction (PDFF) by MRI • Anthropometric assessments • Markers of liver fibrosis Commercially Confidential Information

Key safety assessments	• Physical Examination • Vital Signs • Laboratory Evaluations • Electrocardiogram • Pregnancy assessments • Urinalysis
Other assessments	Commercially Confidential Information
Data analysis	The change from baseline to week 12 in ALT is the primary efficacy variable Commercially Confidential Information

Key words	SGLT inhibitors; Non-alcoholic steatohepatitis (NASH)

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, type 2 diabetes (T2DM) and importantly non-alcoholic fatty liver disease (NAFLD). While there are as yet no medications approved for treatment of NAFLD, numerous medicines are available to treat other obesity-related diseases. Interestingly, relatively few agents that are effective, safe or scalable to the size of the affected population are available for the treatment of obesity itself (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).

The presence of obesity and insulin resistance, often with clinical features of the metabolic syndrome, leads to a high-risk profile for the development of NAFLD. NAFLD is one of the most common liver diseases worldwide with a global prevalence estimated at 25% (Younossi et al 2016). Estimates of obesity among patients diagnosed with NAFLD by imaging show that more than 50% are obese albeit with regional variations; 64% for Asians, 37% for Europeans and 57% for North Americans (Younossi et al 2016). NAFLD encompasses a broad spectrum of disease severity, ranging from isolated steatosis to its more severe form with variable degrees of hepatocyte inflammation, necrosis and liver fibrosis, known as nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and end stage liver disease (Musso et al 2016; Calzadilla and Adams 2016). In support of the link between obesity and fatty liver linked hepatic injury, weight loss either through bariatric surgery, diet or exercise leads to improvement in histologic NASH. This suggests that targeting obesity in NASH patients is likely to limit or reverse liver disease progression (Lassailly et al 2015, Vilar-Gomez et al 2015)

LIK066 is a potent inhibitor of the sodium glucose co-transporters 1 and 2 (SGLTs) that decreases absorption of glucose in the gut and reabsorption in the kidney (Chao and Henry 2010). In the normal state, 90% of the filtered glucose is reabsorbed by SGLT2 in the proximal convoluted tubule cells of the kidney, with the remaining 10% reabsorbed by the SGLT1. Inhibition of SGLT2 results in benign glucosuria, decreased blood glucose and modestly lower body weight in healthy subjects and patients with T2DM (Bays 2013). 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. Combined SGLT1 and SGLT2 inhibition therefore offers the potential for improved efficacy over SGLT2 selective inhibitors in both lowering blood glucose and body weight.

LIK066 is an investigational dual SGLT1/2 inhibitor which is being developed as a novel treatment for obesity. Single and multiple doses of LIK066 induced glucosuria in healthy volunteers (HVs) and patients with T2DM, and significantly lowered glucose area under the time-concentration curve (AUC) after an oral glucose tolerance test (OGTT) in patients with T2DM. LIK066 was found to be safe and tolerated, had a favorable pharmacokinetic profile, and resulted in up to 3% placebo-adjusted weight loss over just 2 weeks in both healthy subjects and patients with T2DM. LIK066 at 150 mg daily dose (as qd, bid or tid) results in a significant

weight loss in obese patients (~ 6%) after 12 week treatment. Furthermore, twelve week treatment with LIK066 at 150 mg qd in normoglycemic and dysglycemic subjects was generally safe and well tolerated with diarrhea observed as a dose-limiting toxicity.

This study is a non-confirmatory, proof of concept study and is planned to assess the safety, tolerability and effect of LIK066 on serum ALT levels after 12 weeks of treatment with either LIK066 (150 mg OR 30 mg once daily) or placebo in either overweight or obese patients with type II diabetes mellitus (T2DM) OR patients with histologic evidence of NASH based on liver biopsy and elevated ALT levels.

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1.2 Nonclinical data

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1.2.1 Teratogenicity and reproductive toxicity data

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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.

Treatment with LIK066 at 150 mg qd for 12 weeks was also shown to be safe and tolerated. AEs were predominantly diarrhea, GI related and were observed after single 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 or magniture of any specific laboratory abnormality or in the number of subjects observed to have an abnormality. 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.

1.3.2 Human pharmacokinetic data

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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 significant lowered 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 purpose of this study is to assess the effects of LIK066 on a variety of metabolic and inflammation biomarkers in patients with NASH.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To determine the effect of LIK066 on Liver Function Test after 12 weeks of treatment	• Circulating alanine aminotransferase (ALT) levels

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To determine the effect of LIK066 on intrahepatic lipid after 12 weeks of treatment.	• Percent (%) Liver fat as measured by Magnetic Resonance Imaging (MRI-PDFF)
• To determine the effect of LIK066 on total body weight after 12 weeks of treatment	• Percent change in total body weight
• To determine the effect of LIK066 on non-invasive markers of liver fibrosis after 12 weeks of treatment	• Enhanced liver fibrosis panel (ELF: PIIINP, TIMP-1, and Hyaluronic acid)
• To determine the safety and tolerability of LIK066	• Adverse events, safety laboratory tests including basic chemistry profile and liver biochemical tests
• To evaluate the pharmacokinetics (PK) of LIK066 in NASH patients	• Cmax, Tmax, AUClast
• To determine the effect of LIK066 on aspartate aminotransferase (AST) after 12 weeks of treatment	• Circulating aspartate aminotransferase (AST) levels

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study in patients with NASH. The sponsor will remain unblinded to the treatment assignment of all patients to allow for continuous unblinded safety monitoring. The study will consist of a 28 day screening period (Day -44 to Day -16), a baseline period of 14 days (Day -15 to Day -1), a treatment period of 12 weeks (Day 1 to Day 84), and a study completion evaluation approximately 28 days after the last drug administration. Finally, there will be a safety follow up phone call 30 days after the last visit. The patients will be advised to maintain their recommended diet during the study. The study design scheme is shown below.

