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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LMB763

CLMB763X2201

# A randomized, patient and investigator blinded, placebo-controlled, multicenter study to assess the safety, tolerability, pharmacokinetics and efficacy of LMB763 in patients with non-alcoholic steatohepatitis (NASH)

Statistical Analysis Plan (SAP)

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## Table of contents

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# 1 Introduction

## 1.1 Scope of document

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

## 1.2 Study reference documentation

Final study protocol (V03) is available at the time of finalization of Statistical Analysis Plan Amendment 1.

## 1.3 Study objectives

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

| ***Primary objective(s)*** | ***Endpoints related to primary objectives*** |
|---|---|
| • To determine the safety and tolerability of LMB763 during 12 weeks of treatment. | • Safety endpoints (including vital signs, physical examination, laboratory measurements, ECG).<br>• Adverse events. |
| • To determine the effect of LMB763 on circulating alanine aminotransferase (ALT) levels. | • Liver function tests. |

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

| ***Secondary objective(s)*** | ***Endpoints related to secondary objective(s)*** |
|---|---|
| • To evaluate the pharmacokinetics (PK) of LMB763 in NASH patients. | • PK blood collection and analysis (Cmax, Tmax, AUC, Racc, etc.). |
| • To determine the effect of LMB763 on intrahepatic lipid after 12 weeks of treatment. | • Percent (%) Liver fat as measured by Magnetic Resonance Imaging (MRI). |
| • To determine the effect of LMB763 on anthropometric assessments after 12 weeks of treatment. | • Weight, BMI, waist-to-hip (WTH) ratio. |
| • To determine the effect of LMB763 on non-invasive markers of liver fibrosis. | • Fibroscan® (in a subset of patients)<br>• Enhanced liver fibrosis panel (ELF) and fibrosis biomarker test (originally known as Fibrotest®/FibroSure®). |
| • To determine the effect of LMB763 on fasting lipid profile. | • Fasting lipid profile. |

| | |
|---|---|
| • To determine the effect of LMB763 compared with placebo with respect to occurrence and impact of potential itch. | • Itch scored on 100 mm visual analog scale (VAS) ratings. |

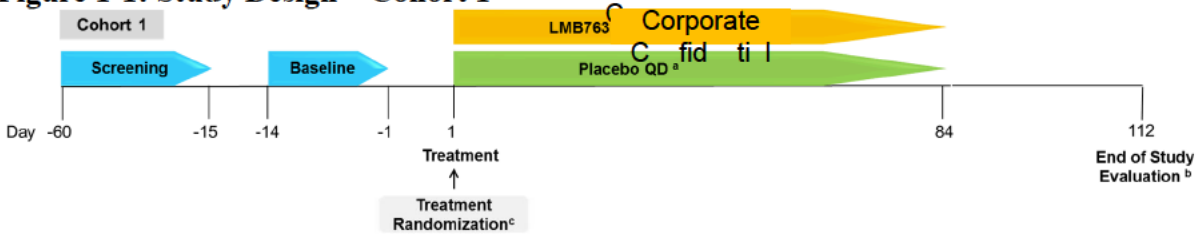
## 1.4 Study design and treatment

This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study, in two cohorts, in patients with NASH.

For cohort 1, the study will consist of a screening period of 45 days, baseline period of 14 days, treatment period of 12 weeks, followed up by a study completion evaluation approximately 28 days after the final drug administration.

