

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)**

Document type: Amended Protocol Version
EUDRACT number: 2016-002833-31
Version number: v03 (Clean)
Clinical Trial Phase: II
Release date: 02-Oct-2017

Property of Novartis
Confidential
May not be used, divulged, published, or otherwise disclosed
without the consent of Novartis

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not be 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.

Table of contents

Site Operations Manual (SOM).....	2
Notification of serious adverse events.....	2
Table of contents	3
List of tables	7
List of figures	7
List of abbreviations	8
Pharmacokinetic definitions and symbols	10
Glossary of terms.....	11
Corporate Confidential Information	
Protocol synopsis.....	16
1 Introduction	21
1.1 Background.....	21
Corporate Confidential Information	
1.4 Study purpose	25
2 Study objectives and endpoints	25
2.1 Primary objectives	25
2.2 Secondary objectives	26
Corporate Confidential Information	
3 Investigational plan	28
3.1 Study design.....	28
3.2 Rationale of study design.....	30
3.3 Rationale for dose/regimen, route of administration and duration of treatment....	31
3.4 Rationale for choice of comparator	32
3.5 Rationale for choice of background therapy.....	32
Corporate Confidential Information	
3.7 Risks and benefits	32
3.7.1 Blood sample volumes	33

4	Population.....	34
4.1	Inclusion criteria	34
4.2	Exclusion criteria	36
5	Restrictions for Study Patients	39
5.1	Contraception requirements.....	39
5.2	Prohibited treatment.....	40
5.3	Dietary restrictions.....	42
6	Treatment.....	42
6.1	Study treatment.....	42
6.1.1	Investigational treatment and control drugs.....	42
6.1.2	Additional study treatment.....	42
6.2	Treatment arms	43
6.3	Treatment assignment and randomization	43
6.4	Treatment blinding.....	44
6.5	Treating the patient.....	45
6.6	Permitted dose adjustments and interruptions of study treatment.....	45
6.7	Emergency breaking of assigned treatment code	49
6.8	Treatment exposure and compliance	49
6.9	Recommended treatment of adverse events	49
6.10	Rescue medication.....	50
6.11	Concomitant treatment.....	50
7	Study completion and discontinuation	50
7.1	Study completion and post-study treatment	50
7.2	Discontinuation of study treatment.....	50
7.3	Withdrawal of informed consent	51
7.4	Lost to follow-up	52
7.5	Study Stopping rules.....	52
7.6	Early study termination by the sponsor	53
8	Procedures and assessments	54
8.1	Assessment schedule	54
8.2	Informed consent procedures.....	57
8.3	Patient screening.....	57
8.4	Patient demographics/other baseline characteristics	57
8.4.1	Hepatitis screen, HIV screen.....	58
8.4.2	Alcohol test, Drug screen.....	58
8.5	Efficacy / Pharmacodynamics	58
8.5.1	Liver function tests (LFTs)	58

8.5.2	Magnetic Resonance Imaging	58
8.5.3	Markers of Liver Fibrosis.....	59
8.5.4	Fasting Lipids.....	59
8.5.5	Anthropometric Assessments.....	59
8.5.6	Clinical Outcome Assessments (COAs)	59
8.6	Safety	59
8.6.1	Physical examination	59
8.6.2	Vital signs.....	60
8.6.3	Laboratory evaluations.....	60
8.6.4	Electrocardiogram (ECG)	60
8.6.5	Pregnancy assessments.....	61
8.7	Pharmacokinetics.....	61
	Corporate Confidential Information	
9	Safety monitoring	63
9.1	Adverse events.....	63
9.2	Serious adverse event reporting.....	65
9.2.1	Definition of SAE	65
9.2.2	SAE reporting.....	66
9.3	Liver safety monitoring	66
9.4	Renal safety monitoring.....	70
9.5	Reporting Medication errors including misuse/abuse	71
9.6	Pregnancy reporting.....	72
9.7	Early phase safety monitoring	73
10	Data review and database management.....	73
10.1	Site monitoring	73
10.2	Data collection.....	74
10.3	Database management and quality control	74
10.4	Data Monitoring Committee.....	75
10.5	Adjudication Committee.....	75
11	Data analysis.....	75
11.1	Analysis sets	75
11.2	Patient demographics and other baseline characteristics.....	75

11.3	Treatments	76
11.4	Analysis of the primary variable(s)	76
11.4.1	Variable(s).....	76
11.4.2	Statistical model, hypothesis, and method of analysis	76
11.4.3	Handling of missing values/censoring/discontinuations	77
11.4.4	Summary statistics of safety.....	77
11.4.5	Sensitivity analyses	77
11.5	Analysis of secondary variable(s).....	77
11.5.1	Efficacy / Pharmacodynamics.....	77
11.5.2	Pharmacokinetics	78
11.5.3	Pharmacokinetic / pharmacodynamic interactions.....	78
11.5.4	Other assessments	79
	Corporate Confidential Information	
11.7	Sample size calculation.....	79
11.8	Power for analysis of key secondary variables	80
	Corporate Confidential Information	
12	Ethical considerations.....	81
12.1	Regulatory and ethical compliance.....	81
12.2	Responsibilities of the investigator and IRB/IEC	81
12.3	Publication of study protocol and results.....	81
13	Protocol adherence	81
13.1	Protocol Amendments	82
14	References	83
15	Appendix 1: The American Heart Association (AHA) Recommended Diet	84

List of tables

Table 5-1	Prohibited medication	41
Table 5-2	Permitted medications if dose is stable for at least 1 month prior to randomization.....	41
Table 6-1	Treatment Assignment Numbering – Cohort 1	43
Table 6-2	Treatment Assignment Numbering – Cohort 2.....	44
Table 6-3	Dosing response to Isolated ALT/AST Elevations	47
Table 9-1	Liver Event Definitions.....	67
Table 9-2	Actions required for Liver Events.....	68
Table 9-3	Exclusion of underlying liver disease	70
Table 9-4	Specific Renal Alert Criteria and Actions.....	70
Table 9-5	Follow-up of renal events.....	71
Table 9-6	Summary of reporting requirements for medication errors.....	72

List of figures

Figure 1-1	Coordinated effects of FXR agonism on metabolism	21
Figure 3-1	Study design – Cohort 1	28
Figure 3-2	Study design – Cohort 2	29

List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CK	creatinine kinase
COAR	Clinical Operations, Analytics & Regions
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
FXR	Farnesoid X Receptor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	Hour
HIV	human immunodeficiency virus
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase

LFT	Liver function test
LLN	lower limit of normal
LLQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRI	Magnetic resonance imaging
NASH	Non-alcoholic steatohepatitis
NCDS	Novartis Clinical Data Standards
o.d.	once a day
p.o.	Oral
PA	posteroanterior
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
ULN	upper limit of normal
ULQ	upper limit of quantification
WBC	white blood cell(s)
WHO	World Health Organization
WTH	Waist to hip

Pharmacokinetic definitions and symbols

AUC _{last}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUC _{tau}	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
C _{max}	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
R _{acc}	The accumulation ratio
T _{1/2,acc}	The effective half-life based on drug accumulation at steady state [time]
T _{max}	The time to reach the maximum concentration after drug administration [time]
V _{z/F}	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

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 (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)
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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.

Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
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
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
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.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm

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, <u>and</u> does not want any further visits or assessments, <u>and</u> does not want any further study related contact, <u>and</u> does not allow analysis of already obtained biologic material

Corporate Confidential Information

Protocol synopsis

Protocol number	CLMB763X2201
Title	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)
Brief title	Study of safety, tolerability, pharmacokinetics and efficacy of LMB763 in patients with non-alcoholic steatohepatitis (NASH)
Sponsor and Clinical Trial Phase	Novartis Phase 2
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to assess the safety, tolerability, pharmacokinetics (PK) of, and early hepatic response to LMB763 administration for 12 weeks in patients with phenotypic non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further development of LMB763 in the treatment of patients with NASH.
Primary Objective(s)	<ul style="list-style-type: none"> To determine the safety and tolerability of LMB763 during 12 weeks of treatment To determine the effect of LMB763 on circulating alanine aminotransferase (ALT) levels
Secondary Objectives	<ul style="list-style-type: none"> To evaluate the pharmacokinetics (PK) of LMB763 in NASH patients To determine the effect of LMB763 on intrahepatic lipid after 12 weeks of treatment To determine the effect of LMB763 on anthropometric assessments after 12 weeks of treatment To determine the effect of LMB763 on non-invasive markers of liver fibrosis To determine the effect of LMB763 on fasting lipid profile To determine the effect of LMB763 compared with placebo with respect to occurrence and impact of potential itch
Study design	<p>This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study in patients with NASH. The study will be conducted in two cohorts:</p> <p>Cohort 1: Corporate Confidential Information Approximately 96 patients will be randomized in a 2:1 ratio to receive LMB763 or matching placebo. The study will consist of a screening period of 45 days, baseline period of 14 days, treatment period of 12 weeks, followed up a study completion evaluation approximately 28 days after the final drug administration.</p> <p>Cohort 2: Approximately 96 patients will be randomized in a 2:1 ratio to receive LMB763 or matching placebo. The study will consist of a screening period of 45 days, baseline period of 20 days, treatment period of 12 weeks, followed up a study completion evaluation approximately 28 days after the final drug administration.</p>