Patients will be required to fast overnight for at least 8 hours before each clinic visit for blood collection and at least 3-4 hours before MRI procedure where applicable. Patients who meet the inclusion/exclusion criteria at screening will present to the study site for baseline assessments, including determination of the percent liver fat content

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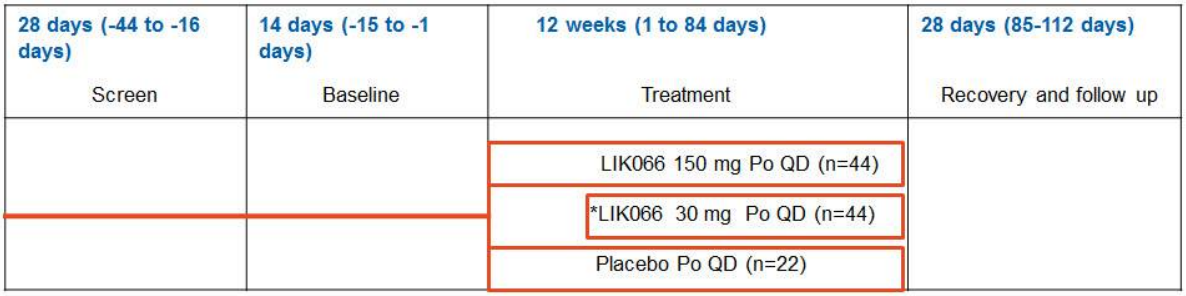
All baseline safety evaluation results must be available prior to the first dosing. At the beginning of the study after eligibility has been confirmed, patients will be randomized in a 2:1 ratio to receive either LIK066 at 150 mg qd OR matching placebo qd, by oral administration. A third, 30 mg qd arm will be initiated after 33 patients have been enrolled in the initial two arm portion of the study. For the entire study, patients will be randomized to either LIK066 at 150 mg qd, 30 mg qd or matching placebo at a ratio of 2:2:1. The placebo group will be supplemented by an equal number of historic controls from trials such as the FLINT study (Neuschwander-Tetri et al 2015) Commercially Confidential Information

As reflected in the inclusion criteria, Asians tend to have NASH at much lower BMI. Therefore, patients with Asian race will be stratified by BMI of <30 kg/m2 or ≥30 kg/m2 at baseline, all other patients will be stratified by BMI of<35 kg/m2 or ≥35 kg/m2 at baseline. The Asian race will be based on the patient self-report captured on the demography eCRF. Finally, patients identifying themselves as Pacific Islanders will be grouped with the non-Asian group.

Figure 3-1 Study Schematic



*30 mg dose arm to start after 33 patients have enrolled into initial two arms of 150mg and placebo cohorts at a 2:1 randomization ratio. After the enrollment of these 33 patients, the randomization will change to a 2:4:1 ratio (150 mg: 30 mg: placebo) to maintain a 2:2:1 ratio across the three arms (150 mg:30 mg: placebo) at study end. Total of approximately 110 subjects will enroll in the study.

The first dose of study medication will be administered to patients under study site personnel supervision with meal on Day 1. Patients will be provided with a supply of study medication and allowed to leave the site to continue the study as outpatients. Detailed instructions for taking study treatment will be provided in the Site Operations Manual (SOM). Patient compliance will be tracked by pill counts at each visit, patient diaries and PK sampling as indicated in the assessment Table 8-1. Patients will continue to take study medication once daily for twelve weeks (Day 2 to Day 84), as instructed by the investigator. Patients will return to the clinical site once weekly for the first 2 weeks (Days 7 and 14) and then return to the clinical site every 2 weeks (days 28, 42 and 56). On day 56, the patients will take the study medication at the site prior to breakfast, following which pharmacokinetic sampling will occur for up to 6 hours post dose. Patients will return to the clinic on Day 84 for study assessments including MRI evaluation at the end of treatment. Finally, there will be an end of study (EOS) evaluation visit approximately 28 days after the last drug administration.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, blood chemistry, urinalysis,) adverse event and serious adverse event monitoring.

Refer to the Assessment Schedule for details of safety, PK, and PD assessments

3.2 Rationale of study design

This randomized, multi-center, patient and investigator blinded, placebo-controlled study is designed to assess the efficacy of LIK066 relative to placebo in patients with NASH.

The completed study will enroll 110 patients who will be randomized in a 2:2:1 ratio to 150 mg daily, 30 mg daily and placebo. However, at the beginning of the study, patients will be enrolled into only two arms: 150 mg daily dose and placebo, randomized at 2:1.

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In order to maintain the scientific integrity of the study, the investigators and patients will remain blinded to their treatment allocation.

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the Novartis Clinical Trial Team (CTT) will be unblinded throughout the study.

To ensure that no bias is introduced by imbalance of severity of disease across different arms of the study, patients will be stratified to active or placebo arms on the basis of BMI.

Currently there is no approved pharmacotherapy for patients with NASH. All patients will be encouraged to adhere to local advice regarding diet and exercise regimens. To keep the dietary intake as constant as possible during the study, patients participating in this study will be advised to adhere to American Heart Association (AHA) diet or equivalent if there is a country specific recommended diet.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The primary efficacy endpoint for dose/exposure-response analysis for LIK066, from previously completed clinical studies, was body weight loss, and other pharmacodynamic endpoints such as urinary and plasma glucose.

