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LIK066

Clinical Trial Protocol CLIK066X2205

A randomized, subject- and investigator-blinded, placebo-controlled pharmacodynamic study of oral LIK066 in overweight and obese women with polycystic ovary syndrome

Document type:	Amended Protocol Version
EUDRACT number:	2017-001373-16
Version number:	v02 (Clean)
Clinical Trial Phase:	II
Release date:	20-Sep-2017

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

ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	coefficient of variation
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulfate
ECG	electrocardiogram
EDxx	effective dose xx%
EDC	Electronic Data Capture
ELISA	enzyme-linked immunosorbent assay
FAI	free androgen index
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram(s)
mL	milliliter(s)
NOEL	no observed effect level
p.o.	oral
PCOS	polycystic ovary syndrome
PD	pharmacodynamic(s)

RBC	red blood cell(s)
SAE	serious adverse event
SD	standard deviation
SGLT	sodium glucose co-transporter
SHBG	sex hormone-binding globulin
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T	testosterone
T2D	type 2 diabetes mellitus
TBL	total bilirubin
t.i.d.	three times a day
ULN	upper limit of normal
ULQ	upper limit of quantification
UTI	urinary tract infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

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.
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”
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.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CLIK066X2205
Full Title	A randomized, subject- and investigator-blinded, placebo-controlled pharmacodynamic study of oral LIK066 in overweight and obese women with polycystic ovary syndrome
Brief title	Study of pharmacodynamics of LIK066 in overweight and obese women with polycystic ovary syndrome
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The purpose of the study is to evaluate whether LIK066 can be developed for the treatment of polycystic ovary syndrome (PCOS) in overweight and obese women
Primary Objective(s)	To assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in subjects with PCOS
Secondary Objectives	To assess the safety and tolerability of LIK066 in subjects with PCOS To evaluate the treatment effect of LIK066 on gonadotropins and sex steroid levels on Day 15
Study design	This is a randomized, subject- and investigator-blinded, placebo-controlled, parallel group, non-confirmatory study in overweight and obese PCOS subjects. Approximately 24 subjects will be randomized in a 1:1 ratio to LIK066 or placebo (12 subjects on LIK066; 12 on placebo). The treatment period is 2 weeks; dosing is oral, 50 mg of LIK066 or matching placebo three times daily before meals for 14 days and a single dose on Day 15 in the morning before the test meal. Each subject will participate in a screening period of up to 6 weeks, a baseline assessment, a treatment period of 2 weeks, and a follow-up period of about 1 week with an end of study visit on approximately Day 22. At screening, subjects should report to the study site after an overnight fast of at least 8 hrs. Blood samples for eligibility criteria should be collected preferably before 8 am. The baseline visit includes an optional overnight stay (starting Day -2). Serial blood samples for hormone levels will be collected between approximately 6 am and 8 am on the following morning (Day -1), followed by a test meal for breakfast (without drug administration) and serial post-prandial blood sampling over a 4 hour period. The investigator must randomize eligible subjects on, or prior to, Day 1. During the treatment period, a follow-up visit should be conducted on Day 8 to check tolerability, safety and compliance. This visit may be conducted either by phone or in person at the site, at the discretion of the investigator. On Day 14, subjects should return to the site for a repeat optional overnight stay to include an overnight fast of at least 8 hours. On Day 15, serial blood samples will be collected during fasting between approximately 6 am and 8 am. This will be followed by last dose administration and by a repeat

	breakfast test meal, similar in composition to the baseline one. Serial blood samples will be collected over the 4 hour post-prandial period. The investigator will discharge subjects after completing Day 15 assessments. The End-of study visit occurs on approximately Day 22, for study completion evaluations. This visit may be performed earlier in the case of early termination.
Population	Approximately 24 subjects with polycystic ovary syndrome (PCOS) will be enrolled in the study. Replacement subjects should be enrolled if subjects are discontinued from the study for reasons other than safety. If more than 2 subjects experience menstrual bleeding during the study, additional subjects may be enrolled to account for those subjects in case they are excluded from the pharmacodynamic analysis set (if ovulation is confirmed based on progesterone assessment). The number of enrolled subjects; excluding replacements, should not exceed 30.

Key Inclusion criteria	• Overweight/obese women with PCOS aged 18 to 40 years, inclusive
	• PCOS diagnosed as:
	  • Hyperandrogenism, clinical OR biochemical, AND
	  • Amenorrhea or oligomenorrhea (less than 8 menses within the last 12 months) AND
	  • Exclusion of other causes of hyperandrogenism (see exclusion criteria)
	• Indicators of reduced insulin sensitivity at screening defined as:
	  • Sex hormone binding globulin, SHBG < LLN OR
	  • Fasting insulin above the median of normal range of assay used
	• Overweight/obese female subjects with BMI ≥ 27kg/m^2 and stable weight +/- 3 kg over previous 3 month (by history)
	• Subjects must use non-hormonal methods of contraception from enrollment until one week after last dose.

Key Exclusion criteria	• Subjects with pre-existing type 1 or type 2 diabetes mellitus, Cushing's syndrome, congenital adrenal hyperplasia, ovarian or adrenal androgen-secreting tumor, uncontrolled thyroid disease, untreated obstructive sleep apnea
	• Subjects with oophorectomy or exogenous causes of hirsutism (such as drug-induced)
	• Menstruation in the 30 days prior to screening or prior to the initiation of treatment (Day 1)
	• Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
	• Abnormal screening labs defined as:
	  • Early morning total testosterone levels ≥ 2.5× ULN or ≥ 200 ng/dl
	  • DHEAS > 2× ULN or > 700 mcg/dl
	  • Prolactin > ULN on early AM sample (allow repeat × 1 for borderline levels, enroll based on 1 normal level)
	  • 17-OHP levels (early AM sample) > 200 ng/dl
	  • TSH levels > 10 uUI/ml and clinical symptoms of hypothyroidism. Subjects with sub clinical hypothyroidism do not need to be excluded. Subjects well controlled on thyroid medication can be enrolled
	• Symptomatic genital or urinary tract infection (UTI) in the 4 weeks prior to screening or the presence of active UTI at screening
	• On-going participation in a weight loss program such as with exercise, diet or drugs.
	• History of significant gastrointestinal surgery or current clinically significant GI disorders
	• Use of prohibited medications.

Study treatment	The investigational drug, LIK066 50 mg and matching placebo tablets will be prepared by Novartis and supplied as single blinded patient specific kits, to be dispensed by the unblinded pharmacist at the investigator site according to the randomization schedule. Subjects will receive either: • LIK066 50 mg three times daily before breakfast, lunch and dinner. • Matching placebo tablets three times daily before breakfast, lunch

Efficacy/PD assessments	• Average of morning fasting free testosterone concentrations • Secondary variables include gonadotropins and sex steroids
Key safety assessments	• Vital signs, ECG and laboratory assessments including serum electrolytes and hematocrit • Physical examination • Adverse events

Data analysis	The primary efficacy endpoint is the average of the three fasting am free testosterone samples. The primary analysis will assess the treatment effect of LIK066 on free testosterone at Day 15. The ratio of Day 15 to baseline free testosterone will be analyzed in an analysis of covariance model with treatment as a categorical factor and baseline free testosterone as a covariate. The logarithm of the ratio and of baseline free testosterone will be applied prior to the analysis. The geometric mean of the ratio to baseline for free testosterone will be estimated from the model for LIK066 and placebo, along with the treatment ratio and the associated p-value and two-sided 90% confidence interval. From these quantities, the following criteria will be assessed: 1. the upper confidence limit of the 90% CI is less than 1, and 2. the estimated treatment ratio is less than 0.75. The first criterion addresses with high certainty whether the effect of LIK066 on free testosterone reduction is superior to placebo. The second criterion addresses whether the observed treatment effect of LIK066 on free testosterone reduction is at least 25%. An effect size of 20-25 % on hyperandrogenism is considered to be clinically meaningful in PCOS as it correlates with improved ovulation and fertility.
Key words	Polycystic ovary syndrome, overweight, obese, testosterone, insulin

1 Introduction

1.1 Background

Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in women, affecting approximately 5–10% of women throughout their reproductive age (Legro et al 2013). The various definitions of PCOS share common features of hyperandrogenism, clinical and/or biochemical and amenorrhea/oligomenorrhea. The NIH definition of PCOS will be used in this study (Legro et al 2013).

