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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LIK066

CLIK066X2204

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

# Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

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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 ***"CLIK066X2204"***.

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

## 1.2 Study reference documentation

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

## 1.3 Study objectives

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

### *1.3.1. Primary objective(s)*

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

### *1.3.2. Secondary objective(s)*

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

| | |
|---|---|
| • To determine the effect of LIK066 on aspartate aminotransferase (AST) after 12 weeks of treatment | • Circulating aspartate aminotransferase (AST) levels |

### *1.3.3. Exploratory objective(s)*

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## 1.4 Study design and treatment

This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study in patients with NASH. Randomization will be stratified by BMI at baseline (<30 kg/m2 or ≥ 30 kg/m2 for patients with an Asian race, or <35 kg/m2 or ≥ 35 kg/m2 for all other patients).

At the beginning of the study after eligibility has been confirmed, patients will be randomized in a 2:1 ratio to receive either LIK066 at 150 mg qd OR matching placebo qd, by oral administration. A third, 30 mg qd arm will be initiated after 33 patients have been enrolled in the initial two arm portion of the study. For the entire study, patients will be randomized to either LIK066 at 150 mg qd, 30 mg qd or matching placebo at a ratio of 2:2:1.Figure 1-1 depicts the steps that will be followed in the study, starting from a 28-day screening period, then a baseline period of 14 days, a treatment period of 12 weeks, and a study completion evaluation approximately 28 days after the last drug administration

**Figure 1-1: Study Design**


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

# 2 First interpretable results (FIR)

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

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FIR will focus on the following analyses:

- Analysis populations (if needed)
- Subject disposition
- Demographics and baseline characteristics. Baseline characteristics include, but not limited to:

  - Age, Weight/Height/BMI, liver function tests: ALT, AST, waist circumference, hip circumference, ELF and its 3 components, HOMA-IR, FIB-4 score. APRI score
- Safety results include but are not limited to:
  - Number and percentage of subjects with adverse events by body system and preferred term with a breakdown by treatment
- Pharmacokinetic (PK) results for plasma:
  - Arithmetic mean (SD) plasma PK concentration-time plot per treatment.
  - Summary statistics for PK parameters.
- Pharmacodynamic (PD) analyses include, but are not limited to:
  - Model estimated treatment effect in change from baseline to Week 12 in ALT
  - Arithmetic mean (SE) ALT plot per treatment (overlaying) over time
  - Model estimated treatment effects of key secondary parameters (Percent liver fat as measured by MRI, Total body weight, anthropometric assessments, ®, ELF panel and AST at Week 12
  - Arithmetic mean (SE) plots of key secondary parameters (Percent liver fat as measured by MRI, Total body weight, anthropometric assessments, ELF panel per treatment and AST (overlaying) and over time.

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# 3 Interim analyses

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# 4 Statistical methods: Analysis sets

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# 5 Statistical methods for Pharmacokinetic (PK) parameters

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

## 5.1 Variables

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUClast and other parameters as relevant (e.g. AUC0-24h) from the plasma concentration-time data.

## 5.2 Descriptive analyses

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## 5.3 Statistical model, assumptions and hypotheses

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# 6 Statistical methods for Pharmacodynamic (PD) parameters

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

## 6.1 Primary objective

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

### 6.1.1 Variables

Change from baseline to Week 12 in ALT is the primary efficacy variable. 'Baseline' is defined as the mean of measurements taken at the Screening (V1) and Baseline (V101) visits.

### 6.1.2 Descriptive analyses

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### 6.1.3 Statistical model, assumptions and hypotheses

**Bayesian approach**

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**Repeated measures approach**

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#### 6.1.3.1 Model checking procedures

Model checking will not be performed in this exploratory study.

#### 6.1.3.2 Sensitivity analysis

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## 6.2 Secondary objectives

### 6.2.1 Variables

The secondary PD variables of this study are:

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

Baseline for all secondary parameters is defined as the last measurement prior to the first dose except for AST where baseline is the mean at Screening (V1) and Baseline (V101)

### 6.2.2 Descriptive analyses

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### 6.2.3 Statistical model, assumptions and hypotheses

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## 6.3 Exploratory objectives

### 6.3.1 Variables

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### 6.3.2 Descriptive analyses

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### 6.3.3 Statistical model, assumptions and hypotheses

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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. Separate tables and listings will be presented indicating event toxicity grade and study drug relationship.

## 7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

# 8 Statistical methods for Pharmacokinetic/Pharmacodynamic/Pharmacogenetic interactions

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# 10 Derivations

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