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Of note, in the 12 week study in obese patients, the 150 mg daily dose was generally safe and well tolerated. The primary AE was diarrhea, which did not lead to any discontinuation of treatment or patient withdrawals from the study.

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Body weight loss is an important factor in therapeutic development for NASH as weight loss through either bariatric surgery or life style modification deters progression of the disease (Lassailly et al 2015, Vilar-Gomez et al 2015).

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Furthermore, exposure of LIK066 in non-cirrhotic NASH patients (patient population in this study) is anticipated to be in the range of that observed in previous studies since these patients are not expected to have hepatic dysfunction.

The duration of the study is based on findings in published literature relating to Obeticholic acid and elafibranor (Mudaliar et al 2013; Neuschwander-Tetri et al 2015; Ratziu et al 2016), which demonstrate that 12 weeks will provide an ample time frame to test biochemical changes likely to result from improvement to the NASH phenotype. In addition observations from other studies with surgical, diet and pharmacotherapy including Novartis' diacylglycerol acytransferase 1 inhibitor(LCQ908; pradigastat) suggest that 12 weeks is also an adequate timeframe to test an effect on liver fat.

3.4 Rationale for choice of comparator

A placebo will be used as a comparator to provide estimates of net drug effects for efficacy and safety/tolerability assessments.

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

There is no anticipated therapeutic benefit expected for patients participating in this study although a small amount of weight loss may be anticipated. The risk to patients 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 7.1.

Risks of LIK066 administration in human subjects may include the development of gastrointestinal adverse reactions, urinary tract infection, , postural hypotension due to volume depletion, ketoacidosis, renal and hepatic toxicity, changes in calcium homeostasis with subsequent effects on bones, hypoglycemia and genitourinary infections (including necrotizing fasciitis of the genitalia and perineum commonly referred to as Fournier's gangrene (see Section 9.8.4).

Doses of LIK066 proposed in this study have been tested and deemed safe in healthy subjects. Patients should be monitored closely and treated according to the standard of care if deemed necessary by the principal investigator.

In long-term clinical studies in patients with T2DM with CVD or at high risk for CVD, an increase in cases of lower limb amputation (primarily of the toe) has been observed with the SGLT-2 inhibitor canagliflozin (Neal et al 2017). No increased risk of lower limb amputations has been reported for other SGLT2 inhibitors. In addition, no lower limb amputations have been seen in LIK066 studies to date, but since this risk may constitute a possible class affect, patients with a higher risk for amputation events should be instructed on routine preventative foot care and maintaining adequate hydration.

LIK066 is considered an aneugen at extremely high doses. With the doses and treatment duration proposed in this study, at least 20-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 must 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.

Blood samples will be collected frequently during the study either via venipuncture or cannula. 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.

MRI makes use of powerful magnetic fields and radio waves, which are believed to cause no direct adverse consequences when used within FDA-approved specifications. No MRI contrast will be administered in this study. Thus in principle, MRI scans can be repeated in the same patient as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons; therefore, sensitivity to enclosed spaces should be queried at screening. Refer to eligibility criteria (Section 4.2) to exclude patients who are not suitable candidates for MRI scanning.

3.6.1 Blood sample volumes

Approximately 325 mL of blood is planned to be collected over a period of approximately 22 weeks, from each patient as part of the study. Additional samples required for monitoring of any safety findings would be in addition to this volume. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Table 8-1 Assessment Schedule.

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information will be contained in the Central Laboratory Manual

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4 Population

Patients with a phenotype consistent with NASH

The study population will be comprised of male and female adult overweight or obese patients with EITHER histologic evidence of NASH on liver biopsy within 2 years prior to randomization and elevated ALT OR phenotypic diagnosis of NASH based on elevated ALT, Type 2 diabetes mellitus by elevated HbA1c and increased BMI; full details are outlined in Section 4.1 (Inclusion criteria). Approximately 110 patients will be randomized in the study. At least 88 subjects are expected to complete the study.

4.1 Inclusion criteria

Patients with a phenotype consistent with NASH, 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. Presence of NASH as demonstrated by ONE of the following:

   EITHER

   Histologic confirmed NASH based on liver biopsy obtained 2 years or less before randomization with a fibrosis level of F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases **AND** ALT ≥ 50 IU/L (males) or ≥ 35 IU/L (females) at screening.

   OR

   Phenotypic diagnosis of NASH based on presence of ALL THREE of the following at screening:

   - ALT ≥ 50 IU/L (males) or ≥ 35 IU/L (females) **AND**
   - BMI ≥ 27 kg/m2 (in patients with a self-identified race other than Asian) or ≥23 kg/m2 (in patients with a self-identified Asian race) **AND**
   - Diagnosis of Type 2 diabetes mellitus by HbA1C: ≥ 6.5% and ≤ 10%
3. Patients must weigh no more than 150 kg (330 lbs.) to participate in the study. Inclusion of subjects with higher weights up to 200 kg (440 lbs.) may occur if a MRI scanner with a table weight of 200kg (440 lbs.) is available.
4. Male and female patients 18 years or older (at the time of the screening visit)
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Patients with a phenotype consistent with NASH, fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. History or presence of other concomitant liver diseases including:
   - Hepatitis B or C virus (HCV, HBV) infection. Patients with history of HCV who attained sustained virologic response more than 3 years prior to screening are **not** excluded.
   - Primary biliary cholangitis (PBC)
   - Primary sclerosing cholangitis (PSC)
   - Alcoholic liver disease
   - Definite autoimmune liver disease or overlap hepatitis
   - Suspected or confirmed Gilbert's syndrome
   - Known bile duct obstruction
   - Suspected or proven hepatocellular cancer

2. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   - History of familial long QT syndrome or known family history of Torsades de Pointes in a first degree relative.
3. Use of GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide; SGLT-2 inhibitors such as canagliflozin, empagliflozin or dapagliflozin; Thiazolidinediones (TZDs) such as pioglitazone; FXR agonists such as obeticholic acid (OCA) and any pharmacologically active weight-loss medications such as lorcaserin prior to 6 weeks of screening visit and up to end of study visit.