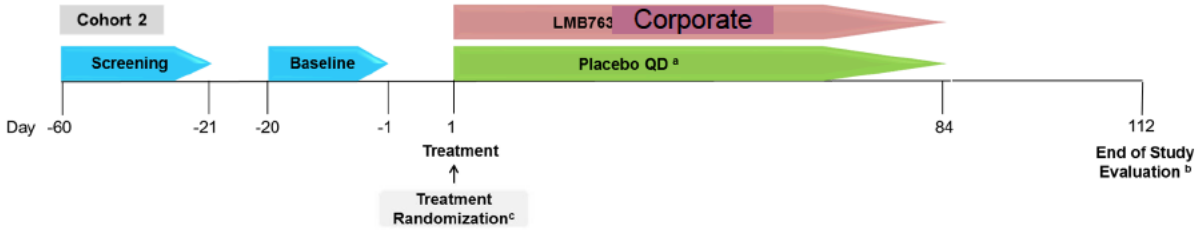
For cohort 2, the study will consist of a screening period of 40 days, baseline period of 20 days, treatment period of 12 weeks, followed up by a study completion evaluation approximately 28 days after the final drug administration.

**Figure 1-1: Study Design – Cohort 1**




[a] Patients will be randomized in a 2:1 ratio to receive LMB763 100 mg (n ~ 64) or matching Placebo (n ~ 32). Study medication will be self administered by patients once daily for 12 weeks. On visit days, study medication will be administered at the site. If additional dosing arms are included, the same study design will be followed.
[b] EOS evaluation to be completed approximately 28 days after the final study drug administration (i.e. Day 112 (± 2 days))
[c] Treatment randomization may occur prior to day 1 as soon as patient eligibility is confirmed from baseline assessments
[d] All visit during the treatment and follow-up periods will have a window of ± 2 days

**Figure 1-2: Study Design – Cohort 2**




a Patients will be randomized in a 2:1 ratio to receive LMB763 (n ~ 64) or matching Placebo (n ~ 32). Study medication will be self administered by patients once daily for 12 weeks. On visit days, study medication will be administered at the site.
b EOS evaluation to be completed approximately 28 days after the final study drug administration (i.e. Day 112 (± 2 days))
c Treatment randomization may occur prior to day 1 as soon as patient eligibility is confirmed from baseline assessments
d All visit during the treatment and follow-up periods will have a window of ± 2 days

# 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
- Subject disposition
- Demographics and baseline characteristics. Baseline characteristics include, but are not limited to:
  - Liver function tests: ALT
- Safety results include but are not limited to:
  - Number and percentage of subjects with adverse events by system organ class
- Pharmacokinetic (PK) results for plasma:
  - Arithmetic mean (SD) concentration-time plot per treatment (overlaying).
  - Summary statistics for PK parameters.
- Pharmacodynamic (PD) analyses include, but are not limited to:
  - Treatment response at Week 12 in ALT
  - Mean (SE) ALT plot per treatment (overlaying) over time
  - Treatment comparison of key secondary parameters (Percent liver fat as measured by MRI, Weight, Fibroscan®, ELF panel, fasting lipid profile and itch as assessed on the VAS scale) at Week 12

- Mean (SE) plots of key secondary parameters (Percent liver fat as measured by MRI, Weight, Fibroscan®, ELF panel, fasting lipid profile and itch as assessed on the VAS scale) per treatment (overlaying) and over time.



# 4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received. All placebo subjects will be pooled. Subjects with dose frequency/dose change due to AE will be analyzed according to the treatment they received up to the dose frequency/dose change.

All patients that received at least one dose of study drug will be included in the safety data analysis “safety population”.

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.

All patients with evaluable PD parameter data and no major protocol deviations impacting PD data will be included in the PD data analysis "PD population".

For the End of Study (EOS) visit only data from study completers will be included in the summary/analysis tables/figures.

The data exclusion for each analysis set based on protocol deviation codes will be captured in the following table, which will be completed in a SAP amendment prior to DBL as needed.