<p>Population</p>	<p>The study population will comprise male and female adult patients with EITHER histologic evidence of NASH on liver biopsy within 2 years prior to randomization and elevated ALT, OR phenotypic diagnosis of NASH based on elevated ALT, Type 2 diabetes mellitus or elevated HbA1c and increased BMI.</p>
<p>Key Inclusion criteria</p>	<p>Cohort 1</p> <ul style="list-style-type: none"> • Male and female patients 18 years or older (at the time of the screening visit) • Presence of NASH as demonstrated by ONE of the following: <p>EITHER</p> <ol style="list-style-type: none"> 1. Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases <ul style="list-style-type: none"> AND ALT \geq 60 IU/L (males) or \geq 40 IU/L (females) <p>OR</p> <ol style="list-style-type: none"> 2. Phenotypic diagnosis of NASH based on the presence of ALL THREE of the following: <ul style="list-style-type: none"> • ALT \geq 60 IU/L (males) or \geq 40 IU/L (females) AND • BMI \geq 27 kg/m² (in patients with a self-identified race other than Asian) or \geq 23 kg/m² (in patients with a self-identified Asian race) AND • Diagnosis of Type 2 diabetes mellitus by having either: <ul style="list-style-type: none"> • HbA1C \geq 6.5% <p>OR</p> <ul style="list-style-type: none"> • Symptoms of diabetes plus hyperglycemia as indicated by <ul style="list-style-type: none"> • fasting plasma glucose \geq 126 mg/dl (\geq 7.0 mmol/l) • two hour plasma glucose concentration \geq 200mg/dl (\geq 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT)) <p>OR</p> <ul style="list-style-type: none"> • Drug therapy for Type 2 diabetes mellitus <p>Cohort 2</p> <ul style="list-style-type: none"> • Male and female patients 18 years or older (at the time of the screening visit) • Liver fat \geq 10% at baseline as determined by the reading of the central MRI laboratory of locally produced images • Presence of NASH as demonstrated by ONE of the following: <p>EITHER</p> <ol style="list-style-type: none"> 3. Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases <ul style="list-style-type: none"> AND ALT \geq 43IU/L (males) or \geq 28 IU/L (females) <p>OR</p> <ol style="list-style-type: none"> 4. Phenotypic diagnosis of NASH based on the presence of ALL THREE of the following:

	<ul style="list-style-type: none"> • ALT \geq 43 IU/L (males) or \geq 28 IU/L (females) AND • BMI \geq 27 kg/m² (in patients with a self-identified race other than Asian) or \geq23 kg/m² (in patients with a self-identified Asian race) AND • Diagnosis of Type 2 diabetes mellitus by having either: <ul style="list-style-type: none"> • HbA1C \geq 6.5% OR <ul style="list-style-type: none"> • Symptoms of diabetes plus hyperglycemia as indicated by <ul style="list-style-type: none"> • fasting plasma glucose \geq126 mg/dl (\geq 7.0 mmol/l) • two hour plasma glucose concentration \geq 200mg/dl (\geq 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT)) OR <ul style="list-style-type: none"> • Drug therapy for Type 2 diabetes mellitus
<p>Key Exclusion criteria</p>	<p>Cohort 1 and 2</p> <ul style="list-style-type: none"> • Current use of obeticholic acid (OCA) • New initiation of GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide or DPP4 inhibitors such as sitagliptin, vildagliptin, saxagliptin or linagliptin within 3 months of screening • Patients on treatment with the following medicines UNLESS they are on a stable dose for at least 1 month before randomization: insulin (no more than \geq25% change in dose), beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 200 IU/day; doses > 800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control. For oral anti-diabetic medications, no more than one step up in local prescribing guidelines will be allowed. • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 days (approximately 5 times the terminal half life) after stopping study medication • Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the AUDIT questionnaire \geq8 as administered by the site as part of the medical history • History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline. Marijuana use is not allowed if it is determined to be medically inappropriate by the investigator • Calculated eGFR less than 60 mL/min (using the MDRD formula) • Presence of cirrhosis on liver biopsy or clinical diagnosis • Clinical evidence of hepatic decompensation or severe liver impairment • History or presence of other concomitant liver diseases • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study • Patients with contraindications to MRI imaging • For those patients that have had a previous biopsy: Significant weight loss (>15%) or change in clinical status (in the opinion of the investigator) since the diagnostic liver biopsy

<p>Study treatment</p>	<p>Study treatments are defined as:</p> <ul style="list-style-type: none"> • LMB763 capsules • LMB763 capsules • LMB763 capsules • Matching placebo capsules <p>Cohort 1: Approximately 96 patients will be randomly assigned in a ratio of 2:1 to receive LMB763 or matching placebo.</p> <p>Cohort 2: An additional approximately 96 patients will be randomized in a 2:1 ratio to receive LMB763 or placebo.</p> <p>All patients who have been enrolled into the initial cohort will complete the protocol at that dose, however no further patients will be recruited into that cohort</p>
<p>Efficacy/PD assessments</p>	<ul style="list-style-type: none"> • Liver function tests (ALT) • Magnetic Resonance Imaging (MRI) • Anthropometric assessments • • Fasting lipids • Visual Analog Scale (VAS) for Itch
<p>Key safety assessments</p>	<ul style="list-style-type: none"> • Physical examination • Vital signs • Laboratory evaluations • Electrocardiogram • Pregnancy assessments
<p>Other assessments</p>	<p>Corporate Confidential Information</p>

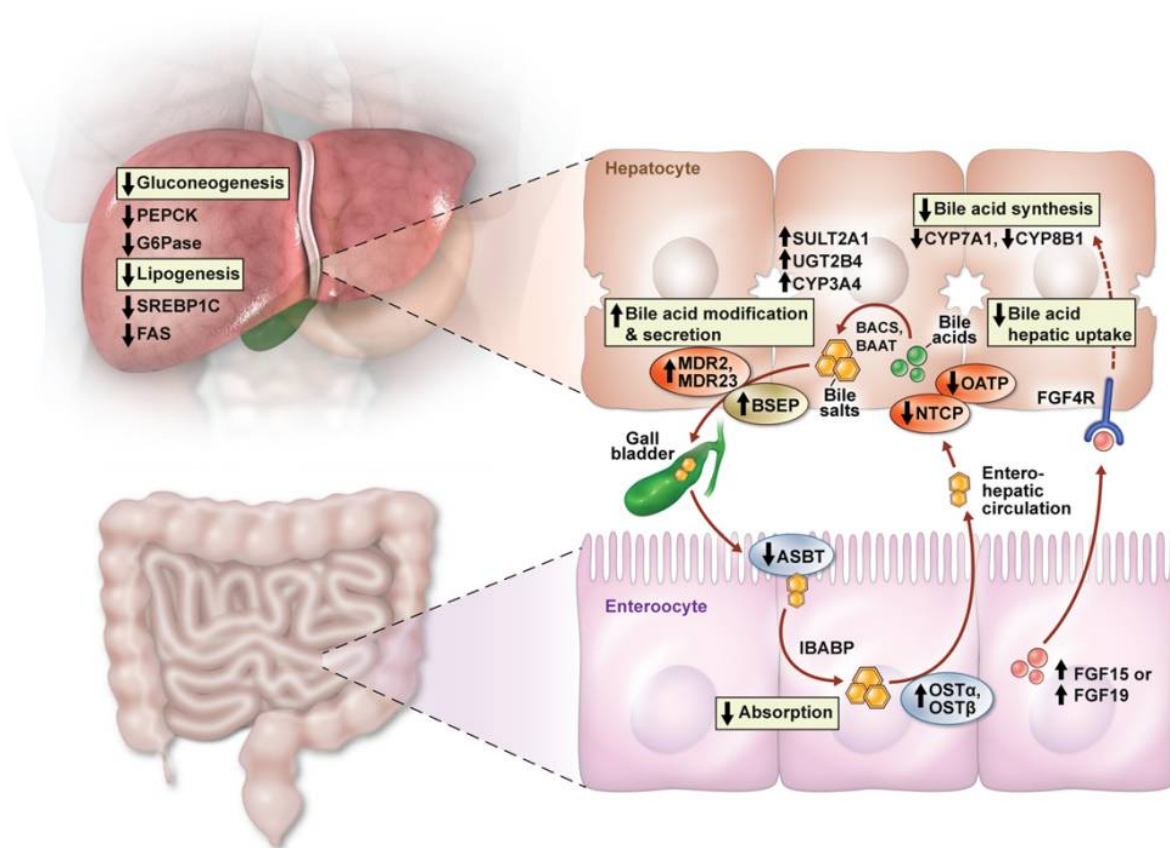
Data analysis	<p>The change from baseline to Week 12 in ALT is the primary efficacy variable.</p> <p>A Bayesian approach will be used to analyze the change from baseline to Week 12 in ALT, which is assumed to follow a normal distribution with a known variance for each treatment arm. An informative prior for the placebo treatment effect and a non-informative prior for the LMB763 treatment effect will be incorporated into the analysis. The variance and the informative prior will be based on historical control data from studies such as the FLINT trial. Median estimates, 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. As a sensitivity analysis, the posterior probabilities will be calculated for 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. An analysis using SAS PROC MCMC without assuming the variance is known in the likelihood function may be performed as well.</p> <p>Additionally a repeated measures analysis of covariance (ANCOVA) will be performed for change from baseline ALT without using historical placebo control data. The model will include effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline, and baseline by visit interaction. An unstructured variance-covariance structure will be used to account for correlation among multiple measurements from the same patient and variance heterogeneity. Point estimates, the associated two-sided 90% confidence intervals as well as the p-values for treatment differences 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. For log-transformed ALT analysis the ratio to baseline results obtained by back transformation will be reported.</p> <p>The cohort effect will be explored and a cohort-wise analysis for both the Bayesian and ANCOVA approaches may be performed as needed.</p> <p>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.</p>
Key words	Non-alcoholic Steatohepatitis, NASH,

1 Introduction

1.1 Background

LMB763 is a potent partial agonist of the bile acid receptor Farnesoid X Receptor (FXR). Proposed indications for LMB763 include non-alcoholic steatohepatitis (NASH), cholestatic and other hepatic disorders caused by over production and malabsorption of bile acids.

Figure 1-1 Coordinated effects of FXR agonism on metabolism



FXR regulates metabolic pathways through multiple mechanisms in the liver and intestine. The processes regulated by FXR are shown in rectangular boxes. Genes are shown with up or down arrows to indicate the direction of regulation by FXR agonists. Arrows are used to show the flow of bile acids in the enterohepatic circulation or the movement of FGF15/19 from the enterocyte to the hepatocyte. In normal physiology, FXR detects increased levels of bile acids and responds by decreasing bile acid synthesis and bile acid uptake while increasing bile acid modification and secretion in the liver. In the intestine, FXR detects increased bile acid levels and decreases bile acid absorption and increases secretion of FGF15/19. The net result is a decrease in the overall levels of bile acids, decrease in gluconeogenesis and lipogenesis in the liver (Redrawn from [Calkin and Tontonoz 2012](#)).

Nonalcoholic steatohepatitis (NASH) is a condition characterized by increased fat accumulation in the liver and attendant hepatocellular damage and inflammation. NASH is a cause of progressive fibrosis and metabolic liver disease, and is a leading cause of cirrhosis and hepatocellular carcinoma. Clinical validation of FXR agonism for therapy of NASH has been shown in a Phase 2 clinical trial ([Neuschwander-Tetri et al 2015](#)) in which a bile acid derived FXR agonist lead to improvements in hepatic fibrosis and in some cases resolution of NASH. Thus, pharmacological activation of FXR is proposed to be an effective treatment for NASH, and LMB763 has a clinical and preclinical profile that supports its use in this indication.