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6. Patients with contraindications to MRI imaging, including:
   - Brain aneurysm clip
   - Implanted neural stimulator
   - Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires
   - Prosthetic heart valves
   - Cochlear implant
   - Ocular foreign bodies that might be ferromagnetic (e.g., metal shavings)
   - Other implanted medical devices (e.g., insulin pumps)
   - Metal shrapnel or bullets still in the body
   - Severe claustrophobia despite use of anxiolytics
   - Tattoos (as determined by the Investigator and Imager)
   - Weight in excess of MRI machine capacity
   - Joint replacements
7. Inability to reliably quantify alcohol consumption based upon local study physician judgment.
8. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average).

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10. Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities:
    - Serum albumin < 32 g/L
    - INR > 1.3
    - Direct bilirubin > 13 mg/L
    - ALT or AST > 8× ULN
    - Alkaline Phosphatase > 3 × ULN
    - History of esophageal varices, ascites or hepatic encephalopathy
    - Splenomegaly

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12. Presence of cirrhosis on liver biopsy or clinical diagnosis of cirrhosis.

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16. Patients taking medications prohibited by the protocol. See Section 5.2 for further details.
17. For those patients that have had a previous liver biopsy: Significant weight loss (>15%) or change in clinical status (in the opinion of the investigator) since the diagnostic liver biopsy to screening (refer to Section 4.1 #3).

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22. History of non-alcohol drug abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline.

23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using basic methods of contraception during dosing and for 5 days (approximately 5 times the terminal half life) after stopping study medication. **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 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.
    - Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. 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), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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The investigator must ensure that all patients being considered for the study meet the above eligibility criteria.

Patient selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Provided patients meet all other eligibility criteria, patients with a single lab value outside of the allowable range may be considered eligible for enrolment, as long as the abnormal lab value is within 10% of the allowable value. Platelets and eGFR values must always fall inside the allowable range as listed in the inclusion and exclusion criteria.

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

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and must agree that in order to participate in the study they must adhere to the contraception requirements specified in Section 4.2 (Exclusion criteria). If there were any question that the patient would not comply reliably, they should not be entered or continue in the study.

Male patients should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after screening.

Table 5-1 Prohibited medication

Medication	Prohibited period
GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide	See Exclusion criteria (Section 4.2)
SGLT2 inhibitors such as empagliflozin, canagliflozin, dapagliflozin OR ertugliflozin	See Exclusion criteria (Section 4.2)
Pharmacologically active weight-loss medications (eg. lorcaserin, phentermine/topiramate, bupropion-naltrexone HCL, orlistat)	See Exclusion criteria (Section 4.2)
Treatment with drugs that alter intestinal motility (e.g. erythromycin, metoclopramide, tegaserod, methylnaltrexone, alvimopan, loperamide, diphenoxylate and atropine (Lomotil) and difenoxin and atropine (Motofen))	From 7 days prior to screening to EOS visit
Treatment with drugs that have a high incidence of diarrhea (e.g. Orlistat, Acarbose).	From 7 days prior to screening to EOS visit
Chronic systemic steroid treatment or systemic steroids for > 7 consecutive days for worsening of an underlying condition.	From 4 weeks prior to screening to EOS visit
Treatment with or use of strong inhibitors of CYP3A4/5 including boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, fazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. Strong CYP3A inducers including avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort.	See Exclusion criteria (Section 4.2)
General UGT inhibitors including probenecid and valproic acid.	See Exclusion criteria (Section 4.2)

Table 5-2 Permitted medications if dose is stable (within 25 percent of current dose) for at least 3 months prior to randomization

Medications
Oral anti-diabetic medications such as metformin, sulfonylureas or DPP-4 inhibitors
Insulin*
Beta-blockers and thiazide diuretics
Fibrates, statins, niacin, ezetimibe**
Vitamin E (400-800 mg)***
Thyroid hormone
Psychotropic medications (phenothiazines or second generation antipsychotics)
Estrogen or estrogen containing birth control
*unless adjustment is required due to intercurrent illness; **unless adjustment is required to treat medically significant increases in LDL that have been confirmed upon repeat testing; ***Only applicable for patients taking ≥400 IU/day

5.3 Dietary restrictions

- Subjects will be asked to fast for approximately 8 hours overnight on certain days where blood samples will be collected to measure various biomarkers and will be asked to fast at least 3-4 hours before MRI procedures as described in the SOM.
- Patients should maintain their usual physical activity and dietary habit and can drink water *ad libitum* to ensure adequate hydration during the study.
- Patients may reduce their carbohydrate intake in order to alleviate diarrhea, the primary adverse events associated with LIK066 administration with meals that contain high percentage of carbohydrate.
- To keep the dietary intake as consistent as possible, patients participating in this study will be counseled regarding appropriate exercise and diet per local standards, e.g. instruction to carefully adhere to American Heart Association (AHA) diet or equivalent if there is a country specific recommended diet.

5.4 Other restrictions

No initiation of strenuous physical exercise (e.g. weight training, aerobics, football) until after Study Completion evaluation.

