

Biostatistics & Statistical Programming /  
Novartis Institutes for BioMedical Research

LIK066

CLIK066X2205

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

## **Statistical Analysis Plan (SAP)**

Personal Data

Document type: SAP Documentation – NIBR

Document status: Final

Release date: 03-October-2017

Number of pages: 14

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## 1 Introduction

### 1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “**CLIK066X2205**”.

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

### 1.2 Study reference documentation

Draft amended study protocol (v01) is available at the time of finalization of Statistical Analysis Plan.

### 1.3 Study objectives

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.

#### 1.3.1. Primary objective(s)

<i>Primary objective(s)</i>	<i>Endpoints related to primary objectives</i>
<ul style="list-style-type: none"><li>To assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in overweight and obese subjects with PCOS</li></ul>	<ul style="list-style-type: none"><li>Change in average morning fasting free testosterone blood concentrations from baseline to Day 15</li></ul>

#### 1.3.2. Secondary objective(s)

<i>Secondary objective(s)</i>	<i>Endpoints related to secondary objectives</i>
<ul style="list-style-type: none"><li>To assess the safety and tolerability of LIK066 in overweight and obese subjects with PCOS throughout the study.</li></ul>	<ul style="list-style-type: none"><li>Adverse events throughout the study, serum electrolytes and hematocrit on Day 15</li></ul>
<ul style="list-style-type: none"><li>To evaluate the treatment effect of LIK066 on gonadotropins and sex steroid levels on Day 15</li></ul>	<ul style="list-style-type: none"><li>LH, FSH, SHBG, androstenedione, DHEA, DHEAS, Total testosterone, free androgen index (FAI)</li></ul>

## **1.4 Study design and treatment**

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

Approximately 24 subjects will be randomized in a 1:1 ratio to LIK066 or placebo and be assigned to one of the following 2 treatment arms:

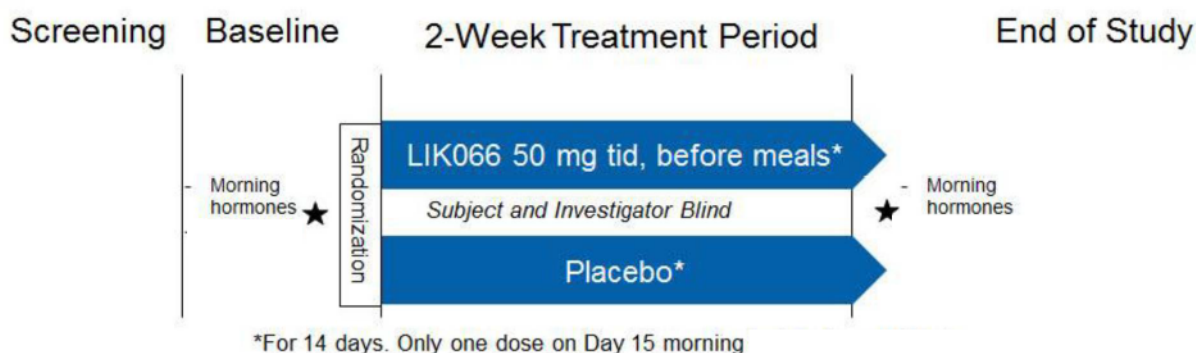
- LIK066 50 mg three times daily; before breakfast, lunch and dinner (12 subjects).
- Matching placebo tablets three times daily; before breakfast, lunch and dinner (12 subjects).

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

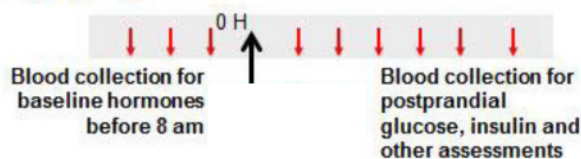
progesterone assessment). The number of enrolled subjects; excluding replacements, should not exceed 30.

As it can be seen from Figure 1-1, 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.