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

| Category<br>Deviation code | Text description of deviation | Data exclusion |
|---|---|---|
| **Subjects are excluded from all *(safety)* analysis in case of these protocol deviations:** | | Exclude subject completely from all ***(safety)*** analysis sets |
| **Subjects are excluded from PK analysis in case of these protocol deviations:** | | Exclude subject from PK analysis set |
| **Subjects are excluded from PD analysis in case of these protocol deviations:** | | Exclude subject from PD analysis set |
| **Subjects are excluded from PK/PD analysis in case of these protocol deviations:** | | Exclude subject from PK/PD analysis sets |

# 5 Statistical methods for Pharmacokinetic (PK) parameters

## 5.1 Variables

The following pharmacokinetic parameters will be determined for each analyte using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUClast, AUCtau, Racc, T1/2, Vz/F and CL/F from the plasma concentration-time data.

## 5.2 Descriptive analyses

LMB763 and LMB763 metabolites Corporate Confidential Information plasma concentrations will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Graphical methods will be employed to show mean and individual concentration-time profiles.

Pharmacokinetic parameters will be listed by treatment and subject and summarized by treatment with descriptive statistics as listed above. Since Tmax is generally evaluated by a nonparametric method, only median, minimum, and maximum will be reported.

## 5.3 Statistical model, assumptions and hypotheses

**Dose proportionality**

An exploratory assessment of dose proportionality for LMB763 and LMB763 metabolites Corporate Confidential Information will be conducted. Log-transformed dose-normalized Day 1 and Day 42 AUC and Cmax will be analyzed separately using an Analysis of Variance (ANOVA) with dose as the classification factor. A comparison between the 2 doses will be made within the ANOVA framework. The ratio of geometric means and the associated 90% confidence interval (CI) will be obtained by back-transforming the least squares mean treatment difference and the corresponding 90% CI in the log domain to the original scale.

# 6 Statistical methods for Pharmacodynamic (PD) parameters

## 6.1 Primary objective

One of the primary objectives of this study is to assess the efficacy of LMB763 in NASH patients during 12 weeks of treatment.

### 6.1.1 Variable

Change from baseline in ALT is the primary efficacy variable. Baseline is defined as the mean of ALT levels at Baseline (V2) and pre-dose (V101) visits.

### 6.1.2 Descriptive analyses

The absolute and change from baseline as well as percent change from baseline ALT measurements will be listed by treatment, subject 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.

Mean (SE) absolute and change from baseline ALT as well as geometric mean ratio to baseline ALT (90% CI) over time will be plotted by treatment.

### 6.1.3 Statistical model, assumptions and hypotheses

**Bayesian approach**

A Bayesian approach will be used to analyze the change from baseline to Week 12 in ALT, which is assumed to follow a normal distribution with a known variance for each treatment arm. An informative prior for the placebo treatment effect and a non-informative prior for the LMB763 treatment effect will be incorporated in the analysis. The variance and the informative prior will be based on historical control data from external and/or internal studies such as the FLINT trial (Neuschwander-Tetri et al 2015). Median estimates, 90% credible intervals and posterior probabilities that the placebo-adjusted ALT reduction by an LMB763 dose is (a) greater than 0 and (b) greater than 19 U/L and/or another cutoff value will be provided within the Bayesian framework.

The cohort effect will be explored and a cohort-wise analysis may be performed as needed.

If placebo data from in-house studies in a similar patient population become available they may be included in an ANCOVA on log-transformed data via informative priors.

**Repeated measures approach**

A repeated measures analysis of covariance (ANCOVA) will be performed for change from baseline ALT. The model will include effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline, and baseline by visit interaction. The BMI group will have the following 2 strata: low BMI (Asian <30 and Non-Asian<35) and high BMI (Asian ≥30 and Non-Asian≥35). An unstructured variance-covariance structure will be used to amount for correlation among multiple measurements from the same patient and variance heterogeneity. If the unstructured covariance causes model convergence issues other simpler covariance structures will be considered. Point estimates, the associated two-sided 90% confidence interval as well as the p-values for treatment differences (including LMB 50 mg vs LMB 100 mg) will be obtained. The null hypothesis of no treatment difference will be tested at the one-sided 0.05 significance level. Both untransformed and log-transformed ALT will be analyzed, with log-transformed baseline in lieu of untransformed baseline as a covariate when log-transformed ALT is analyzed. For log-transformed ALT analysis the ratio to baseline results obtained by back transformation will be reported.