About 28% of obese women have PCOS based on an obese population referred for weight loss interventions (Sirmans and Pate 2014). Obesity is also a risk factor for PCOS, with weight gain reported prior to the diagnosis of PCOS. Weight loss is commonly used as a therapeutic approach for PCOS. Insulin resistance affects 50%–70% of women with PCOS and occurs independently of obesity (Dunaif et al 1989). However, the effect of obesity on insulin resistance is additive to that of PCOS. Clinical manifestations of PCOS can be heterogenous and include features such as hirsutism, acne, obesity, menstrual dysfunction, infertility, and metabolic syndrome (Legro et al 2013). Over time, women with PCOS are at an increased risk of developing type 2 diabetes (T2D) and cardiovascular disease (Legro et al 2013). There is no cure for PCOS. Treatment involves management of symptoms by lifestyle modification such as weight loss, cosmetic interventions, pharmacotherapy for hirsutism, menstrual irregularities and infertility treatments. Metabolic modulation (e.g., metformin) is also used off-label (Legro et al 2013).

Insulin resistance is a common feature of PCOS across the weight spectrum, partly reflecting an intrinsic element of resistance with exacerbation by obesity. The insulin resistance appears to be tissue specific primarily affecting skeletal muscle and adipose tissue, but not ovarian and adrenal tissues. The compensatory hyperinsulinism has tissue-selective effects, which include aggravation of hyperandrogenism, primarily by stimulating activity of the cytochrome P450c 17α in the ovary (Rosenfield and Ehrmann 2016). Hyperinsulinism also acts on the liver to decrease the production of sex hormone binding globulin (SHBG), thus leading to increased circulating levels of free androgens; and possibly at the level of the pituitary gonadotropes, by increasing production of luteinizing hormone (LH), which in turn stimulates ovarian steroidogenesis (Rosenfield and Ehrmann 2016).

Interventions that reduce serum insulin levels such as metformin, insulin-sensitizing thiazolidinediones, and weight loss result in significant improvement of hyperandrogenemia and ovulation in PCOS (Legro et al 2013). Pilot trials in PCOS with a short 10-day course of diazoxide, an inhibitor of insulin secretion, have shown significant reduction in circulating androgen levels (Nestler et al 1989). Metformin lowers insulin levels primarily by reducing hepatic glucose output and opposing glucagon-mediated signalling in the liver, and to a lesser extent by increasing glucose uptake in skeletal muscle (Pernicova and Korbonits 2014). Randomized controlled trials with metformin in PCOS have shown an improvement in androgen measures of about 20% when compared to placebo (Harborne et al 2003). Dapagliflozin, a sodium–glucose cotransporter (SGLT) 2 inhibitor approved for T2D, is currently in a phase 3 clinical trial in PCOS, with and without metformin or exenatide to evaluate the relationship of insulin resistance, body weight and effects on hyperandrogenemia

(NCT02635386). There is a clear association between hyperinsulinism and hyperandrogenism in PCOS and clinical evidence that lowering insulin levels and/or increasing insulin sensitivity improve hyper androgenism and ovulation in these patients.

Sodium–glucose cotransporters (SGLT) 1 and 2 play an important role in glucose homeostasis with SGLT1 being the primary transporter responsible for absorption of glucose and galactose in the intestine, and SGLT 2 being the primary transporter responsible for renal glucose reabsorption (Kalra 2014, Sands et al 2015). SGLT2 inhibitors are approved for the treatment of type 2 diabetes, acting primarily by increasing urinary glucose excretion (UGE) and improving glycemic control. Blockade of enteric SGLT1 results in glucose and galactose malabsorption (Sands et al 2015). There are no approved dual inhibitors of SGLT 1 and 2. Sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, is in Phase III trials for diabetes, type 2 and type 1.

LIK066 is a highly selective, safe and potent dual SGLT1/2 inhibitor that is in development at Novartis for obesity. In humans, the pharmacodynamic effects of LIK066 include increased urinary glucose excretion (UGE), and inhibition of glucose absorption from the gut. Body weight loss has been demonstrated in a phase 2a trial in obesity. LIK066 significantly reduces post-prandial glucose and insulin excursions in , obese populations and T2D populations. This effect is observed with single dose and is acute, meaning that it is observed on the meal immediately following dosing and not 6 hours later, which suggests a direct lumenal effect on gut SGLT1 inhibition. This effect is also dose dependent, with maximal post-prandial insulin suppression at 50 mg or higher. Fasting insulin and glucose levels are not significantly affected by LIK066. To date, there are no data on the effect of LIK066 on androgen levels.

This is a mechanistic study that aims to evaluate whether cumulative post-prandial reduction in insulin levels with LIK066 over a short treatment period will improve circulating androgen levels in overweight and obese women with PCOS. This study could support the evaluation of PCOS in the development plans for the obesity indication.

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

1.4 Study purpose

The purpose of the study is to evaluate whether LIK066 can be developed for the treatment of polycystic ovary syndrome (PCOS) in overweight and obese women.

2 Objectives and endpoints

2.1 Primary objective

Primary objective	***Endpoints related to primary objective***
• To assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in overweight and obese subjects with PCOS	• Change in average morning fasting free testosterone blood concentrations from baseline to Day 15

2.2 Secondary objectives

Secondary objectives	***Endpoints related to secondary objectives***
• To assess the safety and tolerability of LIK066 in overweight and obese subjects with PCOS throughout the study.	• Adverse events throughout the study, serum electrolytes and hematocrit on Day 15
• To evaluate the treatment effect of LIK066 on gonadotropins and sex steroid levels on Day 15	• LH, FSH, SHBG, androstenedione, DHEA, DHEAS, Total testosterone, free androgen index (FAI)

