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Novartis Research and Development

LMB763 (nidufexor)

Clinical Trial Protocol CLMB763X2202 / NCT03804879

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

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ACEI	angiotensin converting enzyme inhibitor
ADA/EASD	American Diabetes Association / European Association for the Study of Diabetes
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANIT	alpha-naphthyl-isothiocyanate
aPTT	activated Partial Thromboplastin Time
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ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
BCRP	Breast cancer resistance protein, a member of the ATP-binding cassette transporters
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulations
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO&PS	Chief Medical Office & Patient Safety
CNS	Central nervous system
CPK	Creatine phosphokinase
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTCAE	Common terminology criteria for adverse events
CV	coefficient of variation
CYP	Cytochrome P450 enzyme (i.e., CYP2C8, CYP2C9, CYP1A2, CYP2A6, CYP2D6, CYP2E1, CYP3A4/5)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EDD	estimated date of delivery
eGFR	Estimated glomerular filtration rate
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
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GCP	Good Clinical Practice
GLP	Good laboratory practice
GLP-1	Glucagon-like peptide-1
h	hour

HbA1c	Glycated haemoglobin
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HDL-C	High density lipoprotein cholesterol
HIV	human immunodeficiency virus
i.v.	intravenous
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-6	Interleukin-6
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
KDIGO	Kidney Disease: Improving Global Outcomes guidelines
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LFT	Liver function test
LLN	lower limit of normal

LP(a)	lipoprotein (a)
LQT724	acyl glucuronide metabolite of LMB763 (nidufexor)
MCP-1	monocyte chemoattractant protein 1
MDRD	Modification of Diet in Renal Disease (equation for estimating eGFR)
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
mm Hg	millimeters of mercury
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NCDS	Novartis Clinical Data Standards
NOAEL	No observed adverse effect level
NOVDD	Novartis Data Dictionary
NSAID	Non-steroidal anti-inflammatory drug
p.o.	oral
PBC	Primary biliary cholangitis
PD	pharmacodynamic(s)

PK	pharmacokinetic(s)
POC	proof of concept
PSC	Primary sclerosing cholangitis
PT	prothrombin time
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QMS	quality management system
QTcF	QTc Fridericia correction formula
RAS	renin-angiotensin system
RBC	red blood cell(s)
SAD/MAD	Single-ascending dose/multiple-ascending dose
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGLT-2	Sodium-glucose linked transporter-2
SMAD3	Mothers against decapentaplegic homolog 3 also known as SMAD family member 3
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TD	Study Treatment Discontinuation
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UACR	Urinary albumin to creatinine ratio
UDP	Uridine 5'-diphospho-glucuronosyltransferase (UGT)
UGT1A1	UDP glucuronosyltransferase 1A1
UGT1A3	UDP glucuronosyltransferase 1A3
ULN	upper limit of normal
ULQ	upper limit of quantification
VAS	Visual Analog Scale
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WTH	Waist-to-hip ratio
γGT or GGT	γ-glutamyl transferase -or- Gamma-glutamyl transferase

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of patients fulfilling certain criteria
Control drug	Any drug(s) (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 patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
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.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
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,” "Investigational Medicinal Product," or “test substance”
LMB763	Investigational Novartis compound (nidufexor) to be studied in this protocol
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Mobile healthcare professional	A qualified healthcare professional, such as a Nurse or Phlebotomist, who performs certain protocol procedures for the participant in a remote location such as a participant’s home.
Nidufexor	Investigational Novartis compound (LMB763) to be studied in this protocol
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
Personal Data	Patient information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes patient identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Remote	A location that is not the investigative site where the investigator will conduct the trial and where source data will be maintained, but is for example the participant’s home or another appropriate location

Run in Failure	A patient who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to patient's medications or other intervention)
Screen Failure	A patient who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Patient	A trial participant (can be a healthy volunteer or a patient)
Patient number	A unique number assigned to each patient upon signing the informed consent. This number is the definitive, unique identifier for the patient and should be used to identify the patient throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed patient, 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 study consent	Withdrawal of consent from the study occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

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Protocol summary

Protocol number	CLMB763X2202
Full Title	A randomized patient-and-physician blinded, placebo-controlled, 24-week study to assess the safety, tolerability and efficacy of nidufexor in patients with diabetic nephropathy
Brief title	A study of the safety and efficacy of nidufexor in patients with diabetic kidney disease
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Nidufexor is a potent partial agonist of the bile acid receptor Farnesoid X Receptor. In diabetic nephropathy, hyperglycemia, dyslipidemia and oxidative stress induce fibrosis and inflammation, resulting in endothelial and podocyte epithelial injury. Nidufexor addresses fibrosis, oxidative stress, inflammation and cell death, and therefore has the potential to improve the management of diabetic kidney disease when added to the standard of care (angiotensin converting enzyme inhibitor or angiotensin receptor blocker). This non-confirmatory Phase 2 study is designed to determine the safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of nidufexor in combination with dose of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) that is the standard of care as judged by the PI or sub-I in patients with type 2 diabetes and nephropathy.
Primary Objective(s)	To compare the effect of nidufexor to placebo on albuminuria in patients with diabetic nephropathy already receiving treatment with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) as measured by serial urinary albumin to creatinine ratio and 24 hour urinary albumin at baseline and end of study. To assess the safety and tolerability of nidufexor, as measured by vital signs, physical examination, laboratory measurements, electrocardiograms, and reports of adverse events
Secondary Objectives	To assess the pharmacokinetic properties of nidufexor at steady state in patients with type 2 diabetes and nephropathy as measured by -plasma concentrations of nidufexor To determine the effect of nidufexor on renal tubular function as measured by free water clearance by the kidney To determine the effect of nidufexor on anthropometric assessments (weight, body mass index, and waist-to-hip ratio) To determine the effect of nidufexor on lipids as measured by a fasting lipid profile

Study design	A non-confirmatory, multicenter, patient and investigator blinded, randomized, placebo-controlled, fixed-dose, proof-of-concept trial assessing nidufexor vs. placebo. The study consists of a 30-day (Day -30 to Day-1) Screening period, followed by a 24-week Treatment Period (Days 1 through 168), at which point End of Study (EOS) assessments will occur on Day 169. PK profiling (up to 6 hours post-dose) will be done on Day 1 and Day 14. Commercially Confidential Information
Population	Approximately 116 men and women, between 18 and 75 years of age, with type 2 diabetes and diabetic nephropathy will be enrolled.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed • Male and female patients ≥ 18 years and ≤ 75 years (at the time of the screening visit) • Diagnosis of type 2 diabetes mellitus, with diagnosis made at least 6 months prior to screening, as determined by American Diabetes Association criteria • Diabetic nephropathy as evidenced by Urine albumin-Cr ratio (UACR) ≥ 300 mg/g Cr while receiving a dose of angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) that is the standard of care as judged by the PI or sub-I • Dose of either (ACEI or ARB) that is standard of care as judged by the PI or sub-I must also be stable, defined as <25% dose change over at least 4 weeks prior to screening.
Key Exclusion criteria	Commercially Confidential Information • History of Type 1 diabetes mellitus, or uncontrolled type 2 diabetes mellitus as evidenced by HbA1c > 11% • The presence of kidney disease, other than diabetic nephropathy; severe renal impairment manifesting as serum creatinine-based eGFR <30 mL/min/1.73 m^2 at screening, as determined by the CKD-EPI formula; history of renal transplant or planned renal transplant during the study, history of: primary kidney disease, including, but not limited to primary glomerulonephritis, focal segmental glomerulosclerosis, polycystic kidney disease, or membranous nephropathy; secondary kidney disease other than diabetic nephropathy, including but not limited to lupus nephritis, obstructive uropathy, and renovascular disease; or acute renal dialysis or acute kidney injury stage 2 or 3. as defined in the Kidney Disease: Improving Global Outcomes [KDIGO] guidelines Commercially Confidential Information • Uncontrolled hypertension despite receiving anti-hypertensive therapy as evidenced by BP >150/90 mm Hg at rest as determined