Additionally a repeated measures ANCOVA treating all post dose adjustment measurements as missing will be performed as well if the number of patients with dose adjustment is not small (for example, >20%).

The cohort effect will be explored and a cohort-wise analysis may be performed as needed.

### 6.1.4 Model checking procedures

Assuming missing at random, a patient with missing value at a visit will still contribute to the estimation of the treatment effect at the particular visit as the likelihood-based repeated measures ANCOVA borrows information from non-missing values of this patient and other patients.

### 6.1.5 Sensitivity analysis

As a sensitivity analysis the Bayesian analysis in Section 6.1.3 will be repeated with varying values of the effective sample size for the placebo prior. A further sensitivity analysis using different values of the common variance assumed in the likelihood function and the prior may be performed as needed. A Bayesian analysis without assuming the variance is known in the likelihood function may be performed as well.

If more than 10% of the data for the Bayesian analysis on the change from baseline to Week 12 in ALT are missing then as a sensitivity analysis the Last Observation Carried Forward (LOCF) approach and/or another method may be used to impute missing data and the Bayesian analysis re-conducted.

### 6.1.6 Supportive analysis

The subgroup of subjects in Cohort 2, meeting the Cohort 1 ALT inclusion criterion (ALT $\geq$ 60 IU/L (males) or $\geq$ 40 IU/L (females)), may also be analyzed separately, if enough subjects meet the criterion. The analyses may include, but not limited to, the same descriptive and inferential analyses described in Sections 6.1.2 and 6.1.3 respectively. Additionally a repeated measures ANCOVA with 4 levels for the treatment effect (100 mg LMB, placebo to 100 mg LMB, 50 mg LMB, placebo to 50 mg LMB) may be performed to compare LMB to placebo within each cohort.

## 6.2 Secondary objectives

### 6.2.1 Variables

The secondary 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
- Non-invasive markers of liver fibrosis:
  - Fibroscan® (in a subset of patients)
  - Enhanced liver fibrosis panel (ELF) and fibrosis biomarker test (originally known as Fibrotest®/FibroSure®).
- Fasting lipid profile: total cholesterol, HDL, LDL and triglycerides
- Itch scored on 100 mm visual analog scale (VAS) ratings.

Baseline for all secondary parameters is defined as the last measurement prior to the first dose.

### 6.2.2 Descriptive analyses

The secondary variables and the corresponding change from baseline and percent change from baseline will be listed by treatment, subject and visit/time and descriptive statistics will be provided by treatment and visit/time, as needed. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum as appropriate.

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

### 6.2.3 Statistical model, assumptions and hypotheses

Log-transformed ratio to baseline % liver fat and fasting lipid profiles as well as change from baseline % liver fat, weight, BMI, WTH ratio and itch VAS score will be analyzed. Parameters with more than one post-treatment measurement will be subjected to the same repeated measures ANCOVA described for the primary analysis using log-transformed baseline in lieu of untransformed baseline as a covariate for the log-transformed data analysis. For parameters with only one post-treatment measurement an ANCOVA with treatment as a classification factor and baseline (or log-transformed baseline if applicable) as a covariate will be employed.

Fibroscan® (in a subset of patients), ELF and fibrosis biomarker test data will be analyzed similarly and the log-transformation applied prior to the analysis as needed. For % liver fat, if historical placebo control data in a similar patient population are identified in the literature or become available from in-house studies later on then they may be incorporated into a Bayesian analysis as described for ALT.

The subgroup of subjects with baseline liver fat $\geq$ 10% may be analyzed separately as needed.

# 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 and subject and summarized by treatment.

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

### Treatment

Use of concomitant medications and data on administration of study drug will be listed by treatment, and subject.