6 Treatment

6.1 Study treatment

The study treatment includes once a day administration of either LIK066 (150mg) OR LIK066 (30mg) OR placebo for 12 weeks. 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 drug(s)

The investigational drug, LIK066 and matching placebo, will be prepared by Novartis and supplied to the Investigator site as double blinded patient packs and will be dispensed based on the IVRS. Study treatments are defined as:

- 50 mg LIK066 tablets
- 10 mg LIK066 tablets
- Matching placebo tablets

6.1.2 Additional study treatment

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

6.2 Treatment arms

Initially patients will be assigned to one of the following two treatments (A or B) in a ratio of 2:1. Study treatments are defined as:

A: LIK066 150 mg

B: Matching placebo

A third, 30 mg qd arm (C) will be initiated after 33 patients have been enrolled in the initial two arm portion of the study. The randomization will change to a 2:4:1 ratio (150 mg: 30 mg: placebo) to maintain a 2:2:1 ratio across the three arms (150 mg:30 mg: placebo) at study end.

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual patients by way of a randomization number. Randomization numbers will be assigned in ascending, sequential order to eligible patients via an IRT system (see Site Operations Manual for details).

The randomization number is only used to identify which treatment the patient has been randomized to receive. The Patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on patient numbering, please see 'Patient numbering' section in the Site Operations Manual.

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

6.4 Treatment blinding

This is a patient and investigator-blinded study. Patients and investigators will remain blinded to study treatment throughout the study, except where indicated below.

Drug product will be supplied as a double blinded patient packs and the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single patient at site for safety reasons (necessary for patient management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff

The sponsor will remain unblinded to the treatment assignment of all patients to allow for continuous unblinded safety monitoring throughout the study.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly but may be unblinded through communication of drug re-supply needs via the IRT system.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project while the study is ongoing.

Table 6-3 Blinding levels

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6.5 Treating the subject

LIK066 will be administered to the subject via the oral route. Patients will be provided with a supply of study medication to self administer once daily for 12 weeks (Day 2 to Day 84) before lunch. See the Site Operations Manual for further details.

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

6.6 Permitted dose adjustments and interruptions of study treatment

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

6.7 Emergency breaking of assigned treatment code

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

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

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

In addition, the investigator must inform the patient on how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given patient and whether the patient can continue in the study.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with LIK066, as detailed in Section 8.7.

The investigator must promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the Investigator and/or study personnel at each visit using pill counts and information provided by the patient. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.9 Recommended treatment of adverse events

Treatment of AEs may be considered at the discretion of the Investigator. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF. In case of intolerable diarrhea, see SOM for guidelines on management of diarrhea.

6.10 Concomitant treatment

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 patient 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 patient 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 patients 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. Documentation of attempts to contact the patient should be recorded in the source documentation.

7.2 Discontinuation of study treatment

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

Study treatment must be discontinued under the following circumstances:

- Patient decision - patients may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the patient or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the patient's safety
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting)
- Discontinuation may be considered when patients have to be treated by prohibited medications on a case by case basis.

- Use of prohibited treatment as per recommendations in Table 5-1
- Hypersensitivity (CTCAE grade 2 or higher) reaction to LIK066 requiring intervention.
- Clinically significant diarrhea, suspected to be related to the study drug and not responsive to recommended management per SOM that may put the patient at risk (identified by investigator after consultation with the sponsor)
- 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 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 consultation with the sponsor
- 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.
- For ALT, AST, total bilirubin and/or alkaline phosphatase elevations mandating study treatment discontinuations, please refer to Section 9.3 and Table 9-1 and Table 9-2 for further instructions and monitoring. Of note, ALT and AST are abnormal at baseline in this study. Thus only elevation to >2X of the baseline value will trigger events listed in Section 9.3.
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the patient, in the opinion of the investigator

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Discontinuation of study treatment and patient withdrawal may occur, under the following circumstances:

- Any protocol deviation that results in a significant risk to the patient's safety in the opinion of the investigator.
- If continuation in the study is deemed detrimental to the patient's well-being in the opinion of the investigator.

The appropriate personnel from the study site and Novartis (including the CTT, medically qualified representatives of the Sponsor, and the investigator) will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

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

Patients 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 (see Section 7.3, Withdrawal of Informed Consent). Where possible, they should return for the assessments as 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 patient/pre-designated contact as specified in Section 7.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule. The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

The investigator must also contact the IRT to register the patients's discontinuation from study treatment.

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 occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand 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.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the Assessment Schedule (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.4 Lost to follow-up

For patients 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 patient 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 severity of adverse events will be graded by the study site Investigator (or designee) based on clinical judgment and captured in the CRF AE page. This information will be used to quantify events that may lead to patient's discontinuation or stopping dose arms or the study.

The study will be placed on hold pending full review of all available clinical safety data and discussion with the Investigator if any of the following occur and may be stopped or amended based on the outcome of the full safety review.

- One patient on study drug experiences any adverse event that is CTCAE Grade 4 or higher that is classified as related to study drug.
- Two or more patients on study drug experience a similar adverse event that is a CTCAE Grade 3 or higher other than ALT elevation.
- The Principal Investigator and the Sponsor consider that the number and/or severity of adverse events justify discontinuation of the study.
- The Sponsor unilaterally requests it.

Safety reviews for study stopping will be conducted jointly between medically qualified representatives of the Sponsor and Investigator and a joint decision will be made.