This is a First-in-Patient, non-confirmatory Phase 2 study to determine the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of LMB763. The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

Corporate Confidential Information

Corporate Confidential Information

1.4 Study purpose

This study is designed to assess the safety, tolerability, pharmacokinetics (PK) of, and early hepatic response to LMB763 administration for 12 weeks in patients with phenotypic non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further development of LMB763 in the treatment of patients with NASH.

2 Study objectives and endpoints

2.1 Primary objectives

<i>Primary objectives</i>	<i>Endpoints related to primary objectives</i>
<ul style="list-style-type: none">To determine the safety and tolerability of LMB763 during 12 weeks of treatment.	<ul style="list-style-type: none">Safety endpoints (including vital signs, physical examination, laboratory measurements, ECG).Adverse events.
<ul style="list-style-type: none">To determine the effect of LMB763 on circulating alanine aminotransferase (ALT) levels.	<ul style="list-style-type: none">Liver function tests (ALT).

2.2 Secondary objectives

Secondary objectives	Endpoints related to secondary objectives
<ul style="list-style-type: none"> To evaluate the pharmacokinetics (PK) of LMB763 in NASH patients. 	<ul style="list-style-type: none"> PK blood collection and analysis (C_{max}, T_{max}, AUC, R_{acc}, etc.).
<ul style="list-style-type: none"> To determine the effect of LMB763 on intrahepatic lipid after 12 weeks of treatment. 	<ul style="list-style-type: none"> Percent (%) Liver fat as measured by Magnetic Resonance Imaging (MRI).
<ul style="list-style-type: none"> To determine the effect of LMB763 on anthropometric assessments after 12 weeks of treatment. 	<ul style="list-style-type: none"> Weight, BMI, waist-to-hip (WTH) ratio.
<ul style="list-style-type: none"> To determine the effect of LMB763 on non-invasive markers of liver fibrosis. 	<ul style="list-style-type: none"> Fibroscan[®] (in a subset of patients) Fibrosis biomarker test (originally known as Fibrotest[®]/FibroSure[®]).
<ul style="list-style-type: none"> To determine the effect of LMB763 on fasting lipid profile. 	<ul style="list-style-type: none"> Fasting lipid profile.
<ul style="list-style-type: none"> To determine the effect of LMB763 compared with placebo with respect to occurrence and impact of potential itch. 	<ul style="list-style-type: none"> Itch scored on 100 mm visual analog scale (VAS) ratings.

3 Investigational plan

3.1 Study design

This is a non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, parallel group study, in two cohorts, in patients with NASH. The sponsor will remain unblinded to the treatment assignment of all patients to allow for continuous unblinded safety monitoring.

The study will be conducted in two cohorts:

Cohort 1: Corporate Confidential Information
Once eligibility has been confirmed at baseline, approximately 96 patients are planned to be randomized in a 2:1 ratio to receive LMB763 or matching placebo.

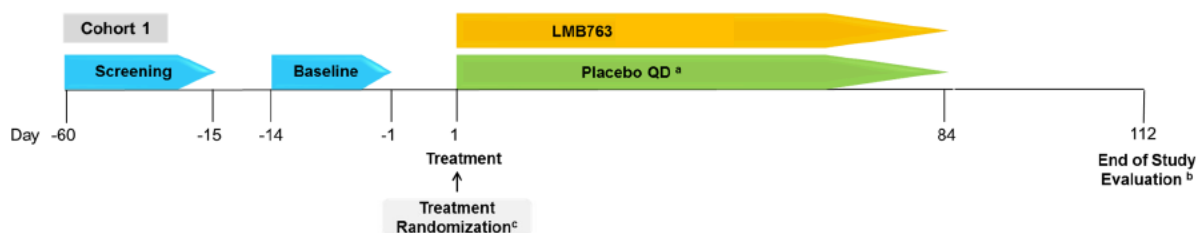
Cohort 2 Corporate Confidential Information
An additional approximately 96 patients will be randomized in a 2:1 ratio to receive LMB763 or placebo to ensure approximately 81 patients complete the study at this dose level.

All patients who have been enrolled into the initial cohort will complete the protocol at that dose, but no further patients will be recruited into Cohort 1 Corporate Confidential Information

Cohort 1

The study will consist of a 45 day screening period (Day -60 to Day -15), a baseline period of 14 days (Day -14 to Day -1), a treatment period of 12 weeks (Day 1 to Day 84), and a study completion evaluation approximately twenty-eight days after the last drug administration (Day 112 +/- 2 days). Patients will be advised to maintain their recommended diet for NASH during the study. The study design scheme is shown below.

Figure 3-1 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

Cohort 2

The study will consist of a 45 day screening period (Day -60 to Day -21), a baseline period of 20 days (Day -20 to Day -1), a treatment period of 12 weeks (Day 1 to Day 84), and a study completion evaluation approximately twenty-eight days after the last drug administration (Day 112 +/- 2 days). Patients will be advised to maintain their recommended diet for NASH during the study. The study design scheme is shown below.

Figure 3-2 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

Cohort 1 and 2

For both cohorts 1 and 2, patients who meet the eligibility criteria at screening will have baseline assessments performed, including determination of the percent liver fat content by MRI.

Randomization will be stratified by BMI at baseline (refer to [Section 6.3](#)).

The Patient's race will be based on the race which the patient self-reports as captured on the demography eCRF.

The first dose of study medication (LMB763 / Placebo) will be administered to patients under fasted conditions on Day 1, following which scheduled assessments will be performed for 6 hours post-dose. A meal will be provided at approximately 4 hours post dose.

Patients will be provided with a supply of study medication for self-administration during the treatment period. Detailed instructions for taking study treatment will be provided in the Site Operations Manual (SOM). Patients will continue to take study medication once daily for twelve weeks (Day 2 to Day 84), as instructed by the investigator, and study assessments will be performed once weekly for the first 2 weeks (Days 7 and 14), then once every 2 weeks on Days 28 and 42, then monthly until the end of treatment (Days 56 and 84). 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 +/- 2 days. An end of study visit will be conducted approximately twenty-eight days (Day 112 +/- 2 days) after the final dose.

During the entire study period, patients will be instructed to contact the investigator at any time if they experience any adverse events of concern. The investigator may choose to place the patient under a period of close observation if adverse events or significant laboratory

abnormalities are noted, until the patient is deemed to have returned to a satisfactory state of health in the opinion of the investigator.

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

Refer to the [Assessment Schedule](#) for details of safety, PK, and PD assessments.

3.2 Rationale of study design

This randomized, multi-center, patient and investigator blinded, placebo-controlled study is designed to assess the safety and tolerability of LMB763 relative to placebo in patients with NASH.

Randomization will be initiated at a **2:1** ratio of active to placebo in order to reduce the sample size. The statistical power of the study will be bolstered by using historical control data from trials like the FLINT study to supplement the placebo arm. Multiple sites are necessitated due to the underlying prevalence of NASH defined in publicly available recruitment data. No known differences exist in regional criteria for the histopathological diagnosis of NASH. Since NASH is more common in those self-identified as Asian at lower body mass index (BMI), specific criteria inclusion criteria have been included for this population.

In order to maintain the scientific integrity of the study, the investigator and patient will remain blinded to their treatment allocation and baseline intra-hepatic lipid content. To allow close monitoring of biochemical safety parameters which overlap with efficacy outcomes (eg. ALT) and understanding of performance of exploratory biomarkers, the Novartis Clinical Trial Team (CTT) will be unblinded throughout the study.

To ensure that no bias is introduced by imbalance in severity of disease across different arms of the study, patients will be stratified to active or placebo arms on the basis of BMI.

The duration of 12 weeks of therapy is supported by GLP-toxicology studies of 13 weeks in duration and it is also a suitable timeframe to test the chosen primary endpoints in the study. In the FLINT trial of a less potent FXR agonist, ALT and GGT levels in the blood dropped as early as after 4 weeks of treatment and most of this effect was noted by 12 weeks of therapy ([Neuschwander-Tetri et al 2015](#)).

To keep dietary intake as consistent as possible, patients participating in this study will be instructed to carefully adhere to American Heart Association (AHA) diet or equivalent if there is a country specific recommended diet.

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

Corporate Confidential Information

The initial dose of LMB763 was chosen on the basis of safety and likely pharmacological activity. Preliminary analysis suggested that the mean increases in biomarkers of target engagement were higher than anticipated ^{Corporate Confidential Information}. In particular an increase in the FXR responsive marker ALP was noted in context of no increase in GGT or 5'NT. No SAEs have been attributed to LMB763 ^{Corporate Confidential Information}.

Corporate Confidential Information

The duration of the study is based on findings in 2 published studies relating to obeticholic acid ([Mudaliar et al 2013](#); [Neuschwander-Tetri et al 2015](#)), which demonstrate that 12 weeks will provide sufficient timeframe to assess biochemical changes likely to result from improvement to the NASH phenotype. In addition, observations from other studies with surgical ([Jiménez-Agüero et al 2014](#)), diet ([Ryan et al 2013](#)) and pharmacotherapy (CLCQ908A2216) also suggest that 12 weeks is an adequate timeframe to test an effect on liver fat ([Neuschwander-Tetri et al 2015](#)).

Corporate Confidential Information

3.4 Rationale for choice of comparator

Currently there is no licensed pharmacological therapy for patients with NASH. A placebo will be used as a comparator in this study to ensure the effects of LMB763 are related to the study drug. All patients will be encouraged to adhere to local advice regarding diet and exercise regimens.

3.5 Rationale for choice of background therapy

Not applicable

Corporate Confidential Information

3.7 Risks and benefits

As well as the risks and potential risks described in the Investigators' Brochure, there may be unknown risks to LMB763 which may be serious and unforeseen.

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring of safety e.g. liver transaminases, dose reduction steps and stopping rules.

Corporate Confidential Information

Women of child bearing potential should be informed that taking the investigational drug may involve unknown risks to the fetus if pregnancy were to occur during the study, and must agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Pruritus and LDL elevations have been noted in clinical trials with a bile acid derived FXR agonist, but have not been noted in _____ studies with non-bile acid FXR partial or full agonists, LMB763 or LJM452, respectively. Both pruritus and serum lipids will be closely monitored in this study.