3 Investigational plan

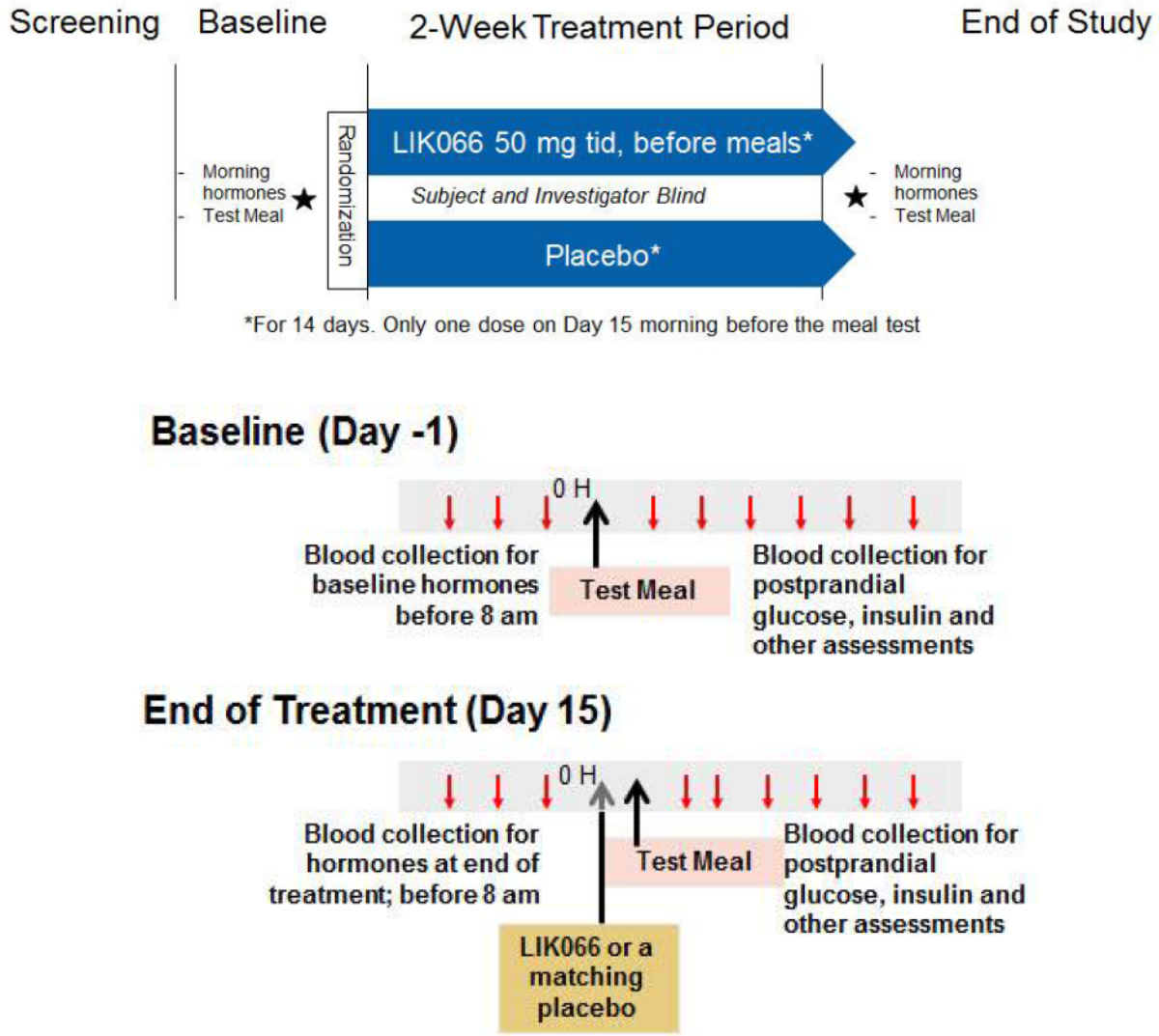
3.1 Study design

This is a randomized, subject- and investigator-blinded, placebo-controlled, parallel group, non-confirmatory study in overweight and obese PCOS subjects.

Approximately 24 subjects will be randomized in a 1:1 ratio to LIK066 or placebo (12 subjects on LIK066; 12 on placebo). Discontinued subjects may be replaced. If more than 2 subjects experience menstrual bleeding during the study, additional subjects may be enrolled to account for those subjects in case they are excluded from the pharmacodynamic analysis set (if ovulation is confirmed based on progesterone assessment). The number of enrolled subjects; excluding replacements, should not exceed 30.

The treatment period is 2 weeks; dosing is oral, just before meals, 50 mg of LIK066 or matching placebo t.i.d. for 14 days and only one dose in the morning on Day 15.

Figure 3-1 Study design



Each subject will participate in a screening period of up to 6 weeks, a baseline period (including an optional overnight stay at the study site), a treatment period of 2 weeks (outpatient visits and one optional overnight stay at end of treatment), and a follow-up period of about 1 week with an end of study visit on approximately Day 22. A subject's duration of participation in the study is up to a total of 9 weeks inclusive of the 6-week screening window.

At screening, subjects should report to the study site after an overnight fast of at least 8 hrs. Blood samples for eligibility criteria should be collected during fasting preferably before 8 am. Subjects who meet all eligibility criteria at screening will be admitted for baseline evaluations.

The baseline visit (Day -1) includes an optional overnight stay (starting Day -2) and an 8-10 hour overnight fast. Serial blood samples for hormone levels will be collected between approximately 6 am and 8 am the following morning (Day -1), followed by the test meal for breakfast (without drug administration) and serial post-prandial blood sampling over a 4 hour period. No other food is allowed during this time.

If the time interval between the screening and baseline visits is more than 21 days or if there is any significant changes in the subject's health condition reported during this interval, then baseline safety labs must be reviewed by the investigator to ensure eligibility criteria (related to safety) continue to be met and to then enable randomization. The investigator must randomize eligible subjects on, or prior to, Day 1 (i.e. assign randomization numbers provided by Novartis as described in the Site Operation Manual; SOM). The site staff must provide subjects with study drug and instructions on drug administration immediately before meals, three times a day. The site staff should inform subjects that they are to avoid high carbohydrate meals in order to minimize GI discomfort with dosing (Details provided in the SOM). The site staff must also make the subjects aware of the symptoms of hypotension, hypoglycemia and ketoacidosis during the dosing period as described in the informed consent form (ICF).

The site staff must also instruct subjects on proper hydration and proper genito urinary hygiene during dosing, as described in the SOM.

During the treatment period, a follow-up visit should be conducted on Day 8 to check tolerability, safety and compliance. This visit may be conducted either by phone or in person at the site, at the discretion of the investigator.

On Day 14, subjects should return to the site for an optional overnight stay. The end of treatment assessment will take place on Day 15 after an overnight fast of at least 8 hours. On Day 15 morning, serial blood samples will be collected during fasting between approximately 6 am and 8 am. This will be followed by last dose administration and by a repeat breakfast test meal, similar in composition to the baseline test meal. Serial blood samples will be collected over the 4 hour post-prandial period. No other food is allowed during this time. The investigator will discharge subjects after completing Day 15 assessments.

The End-of-Study visit will occur on approximately Day 22, for study completion evaluations. This visit may be performed earlier in the case of early termination.

At baseline, the physical examination should include cutaneous manifestations of hyperandrogenism, e.g. hirsutism, acne, androgenic alopecia, as well as acanthosis nigricans and skin tags; baseline measures of body weight, waist circumference, hip circumference and waist/hip ratio. The medical history should include the approximate onset of the last menstrual period and prior history of gestational diabetes.

In this study, endocrine assessments include total testosterone, free testosterone, LH, FSH, SHBG, estradiol, progesterone, DHEAS, DHEA, androstenedione, insulin and glucose. Safety assessments throughout the study will include vital signs, physical examinations, ECGs, standard clinical laboratory evaluations (blood chemistry, hematology, urinalysis), adverse events and serious adverse events.