The number and percent of subjects with dose adjustments may be tabulated and the summary statistics for the study day at which the dose adjustment occurred provided by treatment.

### 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. 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 system organ class 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

The relationship between LMB763 PK parameters (Cmax and AUCtau) and key PD parameters (including, but not limited to ALT, AST, GGT, ALP, FGF19, C4, % liver fat, Cholesterol (total, LDL and HDL) and the relationship between UGT1A1 polymorphism (if data available) and PK parameters as well as the relationship between PD markers (FGF19, C4) and efficacy markers (ALT, GGT, fibrosis markers) may be explored using a graphical approach and descriptive statistics may be provided. The effect of LMB763 Corporate Confidential Information levels on QTcF will also be explored. Additional statistical analysis such as ANOVA or regression may be performed, if necessary. Modelling approach may also be used to explore the PK/PD interactions. Results from the exploratory assessment of the relationship between UGT1A1 polymorphism and PK parameters will be reported in the CSR if the decision to carry-out this exploratory gated assessment is taken prior to or at IA2.

# 10 Derivations

### 10.1.1 HOMA-IR

Depending on the units which fasting glucose and fasting insulin are given in, HOMA-IR will be calculated as:

HOMA-IR = Fasting glucose (mmol/L) x fasting insulin (mU/L) / 22.5

HOMA-IR = Fasting glucose (mg/dL) x fasting insulin (mU/L) / 405

### 10.1.2 Fibrosis biomarker test, originally called Fibrotest®/ Fibrosure®

The score is calculated as:

$z = 4.467 \times \log_{10}(\alpha 2\text{-macroglobulin}) - 1.357 \times \log_{10}(\text{Haptoglobin}) + 1.017 \times \log_{10}(\text{GGT}) + 0.0281 \times \text{Age} + 1.737 \times \log_{10}(\text{Bilirubin}) - 1.184 \times \text{ApoA1} + 0.301 \times \text{Sex (0=female, 1=male)} - 5.540.$

Where:
α2-macroglobulin is given in g/L,
Haptoglobin is given in g/L,
GGT is given in U/L,
Age is given in years,
Bilirubin is given in µmol/L,
ApoA1 is given in g/L,
Sex is given as 0 for female and 1 for male.

Reference: [http://www.google.com/patents/US6631330]

### 10.1.3 FIB-4

FIB-4 = (age * AST) / (platelets * sqrt(ALT)),

where age is given in years, AST and ALT in U/L and platelets in $10^9$/L.

### 10.1.4 APRI

APRI = (AST / ULN (AST)) / platelets,

where platelets are given in $10^9$/L and ULN is the upper limit of the normal range for AST.

### 10.1.5 Disease scores and diagnostic algorithms

#### 10.1.5.1 NAFLD fibrosis score

The NAFLD fibrosis score is calculated as [Angulo et al. (2007)]:

z = -1.675 + 0.037 * age + 0.094 * BMI + 1.13 * diabetes (0=no, 1=yes) + 0.99 * (AST/ALT) – 0.013 * platelets – 0.66 * albumin,

where age is given in years, BMI in kg/$m^2$, platelets in $10^9$/L, albumin in g/dL.

#### 10.1.5.2 Algorithm for diagnosis of NASH

A diagnostic algorithm was developed by [Bazick et al. (2015)]:

Logit(P) = 27.00 + 0.106 * BMI (kg/m2) – 0.035 * waist (cm) + 0.068 * AST (U/L) – 0.016 * ALT (U/L) + 0.71 * albumin (g/dL) + 0.24 * $HbA_{1c}$ (%) + 0.0570 * HOMA-IR (mg/dL * µU/mL/405) + 0.0014 * ferritin (ng/dL) + 0.57 * white (0=no, 1=yes).

A subject is classified as having NASH if the calculated probability P is ≥ 0.77.

## 11 Reference list

Neuschwander-Tetri BA, Loomba R, Sanyal AJ, et al (2015) Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet p. 956-65.