	by the lowest of 3 measurements obtained over approximately 15 minutes while sitting • History or presence of liver disease including serum ALT or AST >1.5 x ULN; active Hepatitis B or C virus (HCV, HBV) infection (*positive HBV surface antigen (HBsAg) test excludes a patient*); primary biliary cholangitis (PBC); primary sclerosing cholangitis (PSC); alcoholic liver disease; cirrhosis; definite autoimmune liver disease or overlap hepatitis; suspected or confirmed Gilbert's syndrome; known bile duct obstruction; suspected or proven liver cancer; liver transplantation or current placement on a liver transplant list (*Note: Patients with NASH or NAFLD **are not excluded,** if their transaminase levels comply with exclusion criterion)*; or clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities: serum albumin <LLN; Total Bilirubin > 120% of ULN; alkaline phosphatase >300 U/L; history of esophageal varices, ascites or hepatic encephalopathy; splenomegaly; platelet count <LLN; or prior or planned (during the study period) bariatric surgery (e.g., gastroplasty, roux-en-Y gastric bypass). • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study
Study treatment	CCI 25 mg nidufexor capsules CCI CCI matching placebo capsules
Efficacy assessments	• Urine albumin-creatinine ratio (UACR) at serial time points, as specified in the Assessment Schedule • 24-hour urinary albumin at baseline and end of study
Pharmacodynamic Assessments	• Estimated glomerular filtration rate (eGFR), as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation • Free water clearance • Weight • BMI • Waist-to-hip (WTH) ratio • Fasting lipid profile
Pharmacokinetic Assessments	• Cmax • Tmax • AUClast
Key Safety Assessments	• vital signs • physical examination • laboratory markers in blood and urine • ECG • adverse event monitoring • Visual analog scale for itch

Other Assessments	Commercially Confidential Information
Data Analysis	The primary objective of this study is to assess the safety and tolerability of nidufexor as well as the efficacy of nidufexor on albuminuria in patients with diabetic nephropathy during 24 weeks of treatment. For efficacy evaluation, log-transformed ratios to baseline UACR and 24-hour urine albumin excretion at Week 24 are the primary endpoints. A repeated measures Analysis of Covariance (ANCOVA) will be performed for log-transformed ratio to baseline UACR measured at each visit. Similarly, an ANCOVA with treatment as the classification factor and log-transformed baseline as the covariate will be conducted for log-transformed ratio to baseline 24-hour urine albumin excretion. For analytical purposes, all safety data, including laboratory measurements, vital signs, adverse events, ECG, are considered primary endpoints. Safety and tolerability data will be summarized. Formal statistical analysis will not be performed on the safety and tolerability data. Log-transformed ratio to baseline for eGFR, free water clearance, HbA1c and fasting lipid profiles (total cholesterol, HDL, LDL, triglycerides and Lp(a)) as well as change from baseline in weight, BMI and WTH ratio will be analyzed using the same repeated measures ANCOVA with baseline in lieu of log-transformed baseline as a covariate for change from baseline analysis.
Key Words	Nidufexor, LMB763, Farnesoid X receptor, placebo-controlled, multicenter, patient and investigator blinded, randomized, placebo-controlled, fixed-dose, proof-of-concept trial, diabetic nephropathy, type 2 diabetes, tolerability, safety, 24-hr urinary albumin, urinary albumin to creatinine ratio (UACR), free water clearance, HbA1c, estimated glomerular filtration rate (eGFR), CKD-EPI, angiotensin receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACEI), fasting lipid profile

1 Introduction

1.1 Background

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

In diabetic nephropathy, hyperglycemia, dyslipidemia and oxidative stress induce fibrosis and inflammation, resulting in endothelial and podocyte epithelial injury. In the kidney, FXR is expressed in the glomeruli and tubules (Marquardt et al 2017, Zhang et al 2014). FXR agonism decreases markers of fibrosis, oxidative stress, inflammation and cell death in rodent models of kidney disease. Specifically, FXR agonism decreases SMAD3 in a mouse renal fibrosis model (Zhao et al 2016), and decreases MCP-1, IL-6, H_2O_2 and markers of apoptosis in a mouse ischemia-reperfusion renal injury model (Gai et al 2016). Furthermore, FXR agonism in uninephrectomized obese mice reduces albuminuria and urinary H_2O_2, and improves renal histology, oxidative stress, lipid accumulation and mitochondrial function (Gai et al 2016, Gai et al 2017). In this same model, nidufexor in combination with angiotensin receptor blockade (ARB) reduced albuminuria better than either nidufexor or ARB alone.

Diabetic nephropathy is the single most common cause of chronic kidney disease in the USA, affecting approximately 16 million Americans. Diabetic nephropathy is a global health problem: a cross sectional study among over 32,000 type 2 diabetic patients from 33 countries revealed that the prevalence of micro- and macroalbuminuria is 38.8% and 9.8%, respectively (Gheith et al 2016). Other analyses suggest that diabetic nephropathy affects approximately 18 million people in India (Pradeepa and Mohan 2017), and approximately 44 million people in China (Ma et al 2018).

The standard of care, primarily angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), is focused on delaying rather than preventing progression to end stage renal disease (Umanath and Lewis 2018). Nidufexor addresses fibrosis, oxidative stress, inflammation and cell death, and therefore has the potential to improve the management of diabetic kidney disease when added to the standard of care ACEI or ARB.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

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1.1.5 Clinical Data

Two clinical studies have been completed for nidufexor: a SAD/MAD safety/tolerability study in healthy subjects and a proof-of concept study in patients with biopsy-proven or phenotypic NASH. (see Protocol Section 1.1.6, and the Investigator's Brochure for additional information).

1.1.6 Human Safety and Tolerability Data

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Study CLMB763X2201 was a randomized, patient- and investigator-blinded, placebo-controlled, multicenter study to assess the safety, tolerability, pharmacokinetics and efficacy of nidufexor in patients with biopsy-proven or phenotypic NASH. A total of 121 patients were randomized of which 81 subjects received nidufexor at starting doses of 100 mg (Cohort 1; N=37) or 50 mg (Cohort 2; N=44). The most commonly reported AE was itch. Discontinuation due to AE was most frequently in the 100 mg nidufexor group. Itch was considered a tolerability but not safety finding, and overall nidufexor was considered generally well tolerated at 50 mg and 100 mg in patients with NASH.

Further details are available in the Investigator’s Brochure.