The test meal consists of a glucose drink containing a total of 75 grams of glucose and food containing fat and protein (meal composition: approximately 50% kcal carbohydrates, 30% kcal fat and 20% kcal protein- approximately 600 kcal in total).

The assessments schedule and the SOM provide additional details.

3.2 Rationale of study design

- **Randomization** reduces the risk of imbalances in baseline subject characteristics between groups, and reduces the risk of bias in the interpretation of pharmacodynamic, safety and tolerability endpoints.
- **Subject- and investigator-blinding** minimizes bias in adverse event reporting by subjects and investigators and in causality assessments by investigators.
- **Parallel treatment arms:** A crossover design would be impractically long due to the need of a prolonged wash-out period to enable the pituitary-gonadal function to get back to baseline.
- **Placebo comparator** supports the analysis of the treatment effect of LIK066 on pharmacodynamic markers, especially given the risk of confounding effects due to biologic and analytic variability of androgen levels in women. Including a placebo arm also helps for causality evaluation of adverse events in relation to study drug, study procedures and/or underlying disease.
- **Domiciling** controls for confounders that influence the circadian rise in testosterone levels, such as overnight fast; enables serial sampling of fasting testosterone over the time period of peak secretion (between about 6 am and 8 am); and ensures an adequate fasting period prior to the breakfast meal, which is important for assessing the treatment effect of LIK066 on insulin secretion.
- **Free testosterone (T) as primary end-point:** Free T and not total T, is considered to be more sensitive as a diagnostic marker of hyperandrogenism in women with PCOS. Total testosterone has inadequate sensitivity to differentiate between normal and PCOS women. Free T is also the biologically active form of testosterone and, unlike total T, free T may significantly change in response to treatment effects on SHBG.

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

The dosing regimen for LIK066 in this study is 50 mg orally (or matching placebo), t.i.d. before each main meal (Quaque ante cibum, q.a.c.) (before breakfast, lunch and dinner) for 14 days. The last dose will be administered on Day 15 morning before the test meal.

LIK066 regimens of either 50 mg or 150 mg once a day are approximately ≥ ED80 for maximal urine glucose excretion (UGE), and are predicted to be ≥ ED90 for body weight loss, reflecting dual SGLT1 and SGLT2 inhibition (internal data analysis). At these doses, LIK066 has been shown to reduce post-prandial incremental insulin and plasma glucose in a dose-dependent manner in clinical studies in healthy, obese and T2D subjects.

Dose level: Gut inhibition of SGLT1 by LIK066 is expected to inhibit absorption of prandial glucose, resulting in lower post-prandial serum glucose excursions and lower post-prandial insulin release. Corporate Confidential Information

In patients with PCOS, reduction of insulin levels by about 25 %, e.g. with metformin, has been associated with improved hyperandrogenism and subsequent ovulation (Harborne et al 2003). Corporate Confidential Information

Dosing regimen of t.i.d. and q.a.c (before each meal): The post-prandial effect of LIK066 on glucose and insulin is observed on the meal that immediately follows dosing, and not significantly with later meals, possibly due to limited lumenal exposure time to LIK066. For example, an LIK066 dose of 150 mg induced acute reduction of post-prandial glucose and insulin but had no apparent effect on a test meal given approximately 6 hours post-dose as reported in the IB. For this reason, LIK066 will be administered immediately before each of the main meals; breakfast, lunch and dinner, i.e. t.i.d. and q.a.c. to ensure repeated pharmacologic reduction in insulin response per meal. This regimen is expected to induce a more sustained reduction in cumulative insulin levels at least during the daytime.

Safety and tolerability: The local gut lumenal exposure to LIK066 has been associated with GI symptoms, notably diarrhea and flatulence that are temporally related to meal intake with dosing. This has been reported with 50 mg, 75 mg and 150 mg and may be mitigated with reduced carbohydrates in the meal. There is no indication of gender specific difference on this tolerability profile to date.

The daily systemic exposure from the 50 mg t.i.d. regimen in the PCOS population is expected to maintain a ≥ 10-fold exposure multiple relative to the NOEL AUC threshold for aneugenicity.

Rationale for treatment duration: A 14 day treatment period is expected to support an effect of LIK066 on androgen levels in this population given the expected magnitude of reduction in overall insulin levels with t.i.d. dosing. A similar treatment duration with insulin inhibitors, such as diazoxide, were shown to reduce hyperandrogenism (Nestler et al 1990; Nestler et al 1989).

Overall, a dosing regimen of LIK066 at 50 mg p.o. t.i.d. and q.a.c. × 14 days is anticipated to be safe and effective for pharmacodynamic evaluation of treatment effect on the androgen and insulin profile in this population.

3.4 Rationale for choice of comparator

A placebo will be used as a comparator to ensure blinding and to determine any study effect.

3.6 Risks and benefits

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

In clinical studies, LIK066 was generally safe and well tolerated up to 350 mg daily dose.

Adverse drug reactions (ADR) that have been observed with LIK066 to date include gastrointestinal events, most commonly diarrhea (> 50% of subjects) (Investigator's Brochure-Section 6). Vulvovaginal infections (~ 5%) and headaches (~ 5%) have also been the most commonly reported ADRs. These adverse events have been mild-to-moderate and none resulted in study drug discontinuation. One subject elected to withdraw from a study (at 50 mg po t.i.d.) for GI tolerability issues. Subjects will be monitored clinically by symptoms, adverse event reporting and clinical labs such as chemistry. The investigator will also instruct subjects on prevention measures such as avoiding high carbohydrate meals with dosing, and good genital hygiene.

Potential risks with LIK066 that are known class effects or related to the mechanism of action include postural hypotension, urinary tract infection, hypoglycemia and ketoacidosis. An increase in cases of lower limb amputation (primarily of the toe) were observed in T2DM patients with cardiovascular disease treated with canagliflozin in long-term clinical studies. No lower limb amputations have been seen in LIK066 studies. This study excludes patients with T2DM. These risks will be monitored as described above. Additional prevention measures will include adequate hydration among other instructions to subjects as described in the ICF.

The investigator should use his/her clinical judgment and treat any adverse events according to the standard of care.

The aneugenicity risk with LIK066 for this study is considered to be minimal at the proposed dosing regimen (Section 1.3.2). LIK066 is not anticipated to increase the risk of adverse developmental or reproductive outcomes in humans at the proposed dosing regimen. The investigator must instruct subjects to avoid pregnancy for the duration of trial because there may be unknown risks of LIK066 to the fetus. Subjects must commit to abiding by the required methods of contraception (Section 4.1). If there is any question that the subject will not reliably comply, they should not be enrolled 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 such as a vaso-vagal reaction may also occur during or shortly after the blood draw.

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

3.6.1 Blood sample volumes

A maximum of 500 mL of blood is planned to be collected over a period of 6-9 weeks from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the SOM. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and Laboratory Manual.

See Section 8.9 regarding the potential use of residual samples.

4 Population

4.1 Inclusion criteria

Subjects with polycystic ovary syndrome (PCOS) 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. Overweight/obese women with PCOS aged 18 to 40 years, inclusive
3. PCOS diagnosed as
   - Hyperandrogenism, clinical OR biochemical, AND
   - Amenorrhea or oligomenorrhea (less than 8 menses within the last 12 months), AND
   - Exclusion of other causes of hyperandrogenism (see exclusion criteria)

   NOTE:

   Clinical hyperandrogenism is defined as
   - moderate to severe hirsutism with a Ferriman-Gallway score equal to or > 8 (Ferriman and Gallwey 1961) AND
   - a free testosterone level that is approximately equal to or > 1.4x the ULN range of the assay used OR
   - calculated free androgen index equal to or > 7

Biochemical hyperandrogenism is defined as free testosterone level that is approximately equal to or > 1.75x the ULN range of the assay used.