A maximum of approximately 442.2 mL of blood is planned to be collected from each patient as part of the study. Additional samples for monitoring of any safety findings may be required, and would be in addition to this volume. Over the course of the 4 to 8 months study period, this is not considered to be a concern for this population.

MRI makes use of powerful magnetic fields and radio waves, which are believed to cause no direct adverse consequences when used within FDA-approved specifications. No MRI-contrast will be administered in this study. Thus in principle, MRI scans can be repeated in the same patient as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons; therefore, sensitivity to enclosed spaces should be queried at screening. Refer to eligibility criteria to exclude patients who are not suitable candidates for MRI scanning.

Patients participating in this study might have reductions in hepatic fat; it is possible that this is a clinical benefit. However, 12 weeks treatment is unlikely to be sufficient to provide benefit in reducing hepatic fibrosis. For this reason, liver biopsies are not performed in this study. There may be patient benefit in the ancillary dietary and exercise counseling accompanying the pharmacologic intervention.

3.7.1 Blood sample volumes

A maximum of approximately 442.2 mL of blood is planned to be collected over a period of approximately 22 weeks, from each patient as part of the study. Additional samples required for monitoring of any safety findings would be in addition to this volume. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the [Assessment Schedule, Section 8.1](#)

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information will be contained in the Central Laboratory Manual.

See [Section 8.9](#) regarding the potential use of residual samples.

4 Population

The study population will be comprised of male and female adult patients with EITHER histologic evidence of NASH on liver biopsy within 2 years prior to randomization and elevated ALT, OR phenotypic diagnosis of NASH based on elevated ALT, Type 2 diabetes mellitus or elevated HbA1c and increased BMI; full details are outlined in [Section 4.1](#) (Inclusion criteria).

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all eligibility criteria at screening and baseline. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Provided patients meet all other eligibility criteria, patients with a single lab value outside of the allowable range may be considered eligible for enrolment, as long as the abnormal lab value is within 10% of the allowable value. ALT and eGFR values must always fall inside the allowable range as listed in the inclusion and exclusion criteria.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

Cohort 1

1. Informed consent must be obtained before any assessment is performed
2. Male and female patients 18 years or older (at the time of the screening visit)
3. Presence of NASH as demonstrated by ONE of the following:

EITHER

Histologic evidence of NASH based on liver biopsy obtained within 2 years prior to randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases

AND

ALT \geq 60 IU/L (males) or \geq 40 IU/L (females)

OR

Phenotypic diagnosis of NASH based on the presence of ALL THREE of the following:

- ALT \geq 60 IU/L (males) or \geq 40 IU/L (females) **AND**
- BMI \geq 27 kg/m² (in patients with a self-identified race other than Asian) or \geq 23 kg/m² (in patients with a self-identified Asian race) **AND**
- Diagnosis of Type 2 diabetes mellitus by having either:
 - HbA1C \geq 6.5%

OR

- Symptoms of diabetes plus hyperglycemia as indicated by
 - fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l)
 - two hour plasma glucose concentration ≥ 200 mg/dl (≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT))

OR

- Drug therapy for Type 2 diabetes mellitus (as long as on a stable dose. Refer to [Section 5.2](#))
4. . Patients must weigh at least 40 kg (88 lbs) and no more than 150 kg (330 lbs.) to participate in the study. Inclusion of patients with higher weights up to 200 kg (440 lbs.) may occur if a MRI scanner with a table weight of 200 kg (440 lbs.) is available.
 5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

Cohort 2

6. Informed consent must be obtained before any assessment is performed
7. Male and female patients 18 years or older (at the time of the screening visit)
8. Presence of NASH as demonstrated by ONE of the following:

EITHER

Histologic evidence of NASH based on liver biopsy obtained within 2 years prior to randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, in the absence of a histological diagnosis of alternative chronic liver diseases

AND

ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) at screening

OR

Phenotypic diagnosis of NASH based on the presence of ALL THREE of the following:

- ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) at screening **AND**
- BMI ≥ 27 kg/m² (in patients with a self-identified race other than Asian) or ≥ 23 kg/m² (in patients with a self-identified Asian race) **AND**
- Diagnosis of Type 2 diabetes mellitus by having either:
 - HbA1C $\geq 6.5\%$

OR

- Symptoms of diabetes plus hyperglycemia as indicated by
 - fasting plasma glucose ≥ 126 mg/dl (≥ 7.0 mmol/l)
 - two hour plasma glucose concentration ≥ 200 mg/dl (≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT))

OR

- Drug therapy for Type 2 diabetes mellitus (as long as on a stable dose. Refer to [Section 5.2](#))

9. Liver fat $\geq 10\%$ at baseline as determined by the reading of the central MRI laboratory of locally produced images. The MRI assessment should only be performed after eligibility has been confirmed from all other baseline assessments.
10. Patients must weigh at least 40 kg (88 lbs) and no more than 150 kg (330 lbs.) to participate in the study. Inclusion of patients with higher weights up to 200 kg (440 lbs.) may occur if a MRI scanner with a table weight of 200 kg (440 lbs.) is available.
11. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Cohorts 1 and 2

Patients with NASH phenotype fulfilling any of the following criteria are not eligible for inclusion in this study:

1. History of severe hypersensitivity to drugs of any kind or sensitivity to those including pyrazole (eg celecoxib or stanozolol) or an imidazole ring (eg antifungals including ketoconazole, anthelmintics including mebendazole and nitroimidazole antibiotics including metronidazole).
2. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days whichever is longer; or longer if required by local regulations.
3. Current use of obeticholic acid (OCA).
4. New initiation GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide or DPP4 inhibitors such as sitagliptin, vildagliptin, saxagliptin or linagliptin within 3 months of screening.
5. Patients taking medications prohibited by the protocol. See [Section 5.2](#) for further details.
6. Patients on treatment with the following medicines UNLESS they are on a stable dose for at least 1 month before randomization: insulin (no more than 25% change in dose), beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 200 IU/day; doses > 800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control. For oral anti-diabetic medications, no more than one step-up or step-down in local prescribing guidelines will be allowed.
7. History of treated or untreated malignancy of any organ system, other than localized basal cell carcinoma of the skin or treated cervical intraepithelial neoplasia, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
8. 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.

9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 5 days (approximately 5 times the terminal half life) after stopping study medication. **Highly effective contraception methods include:**
- Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception)
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
 - Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient
 - Use of oral (estrogen and progesterone), injected or implanted combined hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

10. Sexually active males will be excluded UNLESS they agree to use a condom during intercourse while taking study medication and for 5 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
11. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the AUDIT questionnaire ≥ 8 as administered by the site as part of the medical history.
12. Inability to reliably quantify alcohol consumption based upon local study physician judgment.
13. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening and baseline. Marijuana use is not allowed if it is determined to be medically inappropriate by the investigator.
14. Prior or planned (during the study period) bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass).

15. Type I diabetes and uncontrolled diabetes defined as $HbA_{1c} \geq 9.5\%$ within 60 days prior to enrollment.
16. Calculated eGFR less than 60 mL/min (using the MDRD formula)
17. Presence of cirrhosis on liver biopsy or clinical diagnosis.
18. Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities:
 - Serum albumin < 32 g/L
 - INR > 1.3
 - Direct bilirubin > 13 mg/L
 - ALT or AST > 5 × ULN
 - Alkaline Phosphatase > 3 × ULN
 - History of grade 2 or greater esophageal varices, ascites or hepatic encephalopathy
 - Splenomegaly
19. Platelet count < $120 \times 10^9/L$.
20. History or presence of other concomitant liver diseases including, but not limited to:
 - Hepatitis B or C virus (HCV, HBV) infection
 - Primary biliary cholangitis (PBC)
 - Primary sclerosing cholangitis (PSC)
 - Alcoholic liver disease
 - Definite autoimmune liver disease or overlap hepatitis
 - Suspected or confirmed Gilbert's syndrome
 - Known bile duct obstruction
 - Suspected or proven liver cancer
21. History of liver transplantation or current placement on a liver transplant list.
22. History of inflammatory bowel disease.
23. Known positivity for Human Immunodeficiency Virus (HIV) infection.
24. History of non-adherence to medical regimens, or patients who are considered by the investigator to be unable to reliably comply with the requirements of the study.
25. Chronic use (i.e. > 3 months immediately prior to baseline visit) of high dose Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as evaluated by investigator.
26. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
 - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
 - History of familial long QT syndrome or known family history of Torsades de Pointes
27. Donation or loss of 400 ml or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.

28. Patients with contraindications to MRI imaging, including:

- Brain aneurysm clip
- Implanted neural stimulator
- Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires
- Prosthetic heart valves
- Cochlear implant
- Ocular foreign bodies that might be ferromagnetic (e.g., metal shavings)
- Other implanted medical devices (e.g., insulin pumps)
- Metal shrapnel or bullets still in the body
- Severe claustrophobia
- Tattoos (as determined by the Investigator and Imager)
- Weight in excess of MRI machine capacity

29. For those patients that have had a previous biopsy: Significant weight loss (>15%) or change in clinical status (in the opinion of the investigator) since the diagnostic liver biopsy (refer to Inclusion Criterion #3).

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 Patients

Patients must be informed and reminded of the restrictions outlined in this section throughout the study.

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 must agree that in order to participate in the study they must adhere to the contraception requirements specified in [Section 4.2](#) (Exclusion criteria). If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

Sexually active males should be reminded of the requirement to wear a condom for the following reasons:

- To prevent pregnancy in a female partner

AND

- To prevent delivery of investigational drug via seminal fluid to their partner

If there is any question that the patient will not reliably comply, the patient should not be entered or continue in the study. Male patients should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. Please refer to exclusion criteria ([Section 4.2](#)) for details of contraception requirements for the study.

5.2 Prohibited treatment

Medications or herbal remedies that may have a significant impact on LMB763 metabolism by inhibiting UGT1A1 are prohibited in the study from the first dosing until end of study evaluations have been completed. These include (but not limited to): atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine and zafirlukast and *Silybum marianum* (*milk thistle*) and *Valeriana officinalis* (*valerian*). The non-selective UGT inhibitors diclofenac, probenecid and valproic acid are also prohibited.

