NOVARTIS

Clinical Development

LMB763 (nidufexor)

LMB763X2202 / NCT03804879

A randomized patient-and-physician blinded, placebo-controlled, 24-week study to assess the safety, tolerability and efficacy of LMB763 in patients with diabetic nephropathy

Statistical Analysis Plan (SAP)

Author:	Personal Protected Data
Document type:	SAP Documentation
Document status:	Final
Release date:	23-JUL-2021
Number of pages:	15

Document History – Changes compared to previous final version of SAP

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List of abbreviations

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AE	Adverse event
ANCOVA	Analysis of Covariance

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AUC	Area Under the Curve
BMI	Body Mass Index
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set

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FXR	Farnesoid X receptor
HbA1c	Glycated haemoglobin
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PRO	Patient-reported Outcomes
RAP	Report and Analysis Process
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFLs	Tables, Figures, Listings
VAS	Visual Analog Scale
WHO	World Health Organization

1 Introduction

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

1.1 Study design

This study is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, fixed-dose, proof-of-concept trial assessing LMB763 (nidufexor) vs. placebo in approximately 100 patients receiving standard of care (optimal tolerated doses of ARB or ACEI) for diabetic nephropathy due to type 2 diabetes. The study consists of a 30-day (Day -30 to Day-1) Screening period, followed by a 24-week Treatment Period (Days 1 through 168), at which point End of Study (EOS) assessments will occur on Day 169. All study visit assessments will occur pre-dose, starting on Day 1 of the therapeutic period. PK profiling (up to 6 hours post-dose) will be done on Day 1 and 14. Post Study Safety Contact will occur approximately 28 days after discontinuing study treatment (Day 197).

The study design scheme appears below. On visit days, study medication will be administered by site personnel. Each visit during the treatment and follow-up periods will have an allowable window of +/-5 days.

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

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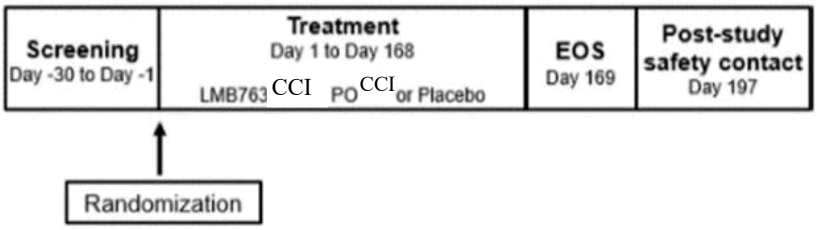
Figure 1-1 LMB763X2202 study design



- Patients will be randomized in a 1:1 ratio to receive nidufexor CCI or placebo.

Approximately 116 patients will be enrolled in the study and randomized. Approximately 100 patients are expected to complete the study.

- Study medication will be self-administered by patients CCI for 24 weeks. On visit days, study medication will be administered at the site.

1.2 Study objectives and endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To compare the effect of nidufexor to placebo on albuminuria in patients with diabetic nephropathy already receiving treatment with ACEI or ARB	• Urine albumin-creatinine ratio (UACR) at serial time points, as specified in the assessment schedule in the protocol • 24-hour urinary albumin at baseline and end of study

• To assess the safety and tolerability of nidufexor	• Safety endpoints including:
	  • vital signs
	  • physical examination
	  • laboratory measurements
	  • ECG parameters
	  • adverse events

Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To determine the effect of nidufexor on renal filtration function	• Estimated glomerular filtration rate (eGFR), as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010)
• To assess the pharmacokinetic properties of nidufexor on day 1 and at steady state in patients with type 2 diabetes and nephropathy	• Cmax, Tmax and AUC0-6h.
• To determine the effect of nidufexor on renal tubular function	• Free water clearance

• To determine the effect of nidufexor on anthropometric assessments	• Assessments
	  • Weight
	  • BMI
	  • Waist-to-hip (WTH) ratio

• To determine the effect of nidufexor on lipids	• Fasting lipid profile, including lipoprotein (a) [Lp(a)]

Objective(s)	Endpoint(s)

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2 Statistical methods

2.1 Data analysis general information

Novartis will be performing primary/final analysis including interim analysis. SAS will be used to generate all the outputs. Baseline will be defined as the last measurement prior to the first administration of the study drug.