The screening labs for free T can be repeated once for borderline levels; the highest level of free T must be considered for eligibility.

4. Indicators of insulin resistance at screening defined as:
   - Sex hormone binding globulin, SHBG < LLN OR
   - Fasting insulin above the median of normal range of assay used
5. Overweight/obese subjects with BMI equal to or > 27 kg/m^2 and stable weight +/- 3 kg over previous 3 month (by history)
6. At screening, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position and again in the standing position as outlined in the SOM. Subjects with mild hypertension and those with treated hypertension are allowed. Sitting vital signs should be within the following ranges:

   oral body temperature between 35.0-37.5 °C
   systolic blood pressure, 90-150 mmHg
   diastolic blood pressure, 50-90 mmHg
   pulse rate, 40-90 bpm

   If vital signs are outside these ranges, the Investigator should obtain two additional readings, so that up to three consecutive assessments are made, following the procedure in the SOM.

   At least the last reading must be within the ranges provided above in order for the subject to qualify.

   Subjects should be excluded if their standing vital signs (relative to sitting) show findings which, in the opinion of the Investigator, are associated with clinical manifestations (such as lightheadness or palpitations) of postural hypotension (i.e. absence of any other cause). Postural hypotension is defined as either a > 20 mmHg decrease in systolic or a >10 mmHg decrease in diastolic blood pressure, accompanied by a > 20 bpm increase in heart-rate (from sitting to standing).
7. Subjects must use non-hormonal methods of contraception from enrollment until one week after last dose. Non-hormonal contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (i.e., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are NOT acceptable methods of contraception.
   - Hysterectomy or tubal ligation at least six weeks before the treatment period.
   - Placement of a non-hormonal intrauterine device (IUD).
   - Male partner sterilization (at least 6 months prior to screening). The vasectomized partner should be the sole partner for that subject.
   - Barrier methods of contraception: Condom or Occlusive cap. For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
8. Able to communicate well with the Investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Subjects with polycystic ovary syndrome (PCOS) fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Subjects with pre-existing type 1 or type 2 diabetes mellitus, Cushing's syndrome, congenital adrenal hyperplasia, ovarian or adrenal androgen-secreting tumor, uncontrolled thyroid disease, untreated obstructive sleep apnea.
2. Oophorectomy.
3. Exogenous causes of hirsutism (such as drug-induced).
4. Menstruation in the 30 days prior to screening or prior to the initiation of treatment (Day 1).
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
6. Abnormal screening labs defined as:
   - Early morning total testosterone levels => 2.5× ULN or => 200 ng/dl
   - DHEAS > 2× ULN or > 700 mcg/dl
   - Prolactin > ULN on early AM sample (allow repeat × 1 for borderline levels, enroll based on 1 normal level)
   - 17-OHP levels (early AM sample) > 200 ng/dl
   - TSH levels > 10 uUI/ml and clinical symptoms of hypothyroidism. Subjects with sub clinical hypothyroidism do not need to be excluded. Subjects well controlled on thyroid medication can be enrolled.
7. Symptomatic genital or urinary tract infection (UTI) in the 4 weeks prior to screening or the presence of active UTI at screening
8. Ongoing participation in a weight loss program such as with exercise, diet or drugs.
9. History of significant gastrointestinal surgery that could affect intestinal glucose absorption (e.g. bariatric surgeries including, Roux-en-Y gastric bypass, sleeve gastrectomy, Nissen fundoplication); active gastrointestinal disorders such as irritable bowel syndrome and inflammatory bowel disease.
10. Clinically significant GI disorder related to malabsorption or that may affect drug or glucose absorption (e.g. swallowing disorder, severe GI motility disorder, chronic diarrhea, glucose/galactose/lactose intolerance)
11. History of hypersensitivity to the study drug (active or placebo), or to drugs of similar chemical classes. Ingredients of the study drug are described in Section 3.2.1 of the Investigators' Brochure.
12. Use of prohibited medications, including:
    - antidiabetic medications or weight loss drugs within 3 months of screening.
    - hormonal therapy including but not limited to estrogen/progesterone contraceptives, estrogens, androgens, gonadotropin-releasing hormone within 3 months of screening, or progesterone contraceptives within 1 month of screening. Thyroid replacement therapy is allowed; subjects must be on a stable dose for at least 3 months prior to screening.

- Infertility treatment e.g. letrozole and clomiphene citrate within 1 month of screening
- muscle anabolic agents/drugs within 3 months of screening.
- Systemic glucocorticosteroid treatment for > 7 consecutive days for worsening of an underlying condition within 4 weeks of screening. Use of topical or inhaled glucocorticosteroids is permitted.
- Strong inhibitors of CYP3A4/5 including boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole at least 7 days prior to the study treatment.
- Strong CYP3A inducers including avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort at least 7 days prior to the study treatment,
- General UGT inhibitors including probenecid, valproic acid at least 7 days prior to the study treatment.
- other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, or longer if required by local regulations. Any other limitation of participation in an investigational trial based on local regulations.
- any drugs with known toxicity to a major organ system within the past 3 months (i.e., cytostatic drugs).
- Unless allowed by the study protocol, any other prescription drugs, new herbal supplements, within four (4) weeks prior to initial dosing, and/or over-the-counter (OTC) medication, new dietary supplements (vitamins included), within 3 days prior to initial dosing. If needed, acetaminophen or ibuprofen is acceptable for incidental and limited use.

13. Malignancy including leukemia and lymphoma (not including basal cell skin cancer which has been adequately treated) within 1 year prior to screening.
14. History of autonomic dysfunction (e.g. history of fainting, clinically significant orthostatic hypotension, clinically significant sinus arrhythmia).
15. Significant cardiovascular disease. active or within 6 months of screening such as myocardial infarct (MI), unstable angina, or clinically significant ECG abnormalities at screening
16. Evidence of clinically significant abnormal liver function tests for any of the labs at screening, confirmed by a repeat assessment:
    - ALT, AST, GGT, alkaline phosphatase > 3 × ULN.
    - serum bilirubin > 1.5 × ULN .
17. Any history of ketoacidosis, lactic acidosis, or hyperosmolar coma.
18. Significant blood loss equaling at least one unit of blood (500 ml) or a blood transfusion within 3 months prior to screening.
19. History of drug or alcohol abuse within the 12 months prior to screening or evidence of such abuse as indicated by the laboratory assays conducted at screening.
20. Evidence of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result at screening.

21. Any finding during screening assessments (vital signs, physical examination, ECG or clinical lab assessments), surgical or medical condition which may significantly alter the absorption, distribution, metabolism, or excretion of drugs, or in the investigator's judgment, which may jeopardize the subject in case of participation in the study, or would interfere with interpretation of the study results.

The investigator must ensure that all subjects meet the study eligibility criteria before they are enrolled in the study. The investigator must not apply any eligibility criteria other than those listed in the protocol. Deviation from **any** of the protocol eligibility criteria excludes a subject from enrollment into the study.