Should a patient have an incidental and limited need for a medication to be taken within the restricted pre-dose timeframe (e.g. analgesia following dental surgery, etc.), the sponsor should be advised, as administration of any concomitant medication may require the patient to be replaced. Decisions regarding replacements will be discussed with the sponsor on a case-by-case basis.

There is a potential for LMB763 to increase exposure of drugs metabolized by CYP2C8 (including repaglinide, pioglitazone and rosiglitazone) and those dependent on export by BCRP (potentially glyburide (glibenclamide), atorvastatin, rosuvastatin and pitavastatin). Careful attention should be paid to the drug interaction sections of the prescribing information for these compounds.

Patients on medications specified in [Table 5-2](#) can be included if these medications are deemed by the investigator to be:

- Medically necessary, and
- Dose has been stable for at least 1 month prior to randomization, and
- Dose is believed to remain stable for the duration of the double-blind treatment period.

No new use of these medications is allowed after entering the study, with the exception of drugs to control medically significant elevations in LDL-cholesterol which have been confirmed upon repeat testing.

A 'stable' dose of insulin is defined as being within 25% of the current dose. A stable dose of oral anti-diabetic medications is defined as up to one step-up or step-down in local prescribing guidelines from the dose at randomization. For all other medications listed in [Table 5-2](#), the definition of stable will be left to investigator discretion.

An overview of the prohibited medication is given in [Table 5-1](#), and the summary of permitted medications if on a stable dose is presented in [Table 5-2](#).

Table 5-1 Prohibited medication

Medication	Prohibited
Specific UGT1A1 inhibitors: atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine, and zafirlukast	Any use from first drug intake to end-of-study visit
Herbal remedies inhibiting UGT1A1: Silybum marianum (silymarin, milk thistle) and Valeriana officinalis (valerian)	Any use from first drug intake to end-of-study visit
Non-selective UGT inhibitors: diclofenac, probenecid, valproic acid	Any use from first drug intake to end-of-study visit
Vitamin E	Doses >800 IU/day
GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide or DPP4 inhibitors such as sitagliptin, vildagliptin, saxagliptin or linagliptin	Newly initiated use within 3 months prior to screening

Table 5-2 Permitted medications if dose is stable for at least 1 month prior to randomization

Medication
Oral anti-diabetic medications such as metformin, sulfonylureas (including glyburide (glibenclamide), meglitinides (such as repaglinide) and thiazolidinediones (including pioglitazone and rosiglitazone))* Insulin (within 25% of the dose at randomization)** Beta-blockers and thiazide diuretics Fibrates, statins*, niacin, ezetimibe*** Vitamin E**** Thyroid hormone Psychotropic medications (phenothiazines or second generation antipsychotics) Estrogen or estrogen containing birth control

Notes: *There is a potential for LMB763 to increase exposure of drugs metabolized by CYP2C8 (including repaglinide,) and those dependent on export by BCRP (potentially glyburide (glibenclamide), atorvastatin, rosuvastatin and pitavastatin). Careful attention should be paid to the drug interaction sections of the prescribing information for these compounds. For oral anti-diabetic medications, one step up in local prescribing guidelines from the dose at randomization will be allowable; **Unless adjustment is required due to intercurrent illness; ***Unless adjustment is required to treat medically significant increases in LDL that have been confirmed upon repeat testing; ****Only applicable for patients taking >200 IU/day;

5.3 Dietary restrictions

On study visit days, all patients will fast (i.e. no food or liquid except water) for at least 6 hours prior to administration of study treatment and will continue to fast for at least 1 hour thereafter. No fluid intake apart from the fluid given at the time of drug intake is allowed from 1 h before until 1 h after dosing.

Alcohol consumption is to be strongly discouraged, and should not exceed 20 g/day in females and 30 g/day in males. Alcohol should be avoided for 8 hours prior to time of drug intake.

Patients can drink water *ad libitum* however, to ensure adequate hydration patients should have a fluid intake of at least 240 mL every 4 hours during waking hours in addition to fluid taken with meals and medication.

To keep the dietary intake as consistent as possible, patients participating in this study will be counseled regarding appropriate exercise and diet per local standards, e.g. instruction to carefully adhere to American Heart Association (AHA) diet or equivalent if there is a country specific recommended diet (see [Appendix 1](#)).

6 Treatment

6.1 Study treatment

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

6.1.1 Investigational treatment and control drugs

The investigational drug, LMB763 and matching placebo, will be prepared by Novartis and supplied to the Investigator site as single blinded patient packs to be dispensed by the unblinded pharmacist at the investigator site. Study treatments are defined as:

- LMB763 capsules
- LMB763 capsules
- LMB763 capsules
- Matching placebo capsules

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Patients will be assigned to one of the following two treatments in a ratio of 2:1. Study treatments are defined as:

Cohort 1:

- LMB763 (1 × LMB763 capsule)
- Matching placebo (1 × Matching placebo capsule)

Cohort 2:

- LMB763 (2 × LMB763 capsules)
- Matching placebo (2 × Matching placebo capsules)

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual patients by way of a randomization number. Randomization numbers will be assigned in ascending, sequential order to eligible patients (see Site Operations Manual for details).

The randomization number is only used to identify which treatment the patient has been randomized to receive. The Patient number assigned to a patient at screening remains the unique identifier for the patient throughout the study. For information on patient numbering, please see ‘Patient numbering’ section in the Site Operations Manual.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of treatment arms to randomization numbers. These randomization numbers are linked to the different treatment arms.

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). The race will be based on the race the patient self-reports as captured on the demography eCRF.

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.

Table 6-1 provides general details of the numbering of patients for randomization into each cohort:

Table 6-1 Treatment Assignment Numbering – Cohort 1

Corporate Confidential Information	Race	BMI (kg/ m ²)	Randomization Numbers
	Asian	<30	5101-5292
	Asian	≥30	5301-5492
	Non-Asian	<35	5501-5692
	Non-Asian	≥35	5701-5892

Table 6-2 Treatment Assignment Numbering – Cohort 2Corporate Confidential
Information

Race	BMI (kg/ m ²)	Randomization Numbers
Asian	<30	9101-9292
Asian	≥30	9301-9492
Non-Asian	<35	9501-9692
Non-Asian	≥35	9701-9892

6.4 Treatment blinding

This is a patient and investigator-blinded study. Patients 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, 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 (LMB763 or placebo) throughout the study.

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

Drug product will be supplied as single blinded patient packs, so an unblinded pharmacist (or appropriately trained site personnel) who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization number and treatment allocation from the IRT system, and will then dispense the appropriate medications to the patient. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Note that the IRT system will not be used for any drug accountability or dispensing procedures. IRT is only used for enrollment tracking in this study.

Sponsor staff

The sponsor will remain unblinded to the treatment assignment of all patients to allow for continuous unblinded safety monitoring throughout the study.

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual patients. The unblinded monitors will also be able to review the treatment allocation provided to the unblinded pharmacist via the IRT system.

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 while the study is ongoing.

6.5 Treating the patient

Study medication will be self-administered by the patient orally once daily (refer to [Section 3.1](#) for 12 weeks (84 days). On visit days, treatment will be administered at the site. All study treatment will be administered under fasted conditions (no food or drink for at least 6 hours). On Day 1 (V3) and Day 42 (V7), a meal will be provided at least 4 hours post-dose. See the Site Operations Manual for further details.

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

6.6 Permitted dose adjustments and interruptions of study treatment

Safety and tolerability

In the event of a significant safety/tolerability concern which does not meet study stopping criteria ([Section 7.5](#)), and is not related to ALT and/or AST elevations, temporary interruption and dose adjustments are permitted as follows in order to allow the patient to continue on study treatment:

- Cohort 1: Reduction in dose frequency to every alternate day
- Cohort 2: Reduction in dose

Investigators must use their medical judgment in regards to what they deem as the best interest of the patient.

Significant isolated ALT and/or AST increase

In the event of a significant ALT and/or AST elevation, temporary interruption and dose reduction is permitted in order to allow the patient to continue on study treatment. The guidance for the modification of study treatment is outlined below and in [Table 6-3](#); this will allow an evaluation of whether such dose reductions are useful in patient management. The ability to reduce the dose is clinically relevant as data generated after dose reduction will provide further information regarding the tolerability and safety of LMB763.

If the patient has symptoms or other LFT abnormalities, in particular elevations of bilirubin and/or PT/INR and/or ALP), refer to [Section 9.3](#) and [Table 9-2](#) for appropriate actions.

Triggers related to ALT and/or AST elevation are described in [Table 9-1](#). A significant ALT and/or AST increase is defined as (i) in the presence of symptoms or other liver function abnormalities $> 3 \times \text{ULN}$, **AND in the case of elevated baseline $> 2 \times \text{Baseline value}$** ; (ii) in the absence of symptoms or other liver function abnormalities ALT and/or AST elevation $> 5 \times \text{ULN}$ **AND in the case of elevated baseline $> 2 \times \text{Baseline value}$** . All cases with ALT and/or AST elevation $> 3 \times \text{ULN}$ will be captured as a liver event per [Table 9-1](#) and instructions for further assessment detailed in [Table 9-2](#). Patients who experience significant isolated ALT and/or AST elevations will be instructed to return to the clinic within 48-72 hours for an additional laboratory evaluation to confirm these results, as defined in [Table 6-3](#). The laboratory tests to be repeated are ALT, AST, GGT, alkaline phosphatase, total bilirubin, and albumin (LFT) and PT/INR.

The guidance for the modification of study treatment is outlined below in [Table 6-3](#).

If the additional laboratory evaluation confirms a significant increase of ALT and/or AST values, the dose frequency will be reduced to every alternate day (cohort 1), or the dose will be reduced (cohort 2); the investigator and site personnel will remain blinded to the identity of treatment. The investigator must document the patient's dose frequency reduction in source documents.

If the additional laboratory evaluation does not confirm the significant increase of ALT or AST values, the patient will continue with the assigned/original treatment.

If the additional laboratory evaluation shows a higher elevation of ALT and/or AST (e.g. > 8 x ULN) as compared to the original elevation (e.g. > 5 x ULN but < 8 x ULN), the guidance for this higher elevation (e.g. > 8 x ULN) should be followed.

Actions should be based on whichever of AST and ALT has a higher multiple of ULN or baseline value. In order to allow for variation in laboratory results, persisting elevation is defined as the value remaining at $\geq 90\%$ of the original elevated value. When there is a marked difference in multiple of ULN between ALT and AST, medical judgment should be applied to distinguish between persisting and decreasing. If at any time the repeat testing shows levels in a higher category, the guidance for the higher category should be followed.