1.1.7 Human Pharmacokinetic Data

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1.1.8 Human Pharmacodynamic Data

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1.2 Purpose

The purpose of this proof-of-concept study is to determine whether LMB763 (nidufexor), an FXR agonist, warrants continued clinical development for the treatment of diabetic nephropathy.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
To compare the effect of nidufexor to placebo on albuminuria in patients with diabetic nephropathy already receiving treatment with ACEI or ARB	Urine albumin-creatinine ratio (UACR) at serial time points, as specified in the Assessment Schedule 24-hour urinary albumin at baseline and end of study
To assess the safety and tolerability of nidufexor	Safety endpoints including: vital signs physical examination laboratory measurements ECG parameters adverse events
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)
To determine the effect of nidufexor on renal filtration function	Estimated glomerular filtration rate (eGFR), as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010)
To assess the pharmacokinetic properties of nidufexor on day 1 and at steady state in patients with type 2 diabetes and nephropathy	Cmax, Tmax and AUC0-6h.
To determine the effect of nidufexor on renal tubular function	Free water clearance
To determine the effect of nidufexor on anthropometric assessments	Assessments Weight BMI Waist-to-hip (WTH) ratio
To determine the effect of nidufexor on lipids	Fasting lipid profile, including lipoprotein (a) [Lp(a)]

3 Study design

This study is a non-confirmatory, multicenter, patient- and investigator-blinded, randomized, placebo-controlled, fixed-dose, proof-of-concept trial assessing nidufexor vs. placebo in approximately 100 patients receiving standard of care (optimal tolerated doses of ARB or ACEI) for diabetic nephropathy due to type 2 diabetes. The study consists of a 30-day (Day -30 to Day-1) Screening Period, followed by a 24-week Treatment Period (Days 1 through 168),

at which point End of Study (EOS) assessments will occur on Day 169. All study visit assessments will occur pre-dose, starting on Day 1 of the therapeutic period. PK profiling (up to 6 hours post-dose) will be done on Day 1 and 14. Post Study Safety Contact will occur approximately 28 days after discontinuing study treatment (Day 197).

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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 CCI for 24 weeks (Day 1-168), as instructed by the investigator, and study assessments will be performed once monthly until the EOS visit (Day 169).

At the investigator's direction and based on benefit-risk considerations of the participant's clinical condition, qualifying patients may be offered the option to have certain clinical trial procedures according to Table 8-1 performed at a remote location. Procedures will be performed remotely under the oversight of the investigator, who retains accountability for oversight and all efficacy and safety decisions with delegation of tasks to mobile health professionals (i.e., research nurses). The remote procedures will be offered in certain countries and sites as determined by Novartis based on national and local regulations. The mobile research nurses will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use their own mobile health professionals that are not provided by Novartis, this must be agreed with Novartis prior to implementation.

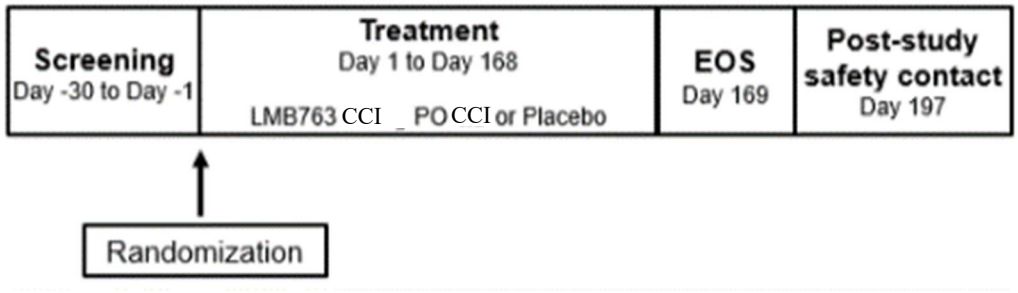
The study design scheme appears below. On visit days, study medication will be administered by site personnel or delegate. Each visit during the treatment and follow-up periods will have an allowable window of +/-5 days.

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.

Figure 3-1 LMB763X2202 study design



Patients will be randomized in a 1:1 ratio to receive nidufexor CCI or placebo. Approximately 116 patients will be enrolled in the study and randomized. Approximately 100 patients are expected to complete the study.

Treatment randomization may occur prior to day 1 as soon as patient eligibility is confirmed from baseline assessments

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of determining the effect of nidufexor on urinary albumin excretion over a 24-week treatment period, in patients with macroalbuminuric diabetic nephropathy on ACEI or ARB therapy. Change in albuminuria (UACR and 24-hour urine albumin excretion) and annualized rate of change in eGFR over the 24-week treatment period are the primary and secondary endpoints, respectively. These two parameters comprise the current gold standard (Levey et al 2015) for assessing stage and progression of proteinuric chronic kidney diseases such as diabetic nephropathy secondary to Type 2 Diabetes.

- Patient- and investigator-blinded study: Blinding of patients and investigators allows for an unbiased assessment of patient readouts such as adverse events.
- Randomized: Randomization decreases the chance of an imbalance in patient characteristics between groups, thereby facilitating an unbiased assessment of safety, tolerability, and efficacy.
- Placebo-controlled: This is critical to establish that any safety, tolerability, or efficacy outcome can be attributed to the study drug as opposed to an effect of study procedures.
- Fixed-dose: This study will not involve dose adjustments unless needed due to tolerability issues (see Section 6.5). The dose selection rationale is described in the next section.

4.1.1 Rationale for choice of background therapy

Pharmacologic blockade of the renin-angiotensin system (RAS) with ACEI or ARB slows and delays progressive decline in kidney function in proteinuric diseases such as diabetic nephropathy. RAS blockade benefits proteinuric kidney disease via several mechanisms, including reduction in intraglomerular pressure, improved blood pressure control, and possibly anti-fibrotic actions. RAS blockade is therefore standard of care for many proteinuric kidney diseases, aiming to reduce urine protein excretion as the key pharmacodynamic marker (Umanath and Lewis 2018).

4.2 Rationale for dose/regimen and duration of treatment

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The CLMB763X2202 study population is expected to have comparable PK to the CLMBX2201 population.

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The duration of the study is based on (a) the high variability typical of urine albumin measurements, and (b) the high variability and slow rate of change in eGFR; the 24-week treatment period will allow more robust assessment of a potential anti-proteinuric effect (primary endpoint) and potential slowing of eGFR decline (secondary endpoint). Since both of these parameters demonstrate high intra- and inter-patient variability, repeated measures over 24 weeks will provide more robust data to detect potential treatment effects.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

ACEI or ARB agents are currently prescribed to patients with type 2 diabetes in an attempt to modulate intraglomerular pressures and prevent diabetic nephropathy. All patients will be receiving stable doses of an ACEI or an ARB agent at screening, and a placebo will be used as a comparator to nidufexor to evaluate the treatment effect of nidufexor added to standard of care (ACEI or ARB).

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the patient will not reliably comply, they should not be entered or continue in the study.

As well as the risks and potential risks described in the Investigator's Brochure, there may be unknown risks of nidufexor, which may be serious and unforeseen. The risk to patients in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, stopping rules, and periodic review of safety data.

Refer to the current section of the nidufexor IB for latest information on identified and potential adverse effects.

A high level summary of risks are provided below.

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In the CLMB763X2201 study (NASH patients), adverse events related to increased ALT were reported more commonly in placebo (4/40; 10%) than in groups receiving 50 mg nidufexor (2/44; 4.5%) or 100 mg nidufexor (1/37; 2.7%); adverse events related to increased AST were reported in 1 (2.5%) patients receiving placebo, and 1 (2.3%) and 4 (10.8%) patients receiving 50 mg and 100 mg nidufexor, respectively. However, no new significant liver enzyme abnormalities were reported in the study due to the study medication. Transaminases will be monitored in this study.