A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

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 agree that in order to participate in the study they must adhere to the contraception requirement outlined in Section 4.1 (Inclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

The medications listed under the exclusion criteria (Section 4.2) are not allowed to be used during the study. The investigator may discontinue subjects if treated with prohibited medications during the study. The investigator should discuss such cases with the Sponsor.

Antihypertensive, dyslipidemia and GERD medications are allowed but subjects must be on a stable regimen for 3 months or more prior to randomization.

Concomitant and prior medications (dose, regimen, indication and treatment duration) must be recorded in the CRF.

5.3 Dietary restrictions and smoking

Subjects will be asked to fast for at least 8 hours overnight on certain days, when blood samples will be collected early morning to measure various biomarkers under fasting state, as described in Section 3 and the SOM.

Smoking/use of nicotine products should be avoided for 8 hours before the study visits as noted in the SOM.

Grapefruit and grapefruit juice should be avoided for approximately 7 days prior to dosing until the end of the study.

Subjects will be instructed to use a low carbohydrate diet during the study treatment. Details will be provided in the SOM. A test meal will be served at baseline and end of treatment as described in Section 3 and the SOM.

5.4 Other restrictions

No strenuous physical exercise (e.g. weight training, aerobics) at least 24 hours before each study visit, and during the visit.

6 Treatment

6.1 Study treatment

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

6.1.1 Investigational treatment and control drug

The investigational drug, LIK066 50 mg tablets and matching placebo tablets in blisters will be prepared by Novartis in single blind patient specific packs to be dispensed by the unblinded pharmacist at the investigator site according to the randomization schedule as described in the SOM.

6.1.2 Additional study treatment

No additional treatment beyond investigational drug is included in this trial.

6.2 Treatment arms

Subjects will be assigned to one of the following 2 treatment arms in a ratio of 1:1

- LIK066 50 mg three times daily; before breakfast, lunch and dinner (12 subjects).
- Matching placebo tablets three times daily; before breakfast, lunch and dinner (12 subjects).

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of 5101-5130.

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

Replacement randomization numbers will be in the range of 6101-6130. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g. Subject 6103 would replace Subject 5103). Any additional subjects enrolled will use sequential subject numbering.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. Treatment allocation cards (noting the randomization numbers) will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

The investigator will enter the randomization number on the CRF (eCRF). If more than one study center recruits subjects simultaneously, the CTL or designee will coordinate assigning randomization numbers across sites as described in the SOM.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

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

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, and schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

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

Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist (or delegate) will receive treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study:

Unblinded field monitor(s)

Unblinded clinical staff managing drug re-supply to site

Unblinded sample analyst(s)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the Monitoring Plan.

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 unblinded site pharmacists.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in the SOM. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

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 at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

6.5 Treating the subject

LIK066 or matching placebo tablets will be administered orally just before meals mostly at home by the subject. See the SOM for further details.

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

6.6 Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible to the investigator 24 hours per day in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of study treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to

determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. The unblinded treatment code must not be recorded on the CRF. The investigator must also immediately inform the study monitor 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 code break cards at any time in case of emergency. The investigator will need to provide:

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

In addition, the investigator must provide oral and written information to inform the subject 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 subject.

6.7 Treatment exposure and compliance

Corporate Confidential Information

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject 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 subject. 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.

6.8 Recommended treatment of adverse events

Based on prior clinical experience with LIK066, which was administered to more than 200 subjects at doses up to 350 mg single dose or up to 150 mg daily for 12 weeks, LIK066-related AEs can be managed by clinical monitoring including vital signs and blood tests. If diarrhea occurs, it can be treated with oral rehydration therapy if needed. More aggressive treatment, if required, will be performed at the discretion and direction of the investigator, with timely communication with the sponsor. Stopping rules (Section 7.5) will be applied as appropriate.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.9 Rescue medication

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

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

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

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

7.2 Discontinuation of study treatment

Discontinuation of study treatment for any given subject is defined as study treatment being stopped earlier than defined in the protocol.

Study treatment **must** be discontinued under the following circumstances:

- Subject/guardian decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of his/her participation in the trial.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy (see Section 8.6 Safety and Section 9.6 Pregnancy reporting)
- Confirmed hypoglycemia CTCAE grade 3 or above necessitating third party intervention

- Metabolic ketoacidosis CTCAE grade 3 or above

Study treatment for an individual subject must be placed on hold until a joint review of the safety data occurs for any of the following events/findings if 1) deemed clinically moderate to severe, 2) puts the subject at a safety risk and 3) suspected related to study drug:

- Diarrhea above grade 2 per CTCAE criteria (CTCAE 2010) **and** deemed to put the subject at safety risk per investigator judgment
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- SAEs

The decision to permanently discontinue treatment for any subject experiencing any of the above will be based on a joint full review of the clinical data by the investigator and the sponsor and a joint decision.

In the event a treatment code is inadvertently broken, site responsible and Novartis will jointly determine whether to discontinue dosing for that subject.

In the event of study drug discontinuation, the investigator must make every effort to determine the primary reason and record this information on the Dosage Administration CRF.

Subjects who discontinue study treatment or who no longer participate in the study should NOT be considered withdrawn UNLESS they withdraw their consent (Section 7.3 Withdraw of Informed Consent). Whenever possible, they should return for the EOS assessments. If they fail to return for these assessments for unknown reasons, the investigator should make every effort (e.g. telephone, e-mail, letter) to contact the subject/pre-designated contact (Section 7.4, Lost to follow-up).

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore and
- Does not want any further visits or assessments and
- Does not want any further study related contacts and
- Does not allow analysis of already obtained biologic material.

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

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

7.5 Study Stopping rules

The investigators and the sponsor will continually review adverse events and laboratory findings during the study.

The study must be halted, i.e. halting new enrollment and halting dosing for all subjects in case of hypoglycaemia CTCAE grade 3 or above requiring third party intervention and in case of grade 3 and above ketoacidosis.

The study may be halted, i.e. halting new enrollment and halting dosing for all subjects in case of safety concerns that are suspected to be related to study drug, such as:

- if 2 or more subjects develop diarrhea above grade 2 per CTCAE criteria **and** deemed to put the subject at safety risk per investigator judgment
- if 2 or more subjects are discontinued from dosing due to safety concerns from similar laboratory abnormalities
- one or more subjects develop a drug-related SAEs

The safety data will be jointly reviewed by the sponsor and investigators. The study may be stopped if justifiable by the number and/or severity of adverse events, such as an increase in severity of known adverse events such as diarrhea (severity greater by 1 CTCAE category), or 2 or more subject develop study drug related SAE, or 1 or more subjects develop an unexpected and severe adverse event. The decision to stop the study must be jointly made by the sponsor and the investigators upon review of all available clinical data. Restart of this clinical trial in such case will be documented by a substantial amendment and following approval by relevant health authorities.