2.2 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment received unless indicated otherwise.

The safety analysis set will include all patients who received any study drug.

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

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data, with data exclusion including but not limited to:

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2. EOS visit assessments when they were done earlier than day 135.
3. EOS visit assessments when they were done > 10 days from the last dose.

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Protocol deviation impact, including the impact due to COVID-19, will be documented appropriately and assessed by the Sponsor study team, including the Medical and Study Leads with input from the trial team.

2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the Safety set and PD analysis set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles may also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by treatment group, system organ class and preferred term.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by treatment group according to the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

2.5 Analysis of the primary objective

The primary objective of this study is to assess the safety and tolerability of LMB763 as well as the efficacy of LMB763 on albuminuria in patients with diabetic nephropathy during 24 weeks of treatment.

2.5.1 Primary endpoint

For analytical purposes, all safety data, including laboratory measurements, vital signs, adverse events, ECG, are considered primary endpoints.

For efficacy evaluation, log-transformed ratios to baseline UACR and 24-hour urine albumin excretion at Week 24 are the primary endpoints.

The raw value, ratio to baseline and log-transformed ratio to baseline of UACR will be plotted for each subject over time.

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Safety endpoints

For all safety analyses, the safety set will be used. Safety and tolerability data will be summarized. Formal statistical analysis will not be performed on the safety and tolerability data.

Adverse events

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

The number (and percentage) of patients with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum CTCAE grade

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs, AEs leading to study discontinuation of study treatment, study-drug related AEs leading to study discontinuation of study treatment, AEs leading to dose interruption/reduction and COVID-19 events.

A patient with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 0% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

In addition, the following figures will be plotted.

1. The pruritus events over time by toxicity grade will be plotted by subject.
2. The dosing records over time will be plotted by subject for those with pruritus events.
3. The pruritus events and dosing records over time will also be plotted in the same figure by subject for those with pruritus events.

Vital signs

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

12-lead ECG

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

Clinical laboratory evaluations

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

2.5.2.2 Efficacy and/or pharmacodynamic endpoints

For all efficacy PD analyses, the PD set will be used.

A Mixed Model for Repeated Measures (MMRM) analysis will be performed for log-transformed ratio to baseline UACR measured at each visit. The model will include effects for log-transformed baseline, treatment, visit, treatment by visit interaction and visit by log-transformed baseline interaction. An unstructured variance-covariance matrix will be used to account for correlation among multiple measurements from the same patient and variance heterogeneity.

Similarly an Analysis of Covariance (ANCOVA) with treatment as the classification factor and log-transformed baseline as the covariate will be conducted for log-transformed ratio to baseline 24-hour urine albumin excretion.

Point estimates, the associated confidence intervals as well as the p-values for treatment difference at each visit will be provided within the MMRM/ANCOVA framework. The null hypothesis of no treatment difference in UACR or 24-hour urine albumin excretion will be tested at the one-sided 0.1 significance level. A treatment difference of at least 25% in favor of LMB763 will be considered clinically significant.

2.5.3 Handling of missing values/multiple values/censoring/discontinuations.

Missing data will not be imputed.

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

For central lab data collected at scheduled visits, the following sequential approach will be taken before data summary and analysis.

1. Take the average by subject, date and time for each parameter first.

2a. Derive baseline as the last available value prior to Day 1 dosing for each subject and parameter.

2b. Take the average by subject and visit for each parameter and then merge with the dataset containing baseline from 2a by subject and parameter.

The same approach as described above will be taken for vital sign and VAS data.

Local lab data will be included along with central lab data in the data listings and liver/renal event tables.

For ECG, 3 measurements on each visit are expected. The mean value will be used in the analyses even though the times are different.

For the analyses of liver abnormality and renal events, the most extreme value expressed as the multiple of the upper limit of normal (xULN) in a visit will be used for analyses.