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LDL-C elevations and reductions in both HDL-C and triglycerides have been noted in clinical trials with a bile acid derived FXR-agonist.

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. Serum lipids will be monitored during this study.

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Refer to Section 7 of the latest version of nidufexor Investigator's Brochure for detailed information on identified and potential adverse effects.

In addition, investigators will be advised to manage glycemic control for all patients in a manner consistent with local treatment guidelines for type 2 diabetes. In the absence of local guidelines, investigators are referred to the joint ADA/EASD guidelines for the management of glucose control in patients with type 2 diabetes (Inzucchi et al 2015).

The assessment of the Benefit/Risk for the study in the context of COVID-19 pandemic concluded the absence of additional risks for the study population and/or related to the investigational medicinal product.

4.5.1 Blood sample volume

A total blood volume of approximately 240 mL is planned to be collected over a period of approximately 32 weeks from each patient as part of the study. Additional samples may be required for safety monitoring, which are not included in the noted estimate. This estimate includes approximate planned overdraw amounts required by locally available blood collection tubes.

Timings of blood sample collections are outlined in the Assessment Schedule and a summary blood log is provided in the Site Operations Manual (SOM). Instructions for sample collection, processing, storage and shipment information may be found in the SOM and the central laboratory manual.

See the Section 8.5.3.2 on the use of residual biological samples.

5 Population

The study population will be comprised of male and female patients with diabetic nephropathy due to type 2 diabetes.

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

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. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation.

Deviation from **any** entry criterion excludes a patient from enrollment into the study. Details on re-screening are located in Section 8.1.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients ≥ 18 years and ≤ 75 years (at the time of the screening visit).
3. Diagnosis of type 2 diabetes mellitus, with diagnosis made at least 6 months prior to screening, as determined by American Diabetes Association criteria
   American Diabetes Association 2010
4. Diabetic nephropathy as evidenced by Urine albumin-Cr ratio (UACR) ≥ 300 mg/g Cr at screening while receiving a dose of ACE-I or ARB that is the standard of care as judged by the PI or sub-I
   - Dose of ACE-I or ARB that is the standard of care as judged by the PI or sub-I *must also be stable, defined as <25% dose change that occurred at least 4 weeks prior to screening.*

5.2 Exclusion criteria

Patients meeting any of the following criteria are not eligible for inclusion in this study.

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3. History of Type 1 diabetes mellitus
4. Uncontrolled type 2 diabetes mellitus as evidenced by HbA1c >11% at screening
5. The presence of kidney disease, other than diabetic nephropathy, at screening including:
   - Primary kidney disease, including, but not limited to primary glomerulonephritis, focal segmental glomerulosclerosis, polycystic kidney disease, or membranous nephropathy;
   - Secondary kidney disease, other than diabetic nephropathy, including but not limited to lupus nephritis, obstructive uropathy, and renovascular disease;
   - History of acute renal dialysis or acute kidney injury stage 2 or 3 as defined in the Kidney Disease: Improving Global Outcomes [KDIGO] guidelines
     (Okusa and Davenport 2014)

6. Severe renal impairment manifesting as serum creatinine-based eGFR <30 mL/min/1.73 m^2 at screening, as determined by the CKD-EPI formula (Levey and Stevens 2010)
7. History of renal transplant or planned renal transplant during the study
8. Diagnostic or interventional procedure requiring any potentially nephrotoxic contrast agent within 4 weeks of the first screening visit, or planned during the study
9. Uncontrolled hypertension (Whelton et al 2018), despite receiving anti-hypertensive therapy, as evidenced by BP >150/90 mm Hg at rest at screening as determined by the lowest of 3 measurements obtained over approximately 15 minutes while sitting
10. History or presence of liver disease at screening including:
    - Active Hepatitis B or C virus (HCV, HBV) infection
      - *Note: A positive HBV surface antigen (HBsAg) test excludes a patient*
    - Primary biliary cholangitis (PBC)
    - Primary sclerosing cholangitis (PSC)
    - Alcoholic liver disease
    - Cirrhosis
    - Definite autoimmune liver disease or overlap hepatitis
    - Suspected or confirmed Gilbert's syndrome
    - Known bile duct obstruction
    - Liver transplantation or current placement on a liver transplant list
    - Suspected or proven liver cancer
      - *Note: Patients with NASH or NAFLD **are not excluded,** if their transaminase levels comply with exclusion criterion 11*
11. Serum ALT or AST >1.5 x ULN at screening.
12. Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities at screening:
    - Serum albumin <LLN
    - Total Bilirubin >120% X ULN or Gilbert's syndrome
    - Alkaline phosphatase >300U/L
    - History of esophageal varices, ascites or hepatic encephalopathy
    - Splenomegaly
    - Platelet count <LLN

18. Receiving any of the prohibited medications listed in Table 6-2, (e.g. UGT1A1 inhibitors, herbal remedies that inhibit UGT1A1, non-selective UGT inhibitors, ACEI and ARB in combination, direct renin inhibitors, SGLT2 inhibitors, GLP1-receptor agonists) and unable to switch to suitable alternatives at least 5 days prior to first study dose and for the duration of the study
19. 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.
20. 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 of screening, regardless of whether there is evidence of local recurrence or metastases
21. History or current diagnosis of ECG abnormalities prior to first study dose indicating significant risk of safety for patients participating in the study
22. 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
23. Known positivity for Human Immunodeficiency Virus (HIV) infection
24. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using basic methods of contraception during dosing of study treatment.

    Basic 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
        - *Note: 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)
        - *Note: For female patients on the study the vasectomized male partner should be the sole partner for that patient*
    - Barrier methods of contraception: condom or occlusive cap (e.g., diaphragm or cervical/vault caps).
    - 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
        - *Note: 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 before taking study treatment. 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 childbearing potential.

25. 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

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No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

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 SOM and on the medication label.

Instructions for administering study treatment

On visit days, study medication will be administered after an overnight fast of at least 6 h by site personnel or delegate. Medication will be administered with a half a glass (approximately 120 mL) of water in the morning. Each patient's mouth must be checked to ensure that the medication was swallowed. Patients must be instructed not to chew the medication, but to swallow it whole.

Patients are encouraged to follow a similar routine for taking study treatment on non-visit days. However it is not essential for medication to be taken under fasted conditions.

Visit days - All doses administered to the patient on visit days will be recorded on the Dosage Form CRF.

Non-visit days - Patients will be provided with individual diaries to record each administration of study treatment on non-visit days. If a patient misses a dose at scheduled time +/- 5 h then this should be recorded as a missed dose and next dose should be taken at the scheduled time the following day.

Novartis will provide the site with an emergency study card to hand over to all study participants who receive a dose of study medication (nidufexor or placebo), which will state that the subject is participating in a clinical study and may have received an investigational drug.

This emergency study card will also include the contact information of the Study Doctor/Investigative Site. Designated study staff will instruct study participants to present this card to a medical care provider if they have any medical issues during the course of the study.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drugs

Investigational/Control Drug				
Investigational/ Control Drug (Name and Strength)	**Pharmaceutical Dosage Form**	**Route of Administration**	**Packaging**	**Sponsor (global or local)**
LMB763 25 mg	Capsule	Oral	Double blind patient specific kits	Novartis
Placebo LMB763	Capsule	Oral	Double blind patient specific kits	Novartis

The investigational drug, nidufexor, and matching placebo will be prepared by Novartis and supplied to the investigator site as double blind patient specific kits to be dispensed by study pharmacist or other approved trained personnel. Study treatments are defined as:

- CCI 25 mg LMB763 capsules CCI
- CCI matching placebo capsules

6.1.1.1 Decentralized Clinical Trial Model (select US sites only)

The study medication and all required clinical study supplies will be distributed via direct-to-participant shipment utilizing an extension of the IND for compliance purposes.