7.6 Early study termination by the sponsor

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

8 Procedures and assessments

8.1 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										Treatment									
Visit Name	Screening	Baseline									Treatment									
Visit Numbers[1]	1	2[13]									101[14]	102[14]	103[15]							
Days	-44 to -3	-1									1	8	15							
Time (post-dose)	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h	-	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h
Informed consent	X																				
Corporate Confidential Information	X																				
Demography	X																				
Alcohol Test and Drug Screen [2]	X																				
Hepatitis screen[2]	X																				
HIV screen[2]	X																				
Pregnancy and assessments of fertility	X	X											X								
Medical history/current medical conditions	X	X[3]																			
Concomitant medications	As needed																				

Epoch	Screening										Treatment									
Visit Name	Screening	Baseline									Treatment									
Visit Numbers[1]	1	2[13]									101[14]	102[14]	103[15]							
Days	-44 to -3	-1									1	8	15							
Time (post-dose)	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h	-	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h
Physical Examination[2]	X[4]	X[3]											X								
Blood Pressure	X[5]	X										X	X								
Pulse rate	X[5]	X										X	X								
Body Temperature	X	X										X	X								
Body Height	X																				
Body Weight	X	X										X	X								
Electrocardiogram (ECG)	X	X											X								
Hematology	X	X											X								
Clinical Chemistry	X[6]	X[7]											X								
Urinalysis	X	X											X								
Subjects domiciled[2,8]		X											X								
Drug administration record											X	X			X						
Drug dispensation[2]											X	X									
Corporate Confidential Information															X	X	X	X	X	X	X
		X[9]	X[9]	X[9]				X[10]		X[10]			X[9]	X[9]	X[9]				X[10]		X[10]
	X[11]		X[12]											X[12]							
Glucose enriched test meal				X											X						
Blood insulin and glucose				X	X	X	X	X	X	X					X	X	X	X	X	X	X
Corporate Confidential Information		X																			

Epoch	Screening										Treatment									
Visit Name	Screening	Baseline									Treatment									
Visit Numbers[1]	1	2[13]									101[14]	102[14]	103[15]							
Days	-44 to -3	-1									1	8	15							
Time (post-dose)	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h	-	-	-2h	-1h	0h	0.5h	1h	1.5h	2h	3h	4h
Adverse Events	As needed																			
Serious Adverse Events	As needed																			
Study completion information																				
Safety Follow up Call[2]																				
Comments	As needed																			

Epoch	Treatment	
Visit Name	EOS	Post Study Safety Contact
Visit Numbers[1]	199	
Days	22	Last Visit +30
Time (post-dose)	-	-
Informed consent		
Corporate Confidential Information		
Demography		
Alcohol Test and Drug Screen [2]		
Hepatitis screen[2]		
HIV screen[2]		
Pregnancy and assessments of fertility		
Medical history/current medical conditions		
Concomitant medications	As needed	
Physical Examination[2]	X	
Blood Pressure	X	
Pulse rate	X	
Body Temperature		
Body Height		
Body Weight	X	
Electrocardiogram (ECG)	X	
Hematology		
Clinical Chemistry		
Urinalysis	X	
Subjects domiciled[2,8]		
Drug administration record		
Drug dispensation[2]		
Corporate Confidential Information		
	X[11]	
Glucose enriched test meal		
Blood insulin and glucose		
Corporate Confidential Information		
Adverse Events	As needed	
Serious Adverse Events	As needed	
Study completion information	X	
Safety Follow up Call[2]		X
Comments	As needed	

[1] Visit structure given for internal programming purpose only
[2] Will not be recorded in the CRF
[3] Should record the following in the CRF: hirsutism, acne, androgenic alopecia, acanthosis nigricans, skin tags, waist circumference, hip circumference, waist/hip ratio and prior history of gestational diabetes. Details in the SOM
[4] Includes Ferriman Gallwey score for hirsutism
[5] Sitting and standing
[6] Screening assessment include early morning measurement of total testosterone, free testosterone, SHBG, LH, FSH, prolactin, 17-OH progesterone, estradiol, DHEAS, DHEA, androstenedione, insulin and TSH
[7] Includes HbA1c measurement at baseline
[8] The night before this visit to ensure overnight fasting and early AM collection of blood samples
[9] Free testosterone, total testosterone, LH and FSH
[10] Total and free testosterone
[11] Progesterone
[12] SHBG, estradiol, progesterone, DHEAS, DHEA and androstenedione
[13] Baseline assessments may be completed within 7 days prior to Day 1. Some of the assessments scheduled at baseline may be completed when subjects are domiciled the night before as explained in the SOM.

[14]

8.2 Informed consent procedures

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

If applicable, in cases where the subject's representative gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

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 subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.1 (Inclusion criteria) and in Section 5.1 (Contraception requirements).

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

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

It is permissible to re-screen a subject if she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

All subjects will be screened for HIV, Hepatitis B and C and substances of abuse. See the SOM for details.

Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Subject demographics/other baseline characteristics

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

Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Medical history should include the approximate onset of the last menstrual period and prior history of gestational diabetes.

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.

At baseline, the physical examination should include cutaneous manifestations of hyperandrogenism, e.g. hirsutism, acne, androgenic alopecia, as well as acanthosis nigricans and skin tags; baseline measures of body weight, waist circumference, hip circumference and waist/hip ratio. Details are outlined in the SOM.

8.6 Safety

Safety assessments are specified below. Details, including methods for assessment and recording are specified in the SOM, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

Safety assessments include:

- Vital signs (body temperature, blood pressure, pulse rate and body weight)
- ECG evaluation
- Laboratory assessments (hematology, blood chemistry and urinalysis)
- Physical examination
- Collection of adverse events

8.8 Other assessments

Corporate Confidential Information

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after **providing written informed consent** for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

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

1. The severity grade.
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAC)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving; recovered/resolved with sequelae; fatal; or unknown).

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

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

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

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 subject or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guideline).

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

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

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last 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.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure Reference Safety Information and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events:

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

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

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 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 follow-up assessments are listed in Appendix 2. The central lab performing the standard blood chemistry assessments may alert the investigator when such changes are observed. Repeats may also be performed using the local laboratory used by the site if needed.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

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/subject or consumer (EMA definition).

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

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

All instances of misuse must be documented in the adverse event (AE) CRF irrespective of the misuse being associated with an AE/SAE. In addition, all instances of misuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse are also to be reported using the SAE form/CRF.

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

9.6 Pregnancy reporting

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

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

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

9.7 Early phase safety monitoring

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

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

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and 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.

Continuous remote monitoring of each site's data may be performed by Novartis or a CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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 11requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Validation checks for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

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

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

10.3 Database management and quality control

Novartis or designated CRO staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site via the EDC system. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site. Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

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

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

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, subjects will be analyzed according to the study treatment(s) received.

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

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 subject.

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

11.4.1 Primary Variable(s)

The primary efficacy endpoint will be the average of the three morning fasting free testosterone concentrations in blood.

11.4.2 Statistical model, hypothesis, and method of analysis

The primary analysis will assess the treatment effect of LIK066 on free T at Day 15. The ratio of Day 15 to baseline free T will be analyzed in an analysis of covariance model with treatment as a categorical factor and baseline free T as a covariate. Additional baseline characteristics that may be predictive of free T may be added to the model as covariates. The logarithm of the ratio and of baseline free T will be applied prior to the analysis.

The geometric mean of the ratio to baseline for free T will be estimated from the model for LIK066 and placebo, along with the treatment ratio and the associated p-value and two-sided 90% confidence interval (CI). From these quantities, the following criteria will be assessed:

1. the upper confidence limit of the 90% CI is less than 1, and
2. the estimated treatment ratio is less than 0.75.

The first criterion addresses with high certainty whether the effect of LIK066 on free T reduction is superior to placebo. The second criterion addresses whether the observed treatment effect of LIK066 on free T reduction is at least 25%. An effect size of 20-25% on hyperandrogenism is considered to be clinically meaningful in PCOS as it correlates with improved ovulation and fertility (Harborne et al 2003).