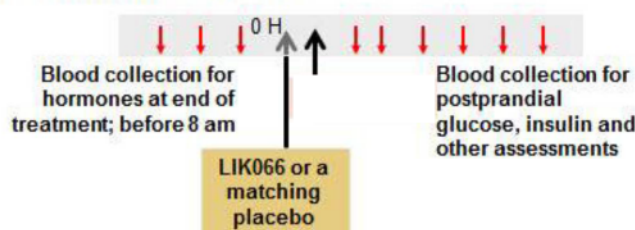
**Figure 1-1 Study design**



### Baseline (Day -1)



### End of Treatment (Day 15)



## 2 First interpretable results (FIR)

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

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## **4 Statistical methods: Analysis sets**

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

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

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



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

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

**Table 4-1 Protocol deviation codes and analysis sets**

<b>Category</b> <b>Deviation code</b>	<b>Text description of deviation</b>	<b>Data exclusion</b>
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<b>Subjects are excluded from PD analysis in case of these PDs:</b>		Exclude subject from PD analysis set
<b>Subjects are excluded from Protocol deviations:</b>	<b>PD analysis in case of these</b>	Exclude subject from PD analysis sets
<i>INCL03</i>	<i>Deviation from inclusion criterion 2</i>	
<i>EXCL04</i>	<i>Deviation from exclusion criterion 4</i>	
<i>EXCL06</i>	<i>Deviation from exclusion criterion 6</i>	
<i>COMD01</i>	<i>Use of prohibited medication during the study</i>	

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

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## **6 Statistical methods for Pharmacodynamic (PD) parameters**

All subjects within the primary PD analysis set will be included in the PD data analysis, unless otherwise stated.

### **6.1 Primary objective**

The primary aim of this study is to assess the treatment effect of LIK066 on hyperandrogenism at Day 15 in overweight and obese subjects with PCOS.

#### **6.1.1 Variables**

The primary efficacy endpoint will be the average of the three-morning fasting free testosterone concentrations in blood from baseline to Day 15.

#### **6.1.2 Descriptive analyses**

The average of the three-morning fasting free testosterone concentrations in blood will be listed by treatment group, patient and visit/time and descriptive statistics will be provided by treatment and visit/time. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum as appropriate. Summary statistics will be also provided for the two post dose measurements of the free testosterone concentrations (at 2h and 4h).

Graphical methods will be employed to show group and individual summary plots over time by treatment.

#### **6.1.3 Statistical model, assumptions and hypotheses**

The primary analysis will assess the treatment effect of LIK066 on free testosterone (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, baseline body weight 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.

#### **6.1.3.1 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 who have no hormonal evidence of ovulation during the study. If one or two of the three morning measurement are missing, the average of observed measurements will be used. If all are missing, there will be no imputation of the missing data.

#### **6.1.3.2 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 LK066 and placebo, along with the treatment difference and the associated p-value and two-sided 90% confidence interval.

### **6.2 Secondary objectives**

#### **6.2.1 Variables**

The secondary PD variables of this study are:

- gonadotropins (LH and FSH)
- the sex steroids (total testosterone, estradiol, progesterone, DHEAS, DHEA, androstenedione)
- SHBG
- Free androgen index

For LH, FSH, and total testosterone, the average of the three morning fasting concentrations at baseline and day 15 will be used as secondary variables.

Baseline for all secondary parameters is defined as the last pre-dosing measurement at baseline or screening if baseline measurement is missing.

#### **6.2.2 Descriptive analyses**

Secondary variables will be listed by treatment group, subject, and visit/time and summarized by treatment and visit/time. The change from baseline and percentage (%) change from baseline will also be listed and summarized. Summary statistics will be provided by treatment and visit/time and will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum as appropriate. In the summary tables, the frequency (n, %) of values below the LLOQ and above the ULOQ, respectively, will be included. To ensure that each biomarker only has numerical values, censored values will be imputed as:

- Values below LLOQ will be replaced by LLOQ/2.
- Values above the ULOQ will be replaced by ULOQ.

Imputed values will be used in descriptive summary, inferential analyses and plots.

### **6.2.3 Statistical model, assumptions and hypotheses**

The ratio of Day 15 to baseline will be analyzed in an analysis of covariance model with treatment as a categorical factor and baseline as a covariate. The logarithm of the ratio and of baseline will be applied prior to the analysis. The geometric mean of the ratio to baseline 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.

#### **6.2.3.1 Graphical presentation of results**

Graphical methods will be employed to show group summary plots over time by treatment as required.

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## **7 Statistical methods for safety and tolerability data**

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

### **7.1 Variables**

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

### **7.2 Descriptive analyses**

#### **Subject demographics and other baseline characteristics**

All data for background and demographic variables will be listed by 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.

#### **Treatment**

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

#### **Vital signs**

All vital signs data will be listed by treatment, 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, 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, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

### **Adverse events**

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

### **Immunogenicity**

Not applicable.

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## **10 Reference list**

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.