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, patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

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	Baseline	Treatment										EOS[2]	Follow up Phone call
Visit Name	Screening	Baseline	Treatment										EOS	
Visit Numbers[1]	1	101	201[3]	202[3]	203[3]	204[3]	205[3]	206				207[3]	399	
Days	-44 to -16	-15 to -1	1	7	14	28	42	56				84	112	142
Time (post-dose)	-	-	0h	-	-	-	0h	0h[3]	1h	2h	4h	6h	0h	-	
Informed consent[4]	X														

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Inclusion / Exclusion criteria	X	X													
Medical history/current medical conditions	X														
Demography	X														
Alcohol Test and Drug Screen	X	X													
Hepatitis and HIV Screen	X														
Pregnancy and assessments of fertility[6]	X		X			X		X					X	X	
Physical Examination	X	X				X		X					X	X	
Body Temperature	X	X	X	X	X	X	X	X					X	X	
Body Height	X														
Body Weight	X	X	X	X	X	X	X	X					X	X	
Waist and hip circumference	X	X	X										X	X	
BMI	X	X	X	X	X	X	X	X					X	X	
waist:hip ratio	X	X	X										X	X	
Blood Pressure and Pulse Rate[7]	X	X[8]	X	X	X	X[8]	X	X[8]					X[8]	X	
ECG evaluation	X	X											X	X	
Blood chemistry	X	X		X	X	X		X					X	X	

Epoch	SCREENING	Baseline	Treatment											EOS[2]	Follow up Phone call
Visit Name	Screening	Baseline	Treatment											EOS	
Visit Numbers[1]	1	101	201[3]	202[3]	203[3]	204[3]	205[3]	206					207[3]	399	
Days	-44 to -16	-15 to -1	1	7	14	28	42	56					84	112	142
Time (post-dose)	-	-	0h	-	-	-	0h	0h[3]	1h	2h	4h	6h	0h	-	
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Hematology	X	X		X	X	X		X					X	X	
Urinalysis	X	X			X	X		X					X	X	
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Coagulation Panel[10]	X	X												X	
Commercially Confidential Information															
PK blood collection					X	X	X	X	X	X	X	X	X		
Commercially Confidential Information															
Dose administration			X[14]												
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MRI[16]		X											X	X[17]	
Comments	As required														
Concomitant therapies	X[18]														
Study completion information														X	
Adverse Events	As required														X
Serious Adverse Events	As required														X

[1] Visit structure given for internal programming purpose only
[2] If a patient withdraws from the study, or if study medication is discontinued for any reason, the patient should be scheduled for a subsequent visit at which time all assessments at the EOS visit should be performed.
[3] All assessments to be performed pre-dose
[4] Informed consent must be provided by all patients before any screening procedures are performed.Commercially Confidential Information

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[6] Serum pregnancy tests will be performed at Screening and end of study; urine tests may be used at other timepoints.
[7] Blood pressure and pulse rate will be measured in a sitting position unless otherwise noted.
[8] Measured in sitting and standing positions to assess orthostatic hypotension.
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[10] Coagulation panel includes PT/INR and aPTT

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[14] Patients will be provided with a supply of study medication to self administer once daily for 12 weeks (Day 2 to Day 84). Patients should bring all used and unused medications, and diaries, to each visit.

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[16] MRI of abdomen and liver in all subjects. Quantification of liver fat will be performed on all subjects;
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[17] Assessment is only to be performed at EOS if a patient withdraws from the study, or discontinues study treatment early for any reason.
[18] A thorough review of any concomitant medications (including medication name, dose, unit, frequency, and route) should be performed at every visit.

8.2 Informed consent procedures

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the patient agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient 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 patient.

Ensure patients are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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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

It is permissible to re-screen a patient 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

Pertinent demographic and baseline characteristic data will be collected on all patients. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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

8.5 Efficacy / Pharmacodynamics

Efficacy of LIK066 will be assessed based on the following assessments:

- Liver function tests (ALT and AST)
- Proton Density Liver Fat Fraction (PDFF) by Magnetic Resonance Imaging (MRI)
- Anthropometric assessments (Height, Body Weight, BMI and waist:hip ratio)
- Markers of liver fibrosis

Pharmacodynamic samples will be collected at the time points defined in the Assessment schedule. Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. Pharmacodynamic (PD) samples will be obtained and evaluated in all patients at all dose levels.

8.5.1 Clinical Outcome Assessments (COAs)

Not applicable.

8.5.2 Body Weight

- Body weight (to the nearest 0.1 kilogram [kg] will be measured on a calibrated scale. The measurement can be performed with the study subject in underwear and without shoes; or while wearing minimal indoor clothing as indicated in Section 8.1 (Assessment schedule). However, body weight measurements must be performed in a consistent manner across all visits for a given patient. Voiding before weight measurement is required. Details of these assessments will be provided in the site operations manual.
- Body mass index (BMI) will be calculated as (Body weight (kg) / [Height (m)]^2)

8.5.3 Body Height

Height will be measured at screening visit and will be used to calculate BMI.

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8.5.5 MRI

Patients will undergo magnetic resonance imaging twice during the course of the study (Baseline and End of Treatment) to quantitate liver fat,
as outlined in Section 8.1 (Assessment schedule). End of Treatment assessment is not to be performed if the patient prematurely discontinues treatment prior to Week 8.

8.5.6 Liver function tests

ALT, AST, GGT, ALP (total), total bilirubin, and albumin will be assessed as indicated in the Assessment schedule. The effect on circulating ALT levels will be the primary efficacy variable for this study.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reactive bilirubin will be quantified.

ALP isoenzymes and 5'NT will also be measured but will not form part of the screening requirements or safety data set.

The methods for assessment and recording are specified in the laboratory manual. Some of the liver function tests may be completed as part of the blood chemistry panel.

8.5.7 Markers of Liver Fibrosis

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- Enhanced liver fibrosis Test (ELF) panel: the following will be assessed: hyaluronic acid (HA), tissue inhibitor of metalloproteinases (TIMP-1), and amino-terminal pro-peptide of procollagen type III (PIIINP).

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Additional information is provided in the site operations manual and central laboratory manual. These markers will be assessed as indicated in Section 8.1 Assessment schedule.