Only one cycle of dose frequency/dose reduction is allowed. If, despite being on a reduced dose, a patient has persistent or new significant ALT and/or AST elevations, the patient must be discontinued from study treatment (refer to [Section 7.2](#)). After discontinuation for a liver-related event, LFT and clinical monitoring should continue until the event is resolved (refer to [Section 9.3](#)). Increasing the dose to the original level is not permitted.

Table 6-3 Dosing response to Isolated ALT/AST Elevations

ALT and/or AST increase	First Action	Result	2nd Action	Result	3rd Action
> 2 x baseline AND ≤5 x ULN	Repeat tests ¹ within 48-72 hours	Elevation ² of ALT and/or AST confirmed	Initiate close observation of patient. Repeat tests ¹ within 48 – 72 hours	Persistent elevation ² of ALT and/or AST for 1 week	Cohort 1: Reduce Dose frequency to alternate day dosing Cohort 2: Reduce LMB763 dose Continue close observation of patient with minimum twice weekly testing ¹ (once weekly if stable) until ALT and AST <3x ULN (or 2x baseline if elevated before drug exposure). If ALT and AST levels remain ≥3x ULN three weeks after dose reduction, discontinue study treatment
		Decreasing ALT and AST ³		Continue assigned study treatment as per protocol	
		Decreasing ALT and AST ³	Continue assigned study treatment as per protocol	--	--
> 2 x baseline AND >5 x ULN but ≤ 8 x ULN	Repeat tests ¹ in 48 hours	Elevation ² of ALT and/or AST confirmed	Cohort 1: Reduce Dose frequency to alternate day dosing Cohort 2: Reduce LMB763 dose Initiate close observation of patient. Repeat tests ¹ within 48 – 72 hours	Persistent elevation ² of ALT and/or AST	Discontinue study treatment
		Decreasing ALT and AST ³		Continue with reduced dose frequency or reduced dose Continue close observation of patient with minimum twice weekly testing ¹ (once weekly if stable) until ALT and AST < 3 x ULN and < 2 x baseline. If ALT and AST levels remain ≥3 x ULN three weeks after dose reduction, discontinue study treatment	
		Decreasing ALT and AST ³	Continue assigned study treatment as per protocol	--	--
>2 x baseline AND >8 x ULN	Discontinue study treatment	--	--	--	--

¹Tests: A physical examination should be performed and recorded in source documents. PT/INR, ALT, AST, GGT, alkaline phosphatase, total bilirubin, and albumin; these repeats must be performed using the central laboratory if possible and captured via the unscheduled lab CRF. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. If tests are performed at local laboratory, results will be captured in source documents only.

²Persistent: either ALT and/or AST remain > 90% of the original elevated level

³Decreasing: both ALT and AST levels decrease to ≤ 90 % of the original elevated level. Medical judgement should be applied if there is a marked difference between ALT and AST multiples

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team 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 IRT at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- patient number

In addition, the investigator must provide information to inform the patient 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 patient and whether the patient can continue in the study.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with LMB763, as detailed in [Section 8.7](#).

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

6.9 Recommended treatment of adverse events

Treatment of AEs may be considered at the discretion of the Investigator. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Use of rescue medication is not allowed during the study.

6.11 Concomitant treatment

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 section of the 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.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each patient 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 patient 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 patients 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 patient should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Patients may voluntarily discontinue study treatment for any reason at any time.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Individual patient withdrawal:

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a patient withdrawal occurs for any reason, the Investigator must make every effort to determine the primary reason for a patient's withdrawal from the study and record this information on the Study Completion CRF.

Individual treatment discontinuation:

Study treatment must be discontinued and the patient withdrawn from the study if the patient withdraws consent.

Study treatment must be discontinued if the following occur:

- Pregnancy.
- Hypersensitivity (CTCAE grade 2 or higher) reaction to LMB763 requiring intervention.
- Adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the patient, in the opinion of the investigator
- An adverse event that is a CTCAE Grade 3 and believed to be related to the study drug (apart from liver and renal events - see below).
- A liver safety event as defined in [Section 9.3](#) (Liver safety monitoring) with ALT, AST, total bilirubin and/or alkaline phosphatase elevations mandating study treatment discontinuation. Please refer to [Section 9.3](#) (Liver safety monitoring), [Table 9-1](#) and [Table 9-2](#) for further instructions and monitoring.
- A renal safety event as defined in [Section 9.4](#) with serum creatinine elevations mandating study treatment discontinuation. Please refer to [Section 9.4](#) for further instructions and monitoring.
- Any protocol deviation that results in a significant risk to the patient's safety in the opinion of the investigator.
- If continuation in the study is deemed detrimental to the patient's well-being in the opinion of the investigator.

The appropriate personnel from the study site and Novartis (including the CTT, medically qualified representatives of the Sponsor, and the investigator) will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

Patients who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for follow up assessments at the end of study visit. If they fail to return for assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them.

7.3 Withdrawal of informed consent

Patients 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 patient:

- 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 patient'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 patient are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

For patients 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 patient, e.g. dates of telephone calls, registered letters, etc. A patient 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 severity of adverse events will be graded by the study site Investigator (or designee) based on clinical judgment and captured in the CRF AE page. This information will be used to quantify events that may lead to patient's discontinuation or stopping dose arms or the study.

Study Stopping Rules

The study will be placed on hold to further enrollment, no new patients may be dosed, however dosing of those without safety concerns may continue. The study may be stopped based on a full review of all available clinical safety data and discussion with the Investigators if any of the following occur:

- One patient on study drug experiences any adverse event that is CTCAE Grade 4 or higher that is classified as related to study drug.
- Two or more patients on study drug experience a similar adverse event that is a CTCAE Grade 3 or higher other than ALT elevation.
- The Principal Investigator and the Sponsor consider that the number and/or severity of adverse events justify discontinuation of the study.
- The Sponsor unilaterally requests it.

Safety reviews for study stopping will be conducted jointly between medically qualified representatives of the Sponsor and Investigator and a joint decision will be made.

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, patients must be seen as soon as possible and treated as a prematurely withdrawn patient. 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 patient'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

Assessment Schedule

EPOCH	SCREENING		Treatment															
	Visit Name	Screening	Baseline ²⁵	Treatment														
Visit Numbers ¹	1	2	101					102 ³	103 ³	104 ³	105					106 ³	107 ³	199
Study Day(s)	-60 to -15	-14/-20 to -1	1					7 -2 +2	14 -2 +2	28 -2 +2	42 -2 +2					56 -2 +2	84 -2 +2	112 -2 +2
Time (post-dose)	-	-	0h ³	1h	2h	4h ⁴	6h	-	-	-	0h ³	1h	2h	4h ⁴	6h	-	-	-
Informed consent ⁵	X																	
Corporate Confidential Information	X																	
Inclusion / Exclusion criteria	X	X																
Medical history/current medical conditions	X	X																
Demography	X																	
Alcohol Test and Drug Screen	X	X																
Hepatitis and HIV Screen	X																	
Pregnancy test ⁷	X	X	X							X						X	X	X
Physical examination	X	X								X						X	X	X
Body height	X																	
Body weight	X	X								X	X					X	X	X
Waist and Hip circumference	X	X								X	X					X	X	X
Body temperature	X	X														X	X	X
Blood Pressure and Pulse Rate ^{8,9}	X	X							X	X						X	X	X
ECG evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X					X	X	X	X					X	X	X
Blood chemistry	X	X	X					X	X	X	X					X	X	X

¹ Visit structure given for internal programming purpose only

² If a patient withdraws from the study, or if study medication is discontinued for any reason, the patient should be scheduled for a subsequent visit at which time all assessments at the EOS visit should be performed.

³ Assessments to be performed pre-dose

⁴ A meal will be provided 4 hours post dose.

⁵ Informed consent must be provided by all patients before any screening procedures are performed. The pharmacogenetic assessment is optional and requires a separate informed consent to be signed

Corporate Confidential Information

⁷ Serum pregnancy tests will be performed at Screening and end of study; urine tests may be used at other timepoints.

⁸ At screening and baseline, if vital signs are out-of-range, the investigator may obtain two additional readings, so that up to three (3) consecutive assessments are made, each after at least 30 minutes, and with the patient seated quietly during the five (5) minutes preceding the assessment. At least the last reading must be within the ranges provided in order for patients to qualify.

⁹ Blood pressure and pulse rate will be measured in a sitting position at all visits.

¹⁰ Lipid panel includes total cholesterol, LDL, HDL (including subfractions HDL-1, HDL-2, and HDL-3), and Triglycerides. Direct LDL will also be measured pre-dose at V101, V105, V107, and EOS (V199). Additional analyses of LDL sub-fraction and ApoC3 at these timepoints may be performed if notable changes in LDL or triglycerides, respectively, are observed.

¹¹

Corporate Confidential Information

²² Patients will be provided with a supply of study medication to self-administer once daily for 12 weeks (Day 2 to Day 84). Study medication will be administered by site personnel on all visit days. Patients should bring all used and unused medications, and diaries, to each visit.

²³ MRI of the abdomen, including liver; see Imaging manual for further instructions.

²⁴ A thorough review of any concomitant medications (including medication name, dose, unit, frequency, and route) should be performed at every visit.

²⁵ Baseline period is 14 days for Cohort 1, and 20 days for Cohort 2.

8.2 Informed consent procedures

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICH E6 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 patient agrees to 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 patient informed consent and should be discussed with the patient 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 patient.

Ensure patients are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

Corporate Confidential Information

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

8.3 Patient screening

In general it is permissible to re-screen a patient if he/she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all patients. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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.

8.4.1 Hepatitis screen, HIV screen

All patients will be screened for HIV, Hepatitis B and C. See the Site Operations Manual for details.

8.4.2 Alcohol test, Drug screen

All patients will be screened substances of abuse and cotinine. See the Site Operations Manual for details.

8.5 Efficacy / Pharmacodynamics

Efficacy of LMB763 will be assessed based on the following assessments:

- Liver function tests (ALT)
- Magnetic Resonance Imaging (MRI)
- Anthropometric assessments
- Markers of liver fibrosis
- Fasting lipids
- Visual Analog Scale (VAS) for Itch

Pharmacodynamic samples will be collected at the timepoints defined in the [Assessment schedule](#). Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. Pharmacodynamic (PD) samples will be obtained and evaluated in all patients at all dose levels.