6.1.2 Additional study treatments

Background therapy must include either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), as per the inclusion criteria. Use of dual renin-angiotensin system inhibitors (ACEI + ARB) is prohibited.

6.1.3 Treatment arms/group

Patients will be assigned at Visit 101 to one of the following treatment arms in a ratio of 1:1.

Study treatments are defined as:

- LMB763 CCI (CCI LMB763 25 mg capsules)
- Placebo (CCI placebo capsules)

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Treatment other than study treatment is permitted through the entire study duration, if such treatment is not prohibited as defined in Section 6.2.2.

Hormonal contraception is allowed during this study (see Section 5.2).

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies or procedures pages.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication.

If in doubt the investigator should contact the Novartis translational medical expert, or designee, before randomizing a patient or allowing a new medication to be started. If the patient is already enrolled, the investigator should contact the Novartis translational medical expert, or designee, to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Persistent Hyperglycemia: Investigators are advised to manage glycemic control for all patients in a manner consistent with local treatment guidelines for type 2 diabetes. In the absence of local guidelines, investigators are referred to the joint ADA/EASD guidelines for the management of glucose control in patients with type 2 diabetes (Inzucchi et al 2015).

Dose Adjustments: Nidufexor may moderately reduce the clearance of medications that are substrates of CYP2C8. Administration of nidufexor with pioglitazone, rosiglitazone, or glyburide (glibenclamide) could result in higher serum concentrations of these medications, thereby increasing the potential for hypoglycemia. Frequent, regular fingerstick blood glucose monitoring is advisable during the treatment phase of this study, with subsequent dose adjustments of these medications as needed.

NSAIDs, COX-2s: Modest doses of non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase-2 (COX-2) inhibitors may be used for a period not longer than 7 days.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-3 are NOT allowed after the start of study treatment until the patient's final dose of oral study medication (nidufexor or placebo).

Nidufexor is metabolized primarily by UGT1A1. There is a potential for inhibitors of UGT1A1 to affect the clearance of nidufexor. There is also a potential that nidufexor will affect the disposition of medications that are substrates of CYP2C8.

Patients with known Gilbert's syndrome and those taking concomitant medications and herbal remedies that inhibit UGT1A1 or are a profound CYP2C8 substrate should be EXCLUDED from clinical trials of nidufexor until formal clinical drug-drug interaction studies have been performed.

Restricted Antihyperglycemic Medications: The SGLT-2 inhibitors (e.g. canagliflozin, dapagliflozin, empagliflozin) and GLP-1 receptor agonists (e.g. exenatide, liraglutide, albiglutide, dulaglutide, semaglutide, lixisenatide) are prohibited medications in this study. A list of generic and trade names is provided in the SOM.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Specific UGT1A1 inhibitors: e.g atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine, and zafirlukast	Any use from first drug intake to end-of-study visit	Discontinue UGT1A1 inhibitor, if possible. Stop nidufexor. Check a random nidufexor level, noting time elapsed since last dose.
Herbal remedies inhibiting UGT1A1:e.g Silybum marianum (sylamarin, milk thistle) and Valeriana officinalis (valerian)	Any use from first drug intake to end-of-study visit	Discontinue herbal remedy. Stop nidufexor and check a random nidufexor level, noting time elapsed since last dose.
Non-selective UGT inhibitors: e.g diclofenac, probenecid, valproic acid	Any use from first drug intake to end-of-study visit	Discontinue non-selective UGT inhibitors, if possible. Stop nidufexor and check a random nidufexor level, noting time elapsed since last dose.
Aliskiren, direct renin inhibitors	Any use from first drug intake to end-of-study visit	Discontinue direct renin inhibitor, if possible. If not possible, stop nidufexor and check a random nidufexor level, noting time elapsed since last dose.
ACEI + ARB in combination	Any use from first drug intake to end-of-study visit	Discontinue either ARB or ACE inhibitor, if possible. If not possible, stop nidufexor and check a random nidufexor level, noting time elapsed since last dose
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Any use from first drug intake to end-of-study visit	Discontinue SGLT2 inhibitors, if possible. If not possible, stop nidufexor and check a random nidufexor level, noting time elapsed since last dose.
GLP-1 receptor agonists	Any use from first drug intake to end-of-study visit	Discontinue GLP-1 receptor agonists, if possible. If not possible, stop nidufexor and check a random nidufexor level, noting time elapsed since last dose.

Patients on medications specified in Table 6-3 can be included if the investigator determines the following criteria have been met:

- Usage is considered medically necessary, and
- Dose has been stable for at least 1 month prior to screening, and
- Dose is expected to remain stable for the duration of the study

No new use of these medications is allowed after entering the study, with the exception of drugs to control medically significant elevations in LDL-C, which has 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 from the dose at randomization, per local treatment guidelines. For all other medications listed in Table 6-3, the definition of stable will be left to investigator discretion.

Table 6-3 Permitted medication 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)[1]
• Insulin (within 25% of the dose at randomization)[2]
• Beta-blockers and thiazide diuretics. Thiazide diuretic use should also be maintained constant throughout the trial, if possible.
• Fibrates, statins[1] niacin, ezetimibe[3]
• Vitamin E
• Thyroid hormone
• Psychotropic medications (phenothiazines or second generation antipsychotics)
• Hormonal (estrogen, progesterone, or estrogen/progesterone containing) birth control

[1]There is a potential for nidufexor 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 MUST be paid to the drug interaction sections of the prescribing information for these compounds

[2]Unless adjustment is required due to intercurrent illness;

[3]Unless adjustment is required to treat medically significant increases in LDL-C that have been confirmed upon repeat testing.

6.2.3 Restriction for study patients

For the duration of the study, the patients should be informed and reminded of the restrictions outlined in this section. See also male and female contraception requirements in Section 5.2

In the event a patient presents with symptoms of COVID-19, the Investigator should ask the patient to quarantine per local guidelines.

6.2.3.1 Dietary restrictions and smoking

No special restrictions for the study. Appropriate diet for type 2 diabetes should be followed.

6.2.3.2 Other restrictions

None.

6.3 Patient numbering, treatment assignment, randomization

6.3.1 Patient numbering

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.

6.3.2 Treatment assignment, randomization

Randomized treatment will be assigned by the IRT 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). However, randomization numbers will not be shared with the study staff, and will remain on the back-end of the IRT system.

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.

The randomization numbers will be generated using the following procedure to ensure that the 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.
  - *Note: These randomization numbers are linked to the different treatment arms.*
- The randomization scheme for patients will be reviewed and approved by a member of the Randomization Office. If a patient is deemed eligible for enrollment into the study, they will be randomized and treatment will be assigned via the IRT system.
- Patients will be assigned randomization numbers 5101-5340.
  - *Note: Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of patients.*

6.4 Treatment blinding

This is a patient- and investigator-blinded study. Patients, investigators, and sponsor staff (see Table 6-4) 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.