Subjects who are deemed to have hormonal evidence of ovulation during the study may be excluded from the primary analysis.

11.4.3 Handling of missing values/censoring/discontinuations

The primary efficacy analysis will be based on all subjects with an evaluable baseline and Day 15 free T profile and that have no hormonal evidence of ovulation during the study.

11.4.4 Sensitivity analyses

As a sensitivity analysis, the change from baseline in free T at Day 15 will be analyzed in an analysis of covariance model of the same form as the one specified for the primary analysis, except no logarithmic transformation will be applied. The least-squares mean change from baseline will be estimated from the model for LIK066 and placebo, along with the treatment difference and the associated p-value and two-sided 90% confidence interval.

11.5 Analysis of secondary variable(s)

The secondary variables will be the gonadotropins (LH and FSH), the sex steroids (total testosterone, estradiol, progesterone, DHEAS, DHEA, androstenedione), SHBG, and free androgen index. For LH, FSH, and total testosterone, the average of the three morning fasting concentrations will be additional secondary variables.

11.5.1 Efficacy / Pharmacodynamics

Each of the secondary variables will be listed by treatment group, subject, and visit/time and summarized by treatment and visit/time. The change from baseline and % change from baseline will also be listed and summarized.

11.5.2 Safety

Vital signs

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

Adverse events

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

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

11.5.5 Other assessments

Not Applicable.

11.7 Sample size calculation

The sample size for this study has been based on a relevant interventional study in a similar population of adults with PCOS (George et al 2016). The mean and standard deviation of free T by LC-MS/MS in this study, as a pooled estimate across all treatment arms at baseline, is 79 pmol/L and 40 pmol/L, respectively. The study reported a decrease in free T of 19% after 7 days of treatment with AZD4901, a neurokinin B receptor antagonist.

The sample size calculation assumes similar baseline characteristics of free T, a 2% reduction in free T in the placebo arm, and a correlation between baseline and Day 14 free T of 0.5. The assumption also is that the true treatment effect of LIK066 is 35% over placebo. We choose to assume a correlation between baseline and Day 15 of 0.5 because, based on results of free T in a published study of metformin in women with PCOS (Kurzthaler et al 2014), we believe it to be smaller than the true correlation, and hence it is likely that the power for achieving the primary study criteria is conservative.

Based on these assumptions, a sample size of 24 subjects in a 1:1 treatment allocation (12 on LIK066; 12 on placebo) will provide 80% probability of achieving the dual criteria specified in the previous section. The probability of a type I error (achieving the criteria when in fact there is no true treatment effect on free T) is 5%. These results are based on 10,000 simulations of the primary analysis.

11.8 Power for analysis of key secondary variables

Not Applicable.

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.

Barth JH, Field HP, Yasmin E, et al (2009) Defining hyperandrogenism in polycystic ovary syndrome: measurement of testosterone and androstenedione by liquid chromatography–tandem mass spectrometry and analysis by receiver operator characteristic plots. Eur J Endocrinol;162:611-615.

CTCAE (2010) Common Terminology Criteria for Adverse Events v4.03 (Internet). Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 31 March 2017).

De Medeiros SF, Yamamoto MMW, de-Medeiros MAS, et al (2017) Should Subclinical Hypothyroidism Be an Exclusion Criterion for the Diagnosis of Polycystic Ovary Syndrome? *Journal of Reproduction & Infertility*;18(2):242-250.

Dunaif A, Segal KR, Futterweit W, et al (1989) Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes; 1165-74.

Escobar-Morreale HF, Carmina E, Dewailly D, et al (2012) Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society, *Human Reproduction Update*;18(2):146–170.

Ferriman D, Gallwey JD (1961) Clinical assessment of body hair growth in women. J Clin Endocrinol Metab; 1440-7.

George JT, Kakkar R, Marshall J, et al (2016) Neurokinin B Receptor antagonism in women with Polycystic Ovary Syndrome: A randomized, placebo-controlled trial. J Clin Endocrinol Metab; 4313-4321.

Harborne L, Fleming R, Lyall H, et al (2003) Descriptive review of the evidence for the use of metformin in polycystic ovary syndrome. Lancet; 1894-901.

Kalra S (2014) Sodium Glucose Co-Transporter-2 (SGLT2) inhibitors: A review of their basic and clinical pharmacology. Diabetes Ther; 355-66.

Kurzthaler D, Hadziomerovic-Pekic D, Wildt L, et al (2014) Metformin induces a prompt decrease in LH-stimulated testosterone response in women with PCOS independent of its insulin-sensitizing effects. Reprod Biol Endocrinol; 98.

Legro RS, Arslanian SA, Ehrmann DA, et al (2013) Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab; 4565-92.

NCT02635386: DAPA, EQW, DAPA/MET ER and PHEN/TPM ER in obese women with PolycysticOvary Syndrome (PCOS). Available from: https://www.clinicaltrials.gov/ct2/show/NCT02635386?term=PCOS&type=Intr&intr=dapagliflozin&rank=1 (Accessed 31 March 2017).

Nestler JE, Barlascini CO, Matt DW, et al (1989) Suppression of serum insulin by diazoxide reduces serum testosterone levels in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab; 1027-32.

Nestler JE, Singh R, Matt DW, et al (1990) Suppression of serum insulin level by diazoxide does not alter serum testosterone or sex hormone-binding globulin levels in healthy, nonobese women. Am J Obstet Gynecol; 1243-6.

Pernicova I, Korbonits M (2014) Metformin-mode of action and clinical implications for diabetes and cancer. Nat Rev Endocrinol; 143-56.

Rosenfield RL, Ehrmann DA (2016) The pathogenesis of Polycystic Ovary Syndrome (PCOS): The Hypothesis of PCOS as functional ovarian hyperandrogenism revisited. Endocr Rev; 467-520.

Sands AT, Zambrowicz BP, Rosenstock J, et al (2015) Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in Type 1 diabetes. Diabetes Care; 1181-8.

Sirmans SM, Pate KA (2013) Epidemiology, diagnosis, and management of Polycystic Ovary Syndrome. Clin Epidemiol; 1-13.

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

Table 15-1 Liver Event Definitions

Definitions	Thresholds
Potential Hy's law cases	ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	ALT or AST > 8 × ULN 5 x ULN < ALT/AST ≤ 8 x ULN 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	ALP > 2 × ULN (in the absence of known bone pathology)
Others	Any clinical event of jaundice (or equivalent term) Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Action required
Potential Hy's Law case	Discontinue the study treatment immediately Hospitalize, if clinically appropriate Establish causality Complete CRFs per liver event guidance*
ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	If confirmed, consider interruption or discontinuation of study drug If elevation persists for more than 2 weeks, discontinue the study drug Establish causality Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	Repeat liver chemistry tests within 48-72 hours If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	Consider study treatment interruption or discontinuation Hospitalize if clinically appropriate Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease	Caeruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase > 50%	Consider causes and possible interventions Repeat assessment within 24-48h if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	Consider causes and possible interventions Assess serum albumin & serum protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: Blood glucose (fasting) Serum creatinine Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: Urine sediment microscopy Assess sCr and urine albumin-creatinine ratio Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder

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

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

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

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	Urine dipstick and sediment microscopy Blood pressure and body weight Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

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