8.5.1 Liver function tests (LFTs)

ALT, AST, GGT, ALP (total), total bilirubin, and albumin will be assessed as indicated in the [Assessment Schedule](#). The effect on circulating ALT levels is the primary efficacy variable for this study.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reactive bilirubin will be quantified.

ALP isoenzymes and 5'NT will also be measured but will not form part of the screening requirements or safety data set.

The methods for assessment and recording are specified in the laboratory manual. Some of the liver function tests may be completed as part of the blood chemistry panel.

8.5.2 Magnetic Resonance Imaging

Patients will undergo magnetic resonance imaging twice during the course of the study (Baseline and End of Treatment) to quantitate liver fat. Optional exploratory MRI based assessments will be performed in a subset of patients to evaluate the effect of LMB763 on other MRI related endpoints as outlined in [Section 8.1 \(Assessment schedule\)](#). All patients who discontinue prematurely must have an end of treatment MRI assessment.

8.5.3 Markers of Liver Fibrosis

- Fibroscan[®] (Optional): will be performed where available to assess liver stiffness (in kPa). If Fibroscan is unavailable, alternative technology to assess liver stiffness may be considered upon consultation with the sponsor
- Enhanced liver fibrosis Test (ELF) panel: the following will be assessed: hyaluronic acid (HA), tissue inhibitor of metalloproteinases (TIMP-1), and amino-terminal pro-peptide of procollagen type III (PIIINP)
- Fibrosis biomarker test (originally called Fibrotest[®]/ Fibrosure[®]): the following will be assessed: α 2-macroglobulin, apolipoprotein A1, total bilirubin, haptoglobin, GGT, and ALT
- Additional fibrosis markers may be assessed, including but not limited to collagen neo-epitopes, FIB4, APRI and NAFLD scores

Additional information is provided in the site operations manual and central laboratory manual. These markers will be assessed as indicated in [Section 8.1 Assessment schedule](#).

8.5.4 Fasting Lipids

Blood samples will be collected for a fasting lipid panel, including total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, free glycerol and free fatty acids as per [Section 8.1 \(Assessment schedule\)](#). Lipid measurements should be collected under fasted conditions. Detailed information will be provided in the central laboratory manual.

8.5.5 Anthropometric Assessments

Height, body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes), and waist and hip circumference in centimeters (cm), will be measured as indicated in [Section 8.1 \(Assessment schedule\)](#). Details of these assessments will be provided in the site operations manual.

8.5.6 Clinical Outcome Assessments (COAs)

Visual Analog Scale (VAS)

10 cm visual analogue scale (VAS) will be used to assess the severity of patients itch (ranging from 0 = no itch at all to 10 = the worst imaginable itch). The score (distance from left) on the VAS will be recorded by the patient marking with a line and used to test for an effect of LMB763 over placebo.

The scale will be completed by patients as indicated in [Section 8.1 \(Assessment schedule\)](#).

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the [Assessment Schedule \(Section 8.1\)](#) detailing when each assessment is to be performed.

8.6.1 Physical examination

See the Site Operations Manual for details.

8.6.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

8.6.3 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials and platelet count will be measured.

Coagulation parameters including APTT, PT, and INR will also be assessed; methods for assessment and recording are provided in the central laboratory manual.

Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, serum phosphate, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, bicarbonate/HCO₃, LDH, GGT, CK, glucose, total cholesterol, triglycerides.

Liver function tests are outlined in [Section 8.5.1](#).

- Homeostasis model assessment (HOMA)-IR will also be derived, but will not be part of the safety dataset

Urinalysis

Dipstick measurements for specific gravity, albumin, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.

8.6.4 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the site operations manual.

PR interval, QRS duration, heart rate, RR, QT, QTc will be assessed.

The Fridericia QT correction formula (QTcF) (calculated with the RR interval expressed in seconds) should be used for clinical decisions.

Clinically significant abnormalities should be recorded on the relevant medical history CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

8.6.5 Pregnancy assessments

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Screening Visit followed by a urine pregnancy test at Baseline Visit and before study drug administration. The urine pregnancy test will be repeated every four weeks up to the follow up visit where a serum pregnancy test will be repeated. See the [Assessment Schedule, Section 8.1](#), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements.

A positive test at Screening Visit and/or Baseline Visit is an exclusion criterion for participating in the study. A positive pregnancy test after start of study drug requires immediate interruption of study drug until serum β -hCG is performed and found to be negative. If positive, the patient will enter the post-treatment follow up period.

If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

8.7 Pharmacokinetics

PK samples will be collected at the timepoints defined in the [Assessment schedule, Section 8.1](#). Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. See [Section 8.9](#) regarding the potential use of residual samples.

Corporate Confidential Information

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

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 patient or clinical investigation patient *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 patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient 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 patient and identifying adverse events. Alert ranges for liver and kidney related events are included in [Section 9.3](#) and [Section 9.4](#), respectively.

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

1. the Common Toxicity Criteria (CTC) AE grade (version 4.0 or higher) for the adverse event. If CTC-AE grading does not exist for an adverse event, use:
 - 1 = mild,
 - 2 = moderate,
 - 3 = severe
 - 4 = life threatening* (see [Section 9.2](#) for definition of a serious adverse event (SAE))
*Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).
 - CTC-AE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).
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 SAE)
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). 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 patient to report any new adverse event (beyond the protocol observation period) that the subject, or the patient'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.

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 patient 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 patient 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 (see Annex IV, 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 patient 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 (see Annex IV, 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 Drug Safety & Epidemiology (DS&E) as per [Section 9.2.2](#).

9.2.2 SAE reporting

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

Note: SAEs reported by patients deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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 patient 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 or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology 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 patient 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 9-1](#) for complete definitions of liver events.

Table 9-1 Liver Event Definitions

	Definition/ threshold
Liver laboratory triggers	<ul style="list-style-type: none"> • ALT or AST $\geq 2 \times$ baseline value • $1.5 \times \text{ULN} < \text{TBL} \leq 2 \times \text{ULN}$
Liver events	<ul style="list-style-type: none"> • ALT or AST $> 3 \times \text{ULN}$ • ALP $> 2 \times \text{ULN}$ (in the absence of known bone pathology) • TBL $> 2 \times \text{ULN}$ (in the absence of known Gilbert syndrome) • ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST $> 3 \times \text{ULN}$ and TBL $> 2 \times \text{ULN}$ [mainly conjugated fraction] without notable increase in ALP to $> 2 \times \text{ULN}$) • Any clinical event of jaundice (or equivalent term) • ALT or AST $> 3 \times \text{ULN}$ accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Follow-up of liver events

Every liver event defined in [Table 9-2](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below and in [Section 6.6](#). Additional details on actions required in case of liver events are outlined in [Table 9-2](#).

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation within 48-72 hours. These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. Should this occur, a sample should also be sent to the central laboratory for analysis. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results maintained in source documents. The result from the central laboratory will be provided via the standard electronic transfer.
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Dose adjustment, interruption and/or discontinuation of the investigational drug (refer to [Section 6.6](#) (Permitted dose adjustments and interruptions of study treatment) and [Section 7.2](#) (Discontinuation of study treatment), if appropriate
- Hospitalization of the patient 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 PT/INR ALT, AST, ALP, and GGT. If total bilirubin is elevated $> 2 \times$ 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 9-3](#).
 - 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.

Table 9-2 Actions required for Liver Events

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality 	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
ALT or AST		
$> 8 \times$ ULN and $> 2 \times$ baseline value	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality 	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
$> 3 \times$ ULN and $> 2 \times$ baseline value and INR > 1.5	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize, if clinically appropriate • Establish causality 	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
$> 5 \times$ ULN and $> 2 \times$ baseline value but $\leq 8 \times$ ULN	<ul style="list-style-type: none"> • Repeat LFT within 48 hours • If elevation is confirmed, refer to Table 6-3 	Refer to Table 6-3 ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)
$> 3 \times$ ULN and $> 2 \times$ baseline value, accompanied by symptoms ^b	<ul style="list-style-type: none"> • Discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality 	Refer to Table 6-3 ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution ^c (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 to ≤ 5 × ULN if normal baseline or >2 × baseline if elevated before drug exposure (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within 48-72 hours If elevation is confirmed, refer to Table 6-3 	<p>Refer to Table 6-3</p> <p>Investigator discretion</p>
ALP (isolated)		
> 2 × ULN if normal baseline (in the absence of known bone pathology)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, establish causality Complete liver CRF 	<p>Investigator discretion</p> <p>Monitor LFT within 1 to 4 weeks or at next visit</p>
TBL (isolated)		
> 2 × ULN if normal baseline (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver CRF 	<p>ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution^c (frequency at investigator discretion)</p> <p>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)</p>
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> Repeat LFT within the next week If elevation from baseline is confirmed, initiate close observation of the patient 	<p>Investigator discretion</p> <p>Monitor LFT within 1 to 4 weeks or at next visit</p>
Jaundice	<ul style="list-style-type: none"> Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver CRF 	<p>ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution^c (frequency at investigator discretion)</p>
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver CRF 	<p>Investigator discretion</p>

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

^aElevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

^b(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

^cResolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Table 9-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	<ul style="list-style-type: none"> IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	<ul style="list-style-type: none"> IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	<ul style="list-style-type: none"> ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	<ul style="list-style-type: none"> Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	<ul style="list-style-type: none"> Ultrasound or MRI
Hypoxic/ischemic hepatopathy	<ul style="list-style-type: none"> Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	<ul style="list-style-type: none"> Ultrasound or MRI, ERCP as appropriate.
Wilson disease	<ul style="list-style-type: none"> Caeruloplasmin
Hemochromatosis	<ul style="list-style-type: none"> Ferritin, transferrin
Alpha-1-antitrypsin deficiency	<ul style="list-style-type: none"> Alpha-1-antitrypsin

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 actions and follow-up assessments are listed in [Table 9-4](#) and [Table 9-5](#), respectively.