2.5.4 Supportive analyses

The raw value, ratio to baseline and log-transformed ratio to baseline of UACR will be plotted for each subject over time.

Absolute change from baseline in UACR and 24 hour UALB will also be analyzed using MMRM and ANCOVA, respectively.

The following supplementary analyses for UACR will be performed CCI separately.

1. Use value from Day 1 24 hour urine collection instead of last measurement prior to 1st dose as the baseline. Subjects without Day 1 value will be excluded from analysis.
2. Set assessments to missing if they were taken after dose reduction/interuption due to AEs and physician decision
3. Exclude subjects with baseline UACR < 300
4. Include all data from all randomized subjects and use the assigned treatment instead of the actual treatment received in the analysis (Intention to Treat, i.e., ITT)
5. Exclude week 24 measurements taken on day 134 or earlier from the ITT analysis
6. Exclude subjects with baseline UACR> 14000

The following supplementary analyses for 24 hour UALB will be performed separately.

1. Set assessments to missing if they were taken after dose reduction/interuption due to Aes and physician decision
2. Exclude subjects with baseline UACR < 300
3. ITT analysis
4. Exclude week 24 measurements taken on day 134 or earlier from the ITT analysis

2.6 Analysis of secondary efficacy objective(s)

2.6.1 Efficacy and/or Pharmacodynamic endpoint(s)

Log-transformed ratio to baseline for eGFR, free water clearance, HbA1c and fasting lipid profiles (total cholesterol, HDL, LDL, triglycerides and Lp(a)) as well as % change from baseline in weight and change from baseline in BMI and WTH ratio will be analyzed using the same MMRM described in Section 2.5.2.2 with baseline in lieu of log-transformed baseline as a covariate for change from baseline 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.

The raw value, change from baseline, ratio to baseline and log-transformed ratio to baseline of HbA1c will be plotted for each subject over time.

The free water clearance (mL/min) will be calculated using the following formula:

(Total Volume (mL) / Elapsed Date & Time (min)) * (1-24 hr Urine Osmolality (mOsmol/kg) / Serum Osmolality (mOsmol/kg))

The result of free water clearance will be rounded to one decimal place prior to statistical analysis.

2.7 Pharmacokinetic endpoints

LMB763 plasma concentration data will be listed by patient and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point,

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Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

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The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, and AUClast from the plasma concentration-time data. The linear trapezoidal rule will be used for AUC calculation.

2.8 PD and PK/PD analyses

The relationship between key efficacy/PD parameters (including, but not limited to UACR, 24-hour urine albumin excretion and eGFR) and LMB763 PK parameters (Cmax and AUC0-6) may be explored using a graphical approach. Additional statistical analysis such as regression may be performed, if necessary. Modeling approach may also be used to explore the PK/PD interactions as well as effect of covariates and their significance on the PK/PD relationship.

2.9 Patient-reported outcomes

Change from baseline itch VAS measurements will be analyzed using the same MMRM described in Section 2.5.2.2.

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2.11 Interim analysis

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3 Change to protocol specified analyses

No changes from protocol specified analysis were made.

4 Appendix

4.1 Rule of exclusion criteria of analysis sets

Table 1 Protocol deviations that cause subjects to be excluded

Deviation Category	Description of Deviation	Exclusion in Analyses
		Excluded from all (safety) analysis set
		Excluded from PK analysis set

Deviation Category	Description of Deviation	Exclusion in Analyses
Treatment	<80% compliant with study drug administration	Excluded from Week 24 PD summary/analysis
Treatment	The assessments of EOS visit are taken more than 10 days after the last dose date	Excluded from Week 24 PD summary/analysis
Treatment	The assessments of EOS visit from patients who took IMP a month longer than protocol	Excluded from Week 24 PD summary/analysis
Other	Week 24/EOS (Day 169) assessments were done on Day 134 or earlier	Excluded from Week 24 PD summary/analysis
COMD	Taking SGLT2 as prohibited medication	Excluded from PD summary/analysis for the affected time period

5 Reference

Not applicable.