6.4.1 Treatment blinding - study staff

All study staff (including study investigator, study nurses/coordinators) will be blinded to study treatment throughout the study. Unblinding a single patient for safety reasons (i.e. necessary for patient safety management) will occur via an emergency system (see SOM and IRT manual for details).

6.4.2 Treatment blinding - sponsor staff

The following are unblinded sponsor roles:

- Sponsor randomization office
- Drug supply (global clinical supplies)
- Study statistician
  - The study statistician will be able to access the randomization list and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes. *For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.*

The following are additional unblinded sponsor roles:

- Medical lead (study safety physician / TME) and sponsor pharmacovigilance staff
  - *Note: The TME and pharmacovigilance staff may have access to individual, group/cohort, or the entire study treatment allocations as needed to oversee safety on the trial.*
- Other sponsor roles:
  - The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the PK samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.
  - Study programmers and other personnel involved in study data analysis (e.g. PK expert, CCI) are allowed to access treatment assignment information for the purpose of conducting interim analyses of the data.
  - 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 at the time of interim analyses while the study is ongoing.
  - All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock ALL roles are considered unblinded.

Table 6-4 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis**
Patient	**B**	**B**	**UI***	**B**
Site staff, including PI, SC, study nurses and mobile health professionals	**B**	**B**	**UI***	**B**
Unblinded Pharmacovigilance sponsor staff	**B**	**UI**	**UI**	**UI**
All other sponsor staff, including: • TME • Study Leader • Bio-analysts, including PK and BMD • Bio-experts, including PK and BMD • Statistical programmers • Data analysts • Clinical trial team members • Sponsor management and decision boards • Supportive functions	**B**	**UI**	**UI**	**UI**
Drug Supply (Global Clinical Supplies)	**UI**	**UI**	**UI**	**UI**
Sponsor Randomization Office	**UI**	**UI**	**UI**	**UI**
Study Statistician	**UI**	**UI**	**UI**	**UI**

Key:

**Unblinding allowed at the single patient level ONLY*

UI: Allowed to be unblinded on individual patient level (includes single patient, group/cohort of patients, or entire study/all patients)

B: Remains blinded

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions should be kept as short as possible and dates recorded in the eCRF. If these are for reasons of significant noncompliance or extended dosing interruptions related to AEs, the investigator should use discretion to discontinue the patient from study treatment. The investigator may consult with the Sponsor medical lead if necessary.

If this modification is not tolerated, the medication should be discontinued. Please refer to Section 9.1.1.

If the reduced dose is tolerated, an attempt to increase the dose after two weeks of reduced dosing could be considered or the reduced dose can continue for the remainder of the study. Use of bile acid binding resins for treatment of pruritus is not recommended.

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 nidufexor.

In the event a patient develops flu-like symptoms during the treatment period and the investigator is concerned the patient may have a COVID-19 infection, treatment interruption may be considered. If an investigator decides to interrupt study treatment for this reason, the investigator must ensure that the patient has a SARS-Cov-2 PCR test to confirm the infection within approximately 5 days.

- If the test is positive, the investigator may decide to extend the treatment interruption and monitor the patient's condition to determine if discontinuation is warranted. Treatment interruption should not exceed 14 days.
- If the test is negative, the investigator may decide to resume study treatment.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

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 (or delegate) 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. Patients who are not >80% compliant with study drug administration will be counseled by the investigator and reminded by site personnel or delegate regarding the importance of taking all doses. Dose reductions due to tolerability issues should not be factored into the compliance calculation.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant non-drug therapies CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the patient safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. 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 Novartis 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 provide:

- protocol number
- protocol title
- patient number

In addition, oral and written information to the patient must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Patients should be discontinued from the study after emergency unblinding but should not be considered withdrawn from the study. Where possible, they should return for end-of-study assessments as described in Section 9.1.1.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT and obtaining the medication number(s).

Nidufexor will be administered to the patient via the oral route. On study visit days, administration will occur in the presence of the study nurse or delegate. At home, the patient will self-administer study medication. See the Site Operations Manual for further details.

7 Informed consent procedures

If applicable, in cases where the patient's representative(s) gives consent (if allowed according to local requirements), the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators, in a separate document, a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed 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.

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 agree that in order to participate in the study they must adhere to the contraception requirements.

Male patients must 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.

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an “X”, the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documentation. Some assessments in the schedule are marked with an "S" indicating that these data are to be evaluated and stored as source data at the site.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. This also applies in the event a patient needs to be quarantined for an amount of time consistent with local policy due to exposure to or suspected or confirmed COVID-19 infection.

For patients who withdraw from the study (i.e. withdrawal of consent), no further assessments will be conducted. Further attempts to contact the patient are not allowed, unless safety findings require communicating or follow up.

All study assessments described in Table 8-1 may potentially be performed remotely. Implementation of decentralized trial models is dependent on local regulations and Sponsor approval.

Table 8-1 Assessment Schedule

Visit Name/Epoch	Screening	Treatment															EOS	Post Study Safety Contact
Visit Numbers[1]	1	101					102					103[2]	104[2]	105[2]	106[2]	107[2]	199	
Days	-30 to -1	1					14 ±5					29 ±5	57 ±5	85 ±5	113 ±5	141 ±5	169 ±5	197 ±5
Time (post-dose)	-	0h[2]	1h	2h	4h	6h	0h[2]	1h	2h	4h	6h	-	-	-	-	-	-	-
Informed consent	X																	
Commercially Confidential Information																		
Inclusion / exclusion criteria	X																	
Medical history/current medical conditions	X																	
Demography	X																	
Body height	X																	
Body weight	X	X					X					X	X	X	X	X	X[4]	

Visit Name/Epoch	Screening	Treatment															EOS	Post Study Safety Contact
Visit Numbers[1]	1	101					102					103[2]	104[2]	105[2]	106[2]	107[2]	199	
Days	-30 to -1	1					14 ±5					29 ±5	57 ±5	85 ±5	113 ±5	141 ±5	169 ±5	197 ±5
Time (post-dose)	-	0h[2]	1h	2h	4h	6h	0h[2]	1h	2h	4h	6h	-	-	-	-	-	-	-
Waist and hip circumferences[5]	X	X					X					X	X	X	X	X	X	
Body temperature	X	X					X					X	X	X	X	X	X[4]	
Blood pressure	X	X					X					X	X	X	X	X	X[4]	
Pulse rate	X	X					X					X	X	X	X	X	X[4]	
Physical examination	S	S					S					S	S	S	S	S	S[4]	
Electrocardiogram (ECG)[6]	X	X					X					X	X	X	X	X	X[4]	
Hepatitis screen	S																	
COVID-19 (SARS- Cov2) testing[21]	S																	
Alcohol test and drug screen	S																	
Pregnancy and assessments of fertility[7]	X																X[4]	
Clinical Chemistry	X	X					X					X	X	X	X	X	X[4]	
Hematology	X	X					X					X	X	X	X	X	X[4]	
PT/INR[8]	X																	
Anticoagulant Panel (PT/INR; aPTT; fibrinogen)		X											X	X				
Plasma osmolality		X															X[4]	
HbA1c	X													X			X[4]	
Fasting lipid panel		X												X			X	
Lipoprotein (a) [Lp(a)]		X												X			X	
PK blood collection[10]		X[2]	X	X	X	X	X[2]	X	X	X	X			X[2]			X[2,4]	
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Urinalysis[12]	X	X					X					X	X	X	X	X	X[4]	
Urine albumin and creatinine[13]	X	X					X					X	X	X	X	X	X[4]	