8.5.8 Waist circumference, Hip circumference and waist:hip ratio

Waist and hip circumference will be measured to the nearest 0.1 cm at visits indicated in Table 8-1. Waist:hip ratio will be measured as described in SOM

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.

8.6.1 Alcohol Test and Drug Screen

All patients will be screened for alcohol and substances of abuse. See the Site Operations Manual for details.

8.6.2 Body Temperature

Body temperature will be measured as stated in the SOM.

8.6.3 Blood chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CRP, γGT, glucose, LDH, CPK, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid. If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.4 Blood Pressure and Pulse Rate

- Blood pressure (BP)
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
- Pulse

8.6.5 Hepatitis and HIV Screen

All patients will be screened for HIV, Hepatitis B and C. See the Site Operations Manual for details.

8.6.6 Hematology

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

Coagulation parameters including aPTT, PT and INR will also be assessed; methods for assessment and recording are provided in the central laboratory manual.

8.6.7 Pregnancy and assessments of fertility

Pregnancy Testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing will be required.

8.6.8 Physical Examination

See Site Operations Manual for details.

8.6.9 Urinalysis

Urine test by dipstick: Leukocytes, Nitrite, pH, Specific gravity, Protein, Glucose, Ketones, Urobilinogen, Bilirubin, Blood/hemoglobin.

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

8.6.10 ECG evaluation

Details of assessment of ECG are provided in SOM. Measurement parameters: PR interval, QRS duration, heart rate, RR, QT, QTc. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

8.7 Pharmacokinetics

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8.8 Other assessments

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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 patient or clinical investigation patient *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 patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination finding, laboratory test finding, or other assessments.

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for liver and kidney related events are included in Section 9.3 and Section 9.4, 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 Common Toxicity Criteria (CTC) AE grade (version 4.0 or higher) for the adverse event. If CTC-AE grading does not exist for an adverse event, use:

1 = mild

2 = moderate

3 = severe

4 = life threatening* (see Section 9.2 for definition of a serious adverse event (SAE))*Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

CTC-AE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).

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)

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

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (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 patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (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 patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit] must be reported to Novartis **within 24 hours of learning of its occurrence** as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by patients 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 patient 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 patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed. The following two categories of laboratory abnormalities and AEs have to be considered during the course of the study 1) Liver laboratory triggers which will require repeated assessments of the abnormal laboratory parameter and 2) Liver events which will require close observation, follow up monitoring,and the completion of the standard base liver eCRF pages.

Please refer to Table 9-1 for complete definitions of liver events.

Table 9-1 Liver Event Definitions

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

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

Follow-up of liver events

Every liver event defined in Table 9-1 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 9-2.

For liver laboratory triggers

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation within the next 7 days. If any of the lab tests described in Table 9-1 are abnormal, all tests should be repeated. These liver chemistry repeats should preferentially be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For Liver Events

- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event

Thorough follow-up of the liver event should include:

- Repeating liver chemistry tests to confirm elevation as appropriate. Testing should include PT/INR ALT, AST, ALP, 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 should be done once a week if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution or stabilization as described above.
- 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 9-3.
- Imaging such as abdominal US, CT or MRI, as deemed appropriate by the investigator
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultation.

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

Table 9-2 Actions required for Liver Events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 10 × ULN	• Repeat within 48 hr • If elevation persists, discontinue drug • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN AND INR > 1.5	• Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 10 × ULN	• Repeat LFT within 1 week • If elevation persists continue follow up, • If elevation persists for more than 3 weeks discontinue drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN AND accompanied by symptoms[b]	• Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN if normal baseline or >2 x baseline if elevated before drug exposure (patient is asymptomatic)	• Repeat LFT within 1 week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN if normal baseline (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN if normal baseline (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation from baseline is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	• Discontinue the study drug immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study drug interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Table 9-3 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
Primary biliary cholangitis	• Anti-mitochondrial antibody

9.4 Renal safety monitoring

9.4.1 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended actions and follow-up assessments are listed in Table 9-4 and Table 9-5, respectively.

Table 9-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase > 50 % compared to baseline	Confirm > 50 % within 24-48 hours after receipt of the abnormal value If confirmation of abnormal value is not possible in this timeframe study drug must be withheld until further evaluation is possible Consider drug interruption Consider patient hospitalization / specialized treatment
Albumin- or Protein-creatinine ratio increase ≥ 2-fold compared toscreening or baseline levels whichever is higher New onset dipstick proteinuria ≥ 3+ Protein-creatinine ratio (PCR) ≥ 1000 mg/g or ≥ 100 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider drug interruption / discontinuation
New onset dipstick glucosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New onset dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR

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

Whenever a renal event is identified, a detailed patient 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 9-5 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. Monitor patient regularly (frequency at investigator's discretion) until:	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output • 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.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (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 9-6 summarizes the reporting requirements.

Table 9-6 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

9.6 Pregnancy reporting

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

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

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

The study drug must be discontinued, though the patient 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 patient 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 (email) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

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

9.8 AEs of special interest

9.8.1 Ketoacidosis

In rare cases, SGLT-2 inibitors can lead to ketoacidosis. Therefore, investigators must pay close attention for any signs of ketoacidosis. Signs and symptoms of ketoacidosis may include deep and rapid breathing, nausea, vomiting, severe abdominal pain, confusion, unusual fatigue or sleepiness and coma. All signs and/or symptoms and results from relevant laboratory tests must be reported on the AE eCRF. If ketoacidosis is confirmed, the study treatment should be handled as per Section 7.2 and appropriate measures must be taken to correct the acidosis and monitor glucose levels according to standard of care.