Table 9-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	<p>Confirm 25% increase after 24-48h</p> <p>Follow up within 2-5 days</p>
Serum creatinine increase $\geq 50\%$ compared to baseline	<p>Confirm $\geq 50\%$ within 24-48 hours after receipt of the abnormal value</p> <p>If confirmation of abnormal value is not possible in this timeframe study drug must be withheld until further evaluation is possible</p> <p>Consider drug interruption</p> <p>Consider patient hospitalization / specialized treatment</p>
Albumin- or Protein-creatinine ratio increase ≥ 2 -fold	<p>Confirm value after 24-48h</p> <p>Perform urine microscopy</p>
Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; New dipstick proteinuria $\geq 1+$	<p>Consider drug interruption / discontinuation</p>
Protein-creatinine ratio (PCR) ≥ 150 mg/g or ≥ 15 mg/mmol	
New dipstick glucosuria $\geq 1+$ not due to diabetes	<p>Blood glucose (fasting)</p> <p>Perform serum creatinine, ACR</p>
New dipstick hematuria not due to trauma	<p>Urine sediment microscopy</p> <p>Perform serum creatinine, ACR</p>

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 patient 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 9-5 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.	<ul style="list-style-type: none"> • Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor patient regularly (frequency at investigator's discretion) until:	<ul style="list-style-type: none"> • Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) <p>or</p> <ul style="list-style-type: none"> • Event stabilization: sCr level with $\pm 10\%$ variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm 50\%$ 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.

9.5 Reporting Medication 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 or consumer (EMA definition).

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

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. [Table 9-6](#) summarizes the reporting requirements.

Table 9-6 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

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 patient 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 Drug Safety and Epidemiology 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 patient 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 patient may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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 (email) 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 (email) (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 CRFs 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 patient records, the accuracy of entries on the CRFs, 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.

The investigator must maintain source documents for each patient 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 patient's file. The investigator must also keep the original informed consent form signed by the patient (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 CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility 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 patients 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 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to 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 patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual 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 a designated CRO) will 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 using an electronic data query. Designated investigator site staff are 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 (or a designated CRO) 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 samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any 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 the treatment codes will be unblinded 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.

Corporate Confidential Information

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all patient 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, patients will be analyzed according to the study treatment received.

The safety analysis set will include all patients that 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 on PK data.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided by treatment group.

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

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

The primary objective of this study is to assess the safety and tolerability of LMB763 as well as the efficacy of LMB763 on ALT in NASH patients during 12 weeks of treatment. Safety/tolerability data will be summarized. Further details are provided in [Section 11.4.4](#).

11.4.1 Variable(s)

Change from baseline to Week 12 in ALT is the primary efficacy variable. 'Baseline' is defined as the mean of ALT levels at baseline (V2) and pre-dose (V101) visits.

11.4.2 Statistical model, hypothesis, and method of analysis

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 into the analysis. The variance and the informative prior will be based on historical control data from studies such as the FLINT trial ([Neuschwander-Tetri et al 2015](#)). Median estimates, 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. As a sensitivity analysis, the posterior probabilities will be calculated for 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. An analysis using SAS PROC MCMC without assuming the variance is known in the likelihood function may be performed as well.

Additionally a repeated measures analysis of covariance (ANCOVA) will be performed for change from baseline ALT without using historical placebo control data. The model will include effects for treatment, visit, treatment by visit interaction, stratification factor (BMI group), baseline, and baseline by visit interaction. An unstructured variance-covariance structure will be used to account for correlation among multiple measurements from the same patient and variance heterogeneity. Point estimates, the associated two-sided 90% confidence intervals as well as the p-values for treatment differences 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. For log-transformed ALT analysis the ratio to baseline results obtained by back transformation will be reported

The cohort effect will be explored and a cohort-wise analysis for both the Bayesian and ANCOVA approaches 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.

11.4.3 Handling of missing values/censoring/discontinuations

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

11.4.4 Summary statistics of safety

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.

ECG evaluations

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 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 patient.

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

Other safety evaluations

Not applicable.

11.4.5 Sensitivity analyses

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

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

Log-transformed ratio to baseline % liver fat and fasting lipid profiles (total cholesterol, HDL, LDL, triglycerides) as well as change from baseline % liver fat, weight, BMI, WTH ratio will be analyzed using the same repeated measures ANCOVA described in [Section 11.4.2](#) with

log-transformed baseline in lieu of baseline as a covariate for lipid parameters. 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 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. 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.

11.5.2 Pharmacokinetics

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, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

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. 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. Pharmacokinetic parameters will be calculated as described in [Section 8.7](#) and will be listed by patient.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

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, AUClast, AUCtau, Racc, T1/2, Vz/F and CL/F from the plasma concentration-time data. The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 will include at least 3 data points after Cmax. If the adjusted R² value of the regression analysis of the terminal phase is less than 0.75, no values will be reported for T1/2, AUCinf and CL/F.

An assessment of dose proportionality of LMB763 exposure will be conducted using Cmax and AUC. An Analysis of Variance (ANOVA) with dose as the classification factor will be performed on log-transformed dose-normalized parameters. 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.

11.5.3 Pharmacokinetic / pharmacodynamic interactions

The relationship between LMB763 PK parameters (Cmax and AUCtau) and key PD parameters (including, but not limited to FGF19, C4, ALP, Cholesterol (total LDL and HDL)) may be explored using a graphical approach and descriptive statistics may be provided. Additional statistical analysis such as ANOVA or regression may be performed, if necessary. Modeling approach may also be used to explore the PK/PD interactions.

11.5.4 Other assessments

Change from baseline itch VAS measurements will be analyzed using the same repeated measures ANCOVA described in [Section 11.4.2](#).

Corporate Confidential Information

11.7 Sample size calculation

A mean decrease of 11 U/L from baseline to Week 12 in ALT was observed in the placebo group (N=142) of the FLINT trial. Historical placebo control data from trials such as the FLINT study will be used when analyzing ALT data from the current study by including prior information in a Bayesian approach.

Data from 54 patients in an LMB763 dosing arm and 54 placebo patients (placebo data from the current study supplemented by historical placebo control data), will provide approximately

76% power to detect a 19 U/L placebo-adjusted reduction from baseline ALT. The sample size calculation was done using a one-sided test at the 0.05 significance level, assuming a standard deviation of 41.16 U/L which was derived from the FLINT trial. A placebo-adjusted 19 U/L reduction in ALT corresponds to a 30 U/L decrease if the mean reduction induced by the placebo treatment is 11 U/L as reported in the FLINT study.

The corresponding power without using any historical placebo control data will be 61% if 54 patients in a LMB763 dosing arm and 27 patients in the placebo arm complete the study.

To make allowance for potential dropouts approximately 96 patients will be enrolled in the each dosing cohort. All patients who have been enrolled into the initial cohort will complete the protocol at that dose, however no further patients will be recruited into that cohort

Corporate Confidential Information

11.8 Power for analysis of key secondary variables

Data from a total of 81 patients (54 from an LMB763 dosing arm and 27 placebo patients) will provide 52% and 82% power to detect a 1.64% and 2.46% difference in absolute change from baseline % liver fat between the 2 treatments, respectively, based on a one-sided test at the 0.05 significance level. It is assumed the standard deviation equals to 4.02%, derived from the summary results in a recently completed Novartis study that enrolled non-alcoholic fatty liver disease patients with baseline liver fat >10% as measured by MRI. Since the observed overall mean baseline % liver fat in that study is 16.39%, a placebo-adjusted absolute decrease of 1.64% and 2.46% corresponds to a relative reduction of 10% and 15%, respectively.

Corporate Confidential Information

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, patient recruitment procedures (e.g. advertisements) and any other written information to be provided to patients. 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 around 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.

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 patients 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 patients 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 patient 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

Calkin AC, Tontonoz P (2012) Transcriptional integration of metabolism by the nuclear sterol-activated receptors LXR and FXR. *Nat. Rev. Mol. Cell Biol.* p. 213-24.

Jiménez-Agüero R, Emparanza JI, Beguiristain A, et al (2014) Novel equation to determine the hepatic triglyceride concentration in humans by MRI: diagnosis and monitoring of NAFLD in obese patients before and after bariatric surgery. *BMC Med.* p. 137

Mudaliar SU, Henry RR, Sanyal AJ, et al (2013) Efficacy and safety of the farnesoid X receptor agonist obeticholic acid in patients with type 2 diabetes and nonalcoholic fatty liver disease. *Gastroenterology* p. 574-82.

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.

Patel YA, Imperial JC, Muir AJ, et al Liver Forum's Data Standardization Working Group (2017) Baseline Parameters in Clinical Trials for Nonalcoholic Steatohepatitis: Recommendations From the Liver Forum. *Gastroenterology.* 153(3):621-625.

Ryan MC, Itsiopoulos C, Thodis T, et al (2013) The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol.* p. 138-43.

15 Appendix 1: The American Heart Association (AHA) Recommended Diet

Optimization of nutrition-related practices can result in a marked triglyceride-lowering effect that ranges between 20% and 50%. These practices include weight loss, reducing simple carbohydrates at the expense of increasing dietary fiber, eliminating industrial-produced trans fatty acids, restricting fructose and saturated fatty acids, implementing a Mediterranean-style diet, and consuming marine-derived omega-3 PUFA.

AHA recommends the following:

Eat a variety of fruit and vegetable servings every day. Dark green, deep orange, or yellow fruits and vegetables are especially nutritious. Examples include spinach, carrots, peaches, and berries. Eat a variety of grain products every day. Include whole-grain foods that have lots of fiber and nutrients. Examples of whole grains include oats, whole wheat bread, and brown rice. Eat fish at least 2 times each week. Oily fish, which contain omega-3 fatty acids, are best for your heart. These fish include tuna, salmon, mackerel, lake trout, herring, and sardines. Stay at a healthy weight by balancing the amount of calories you eat with the activity you do every day. If you want to lose weight, increase your activity level to burn more calories than you eat.

Eat foods low in saturated fat and cholesterol. Try to choose the following foods:

- Lean meats and meat alternatives like beans or tofu
- Fish, vegetables, beans, and nuts
- Nonfat and low-fat dairy products
- Polyunsaturated or monounsaturated fats, like canola and olive oils, to replace saturated fats, such as butter

Read food labels and limit the amount of trans fat you eat. Trans fat is found in many processed foods made with shortening or with partially hydrogenated or hydrogenated vegetable oils. These foods include cookies, crackers, chips, and many snack foods.

Limit sodium intake to less than 2,300 mg of sodium a day (about one teaspoon). Choose and prepare foods with little or no salt.

Limit alcohol intake to 2 drinks a day for men and 1 drink a day for women.

Limit drinks and foods with added sugar.