Visit Name/Epoch	Screening	Treatment															EOS	Post Study Safety Contact
Visit Numbers[1]	**1**	**101**					**102**					**103**[2]	**104**[2]	**105**[2]	**106**[2]	**107**[2]	**199**	
Days	**-30 to -1**	**1**					**14 ±5**					**29 ±5**	**57 ±5**	**85 ±5**	**113 ±5**	**141 ±5**	**169 ±5**	**197 ±5**
Time (post-dose)	**-**	**0h**[2]	**1h**	**2h**	**4h**	**6h**	**0h**[2]	**1h**	**2h**	**4h**	**6h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Urine protein[13]	X	X										X	X	X	X	X	X[4]	

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24-hr urine collection[16]		X															X[4]	
Visual analog scale (VAS) - Itch[17]		X					X					X	X	X	X	X	X	
Randomization		X																
Study drug administration[18]		X					X					X	X	X	X	X		
Collect study drug/drug accountability[19]							X					X	X	X	X	X	X[4]	
Dispense study medication		X					X					X	X	X	X	X		
Concomitant medications[20]	X	X					X					X	X	X	X	X	X[4]	
Serious adverse events	**As required**[4]																	
Comments	**As required**																	
Study completion information																	X[4]	
Safety follow up call																		X

[X] Assessment to be recorded in the clinical database
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Assessments must be performed pre-dose
[3] Commercially Confidential Information

[4] Priority in the event of early discontinuation or withdrawal
[5] Waist and hip circumferences (measured in cm); see the SOM for detailed explanation
[6] ECG as triplicate measures
[7] A serum pregnancy test will be performed at screening; a urine pregnancy test will be used at end of study.
[8] Prothrombin Time/International Normalized Ratio
[9] Intentionally deleted in Protocol Amendment V03
[10] PK samples will be collected after patients have been fasting for at least 6 hours
[11] Commercially Confidential Information
[12] Dipstick measurements/macroanalysis for specific gravity, protein, glucose and blood will be performed. Microscopy, WBC, RBC and sediments will also be assessed in case of an abnormal dipstick test.
[13] Urine creatinine is collected in parallel with urine albumin and urine protein for the calculation of urine albumin-to-creatinine ratio (UACR). *Note: The sample should be obtained from the 24-hour urine sample at time points when 24-hour collection is required. For visits that are not preceded by a 24-hour collection or due to a premature discontinuation, a separate spot urine sample will be collected and processed during the visit. A second morning void is preferred. If sample quantify is sufficient, then the same 2nd morning void may be used for other urine related assessments.*
[14] Intentionally deleted in Protocol Amendment V03
[15] At time points when 24-hour collection is done prior to a visit, a separate spot urine sample will be collected and processed promptly. A second (2nd) morning void is preferred. If sample quantify is sufficient, then the same 2nd morning void may be used for other urine related assessments.
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[16] 24-hour urine collection should be performed as an outpatient, within 1-2 days prior to the study visit, and brought to the study visit, using supplied collection kit + instructions, as applicable. Quantify the urine volume and measure sodium, creatinine, protein, osmolality, and albumin (assays).
[17] PRO: VAS assessment for itching of the skin
[18] On study visit days, study drug should not be taken until after study visit assessments are completed
[19] Collect unused study drug, perform drug accountability (pill count) and document compliance with protocol instructions
[20] A thorough review of any concomitant medications (including medication name, dose, unit, frequency, and route) should be performed at every visit.
[21] It is highly recommended that PCR testing for COVID-19 be completed within 1 week prior to first dosing.

8.1 Screening

In general, it is permissible to re-screen a patient if he/she fails the initial screening, if deemed feasible or necessary by the study site investigator. If a subsequent re-screen is required after the first permissible re-screening (i.e. an additional re-screening attempt), the case should be discussed with the Sponsor. Additional re-screenings may be approved on a case-by-case basis. Further information on re-screening is outlined in the Site Operations Manual.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason are considered a screen failure. Information on data collected for screening failures is available in the SOM.

8.2 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data will be collected on all enrolled patients. Details on additional data collected 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.

8.2.1 Hepatitis screen

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

8.2.2 Alcohol test, Drug screen

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

8.3 Efficacy and Pharmacodynamics

Efficacy and Pharmacodynamics (PD) of nidufexor will be assessed based on measures including renal function and type 2 diabetes status.

Pharmacodynamic samples will be collected at the time points defined in the Assessment Schedule. Follow the instructions outlined in the Site Operations 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. Results will remain blinded to the patient, investigative personnel, and blinded sponsor personnel regarding the associated treatment assignment throughout the study, as applicable. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. The PD samples will be obtained and evaluated in all patients.

8.3.1 Renal function assessments, markers of diabetic nephropathy

The following assessment will profile renal function, which are markers of diabetic nephropathy:

- Urine albumin-creatinine ratio (UACR) at serial time points, as specified in the Assessment Schedule

- 24-hour urinary collection at baseline and end of study, measured for albumin
- Estimated glomerular filtration rate (eGFR), as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. (Levey and Stevens 2010)
- Free water clearance

8.3.2 Type 2 diabetes measures

The following assessments will be used to measure Type 2 diabetes status:

- HbA1c
- Weight, BMI, waist-to-hip ratio
- Fasting lipid profile to include total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Lp(a)

8.3.3 Appropriateness of efficacy assessments

Change in albuminuria (UACR and 24-hour urine albumin excretion) and annualized rate of change in eGFR over the 24-week treatment period are the primary and secondary endpoints, respectively. These two parameters comprise the current gold standard (Levey et al 2015) for assessing stage and progression of proteinuric chronic kidney diseases such as diabetic nephropathy secondary to Type 2 Diabetes. The efficacy measures for renal function demonstrate the sensitivity and specificity required to serve as the gold standard diagnostic measures in clinical practice. (UACR sensitivity = .85 and specificity =.88; eGFR sensitivity =.91 and specificity =.87). The efficacy measures for type 2 diabetes are recognized by medical professionals, diabetes organizations, and payers as the essential surrogate and diagnostic measures used for patient monitoring to help patients manage the disease, reduce diabetes symptoms and, if well controlled, minimize or ameliorate diabetes related end organ damage.

8.4 Safety and Tolerability

Safety assessments are specified within the section below. The methods for recording the assessments are specified in the Site Operations Manual. The Assessment Schedule (Table 8-1) details the timing of when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10.1.1).

8.4.1 Physical examination

Information for all physical examinations must be included in the source documentation. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. See the SOM for details.

8.4.2 Vital signs

Vital signs include BP and pulse measurements. See the SOM for details.

8.4.3 Laboratory evaluations

A central laboratory will be used for analysis of all safety specimens collected, and will also be used for a repository for select bio samples.

Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators is in the laboratory manual. Repository samples may be shipped to a Novartis analysis laboratory or contracted analysis laboratory at any time during the study for processing and analysis.

Clinically notable laboratory findings are defined in Appendix 1 and the Laboratory Manual. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF/ e(CRF) page as appropriate. 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.

8.4.3.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured. A coagulation panel including PT/INR, aPTT, and fibrinogen will be measured.