Every case of ketoacidosis must be reported to the Ketoacidosis adjudication committee and the ketoacidosis adjudicaton eCRF must be completed.

9.8.2 Hypoglycemia

Stopping rule for 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 may be discontinued and the patient will be treated according to standard of care for hypoglycemia.

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

Education and reporting of hypoglycemia:

Patients with T2DM, treated with antidiabetic medications, especially with sulphonyurea or insulin, may be at increased risk of hypoglycemia. The doses of antidiabetic medications should be adjusted in patients, who, according to the investigator, could be at a safety risk of developing severe hypoglycemia. Every patient (all diabetic patients) must be educated regarding hypoglycemic symptoms and treatment. This education should include general review of hypoglycemia and use of glucometer as follows:

- Explain of possible triggers of hypoglycemia (eg, strenuous exercise, delayed meals, changes in meal composition, illness, etc.).
- Explain the symptoms of hypoglycemia such as dizziness, lightheadedness; palpitations, heart racing/pounding, shaking; sweating, hunger, blurred vision, impairment of motor function, confusion.
- Review of appropriate treatment for hypoglycemic events (oral glucose intake).

Each patient will receive a home glucose monitor with all appropriate supplies. When a subject experiences symptoms of hypoglycemia, blood glucose should be measured. At any time when the subject experiences symptoms of hypoglycemia, the subject should treat the event as appropriate. Information related to the event should be recorded in the glycemia study diary as follows:

- The glucose value.
- Circumstances (strenuous exercise, delayed or missed meals, alcohol consumption etc.) under which the hypoglycemic event occurred.
- Time of occurrence in relation to the last medication and to the last meal intake.
- Time when the event starts and ends.
- Additionally, if a subject performs routine self-monitoring of blood glucose, any asymptomatic plasma glucose < 70 mg/dL (< 3.9 mM) should be treated and recorded in the glycemia study diary.

The subject must return the study diary at the next scheduled visit.

9.8.3 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).

9.8.4 Fournier's gangrene

FDA recently issued a safety warning about reported occurrences of a rare but serious and life-threatening infection of the genitals and area around the genitals, necrotizing fasciitis of the genitalia and perineum, commonly referred to as Fournier's gangrene (FG), associated with the SGLT2 inhibitor class of drugs for the treatment of type 2 diabetes. Outcomes have included hospitalizations, multiple surgeries, and death. This serious medical condition requires urgent antibiotics and surgical intervention. While no such cases have been reported with clinical trials of LIK066, patients who present with pain, tenderness, erythema or swelling of the genitals and the perineum along with fever or malaise, should be evaluated for necrotizing fasciitis of the genitals and perineum. If FG is suspected, LIK066 treatment should be discontinued and appropriate medical (including broad-spectrum antibiotics) and surgical treatment initiated as appropriate.

In general, subjects receiving LIK066 should be instructed to pay attention to genital hygiene and have appropriate hydration to reduce the risk of development of genitourinary infections including Fournier's gangrene.

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 data capture requirements (i.e. eSource or eCRFs) 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 data capture / data entry, 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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and 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 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 (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

Novartis (or a designated CRO) will 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 (or designated CRO) 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 centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

MRI data will be collected by the sites and will be transferred to imaging CRO for analysis. The data will then be electronically sent to Novartis.

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

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

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

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

11 Data analysis

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

11.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment received. The safety analysis set will include all patients who received any study drug.

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

The PD analysis set will include all patients 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 group and subject. Summary statistics will be provided by treatment group.

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

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment group and patient.

11.4 Analysis of the primary variable(s)

The primary objective of this study is to assess the efficacy of LIK066 on ALT in NASH patients during 12 weeks of treatment.

11.4.1 Primary Variable(s)

Change from baseline to Week 12 in ALT is the primary efficacy variable. ‘Baseline’ is defined as the mean of ALT levels at baseline (V101) and pre-dose (V201) visits.

11.4.2 Statistical model, hypothesis, and method of analysis

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11.4.3 Handling of missing values/censoring/discontinuations

Commercially Confidential Information

11.4.4 Sensitivity analyses

Commercially Confidential Information

Commercially Confidential Information

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

The secondary PD variables of this study are:

- Intrahepatic lipid: Percent (%) Liver fat as measured by Magnetic Resonance Imaging (MRI).
- Anthropometric assessments: Weight, BMI, waist-to-hip (WTH) ratio
- AST: Change from baseline to week 12
- Non-invasive markers of liver fibrosis:
  - Enhanced liver fibrosis panel (ELF)

Baseline for all secondary parameters is defined as the last measurement prior to the first dose except for AST where baseline is the mean at baseline (V101) and pre-dose (V201) visits.

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11.5.2 Safety

Vital signs

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

ECG evaluations

All ECG data will be listed by treatment group, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Selected lab markers such as AST, bilirubin, ALP, GGT, creatinine and BUN will be analyzed using the repeated measures ANCOVA as described in Section 11.4.2.

Adverse events

All information obtained on adverse events will be displayed by treatment group and patient.

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

11.5.3 Pharmacokinetics

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11.5.4 Pharmacokinetic / pharmacodynamic interactions

Commercially Confidential Information

11.5.5 Other assessments

Not Applicable.

11.6 Analysis of exploratory variables (if applicable)

Commercially Confidential Information

Commercially Confidential Information

11.6.1 Exploratory biomarkers

Commercially Confidential Information

11.7 Sample size calculation

Commercially Confidential Information

11.8 Power for analysis of key secondary variables

Commercially Confidential Information

11.9 Interim analyses

Commercially Confidential Information

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 by 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.

12.4 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

13 Protocol adherence

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

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

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request.

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