8.4.3.2 Clinical chemistry

Sodium, potassium, creatinine, BUN/urea, uric acid, chloride, albumin, calcium, phosphate, bicarbonate/HCO_3, LDH, amylase, lipase, creatine kinase (CK), glucose

8.4.3.3 Liver function tests

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBL), serum albumin (Alb), prothrombin time (PT)/ international normalized ratio (INR), alkaline phosphatase (ALP), gamma-glutamyl transferase (γGT)

8.4.3.4 Urinalysis and renal function

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

The following assessments for renal function will also be completed:

- Urine albumin-creatinine ratio (UACR) at serial time points, as specified in the Assessment Schedule
- 24-hour urinary collection at baseline and end of study, measured for albumin
- Estimated glomerular filtration rate (eGFR), as determined by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey and Stevens 2010).
- Free water clearance

8.4.3.5 Type 2 diabetes and glycemic control

- HbA1c
- Fasting lipid profile (total cholesterol, HDL-C, LDL-C, triglycerides and Lp(a))

8.4.4 Electrocardiogram (ECG)

Triplicate twelve-lead ECGs will be collected at the time-points specified in the Schedule of Assessments. At each time point, three serial 12-lead ECGs, at 5 minute intervals, will be recorded. Full details of all procedures relating to the triplicate ECG collection and reporting are contained in the ECG technical manual and SOM.

- 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
- If clinically significant abnormalities are identified that were present prior to the informed consent signature, then it should be recorded on the relevant medical history CRF page.
- After informed consent signature, any clinically significant abnormalities are recorded on the Adverse Events page thereafter.
    - Clinically significant findings MUST be recorded on the AE CRF and should be discussed with the sponsor in a timely fashion.

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed at selected time points during the study. See the Assessment Schedule, Table 8-1, for timing of the protocol required pregnancy testing.

Additional pregnancy testing may be performed to meet local requirements. A positive pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

If positive, the patient will enter the post-treatment follow up period (see Section 10.1.4).

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

8.4.6 Appropriateness of safety measurements

Planned safety assessments are based upon expected organ toxicity as discussed in the rationale of study design (Section 4.1) and risk-benefit sections (Section 4.5).

8.5 Additional assessments

8.5.1 Clinical Outcome Assessment - Visual Analog Scale (VAS)

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s).

The site personnel or delegate should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file.

Completed measure(s) (including when using paper PRO measures and any unsolicited comments written by the participant) must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations are performed. This assessment should be documented in study source records. If AE or SAE are confirmed, the study investigator should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10.1.1 of the study protocol.

A 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 itch imaginable itch). The score (distance from left) on the VAS will be recorded by the patient by marking with a line and used to test for an effect of nidufexor over placebo. The scale will be completed by patients as indicated in Table 8-1 (Assessment schedule).

8.5.2 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule, Table 8-1. Follow instructions outlined in the central laboratory manual and SOM regarding sample collection, numbering, processing and shipment. See Section 8.5.3.2 regarding the potential use of residual samples.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the patient or the investigator.

The investigator must discontinue study treatment for a given patient if he/she believes that continuation would negatively impact the patient's well-being.

Study treatment MUST be discontinued under the following circumstances:

- Hypersensitivity (CTCAE grade 2 or higher, CTCAE Version 5.0) reaction to nidufexor.
- 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 CTCAE Version 5.0 and believed to be related to the study drug (apart from liver and renal events - see below).
- A liver safety event with ALT, AST, total bilirubin and/or alkaline phosphatase elevations mandating study treatment discontinuation. Please refer to Section 10.2.1 (Liver safety monitoring), Table 16-1 and Table 16-2 for further instructions and monitoring.

- A renal safety event with serum creatinine elevations mandating study treatment discontinuation. Please refer to Section 16.3 and Table 16-3 for further instructions and monitoring.
- Pregnancy (see Section 10.1.4)
- Any protocol deviation that results in a significant risk to the patient's safety, in the opinion of the investigator.
- Following emergency unblinding

If a patient presents with COVID-19 symptoms, this does not require the patient to be discontinued. Please refer to Section 6.5 for further instructions.

If discontinuation of study treatment occurs, the investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the applicable CRF.

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 (Section 9.1.2). Where possible, they should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit should be performed, with top priority for assessments as noted in the Assessment Schedule for the EOS visit. At this final visit, all dispensed investigational product must be collected, and reconciled.

If they fail to complete these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the patient/pre-designated contact as in Section 9.1.3 (Lost to follow-up). This contact preferably should be done according to the study visit schedule.

After study treatment discontinuation, the following data (at a minimum) should be collected at abbreviated study visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to emergency breaking of treatment code, Section 6.6.3.

All patients that complete the study should have a post study safety follow-up phone call conducted approximately 28 days after last dose. In the event of premature discontinuation from the study, the study staff should attempt a post study safety follow-up phone call approximately 28 days after the patient's last visit. In the event of withdrawal of consent, the study staff should follow the guidance in **Section 9.1.2**. The information collected is kept as source documentation. All SAEs reported during this time must be reported as described in Section 10.1.3.

9.1.1.1 Replacement policy

Patients will not be replaced.

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs ONLY when a patient satisfies the following:

- Does not want to participate in the study anymore

AND

- Does not allow further collection of personal data
  - *Note*: In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

If withdrawal of consent occurs, then the study treatment must be discontinued, 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.

All efforts should be made to complete the allowable, necessary assessments prior to study withdrawal, if possible. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the Assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a patient's samples until their time of withdrawal) according to applicable law.

For US: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and the Rest of World: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For patients whose status is unclear because they fail to complete study visits without stating an intention to discontinue or withdraw, the investigator must 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 should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Study stopping rules

Enrollment in the study will be placed on hold and safety review undertaken if any of the following occurs cumulatively across all of the cohorts:

- Two or more study treatment-related SAEs
- Two or more patients experience study treatment-related hypersensitivity reactions of CTCAE (Version 5) Grade 3 or higher in intensity;
- Three or more patients experience a similar AE as assessed by the Sponsor which was assessed as CTCAE (Version 5) Grade 3 or higher in intensity, and study treatment-related;
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review, if the Sponsor judges it safe to proceed. The study will be stopped, and no further dosing will be taken pending a full safety review, if the investigator and the Sponsor agree that it is unsafe to continue dosing.

9.1.5 Early study termination by the sponsor

Novartis can terminate the study 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. In making the decision to terminate, Novartis will always consider patient welfare and safety. Should early termination be necessary, patients must be seen as soon as possible (provide instruction for contacting the patient, when the patient should stop taking drug, when the patient should come for a final EOS visit) 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 or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 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. The last day of study treatment is Day 168, the day before the End of Study visit. Study treatment should not be taken on Day 169 – End of Study.

Study completion is defined as when the last patient completes their End of Study 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 randomized and/or treated patients should have a post-study safety follow-up contact conducted approximately 28 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time must be reported as described in Section 10.1.3 and the SOM. Documentation of attempts to contact the patient should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician based on patient availability for follow-up. This care may include follow-up and treatment of all documented medical conditions according to local or global standards of care. Novartis will not provide nidufexor for continuing care beyond the last visit for any patient.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., 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. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual patient and identifying adverse events.

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

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 findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2).

1. Severity grading

Common Toxicity Criteria (CTC) AE grade (version 5.0) will be used in this study. Grade refers to the **severity** of the AE. The CTC-AE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1: Mild

- Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate

- Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL*

Grade 3: Severe

- Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Grade 4: Life-threatening

- Life-threatening consequences; urgent intervention indicated

Grade 5: Death

- Death related to AE

Notes:

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 on the AE case report form but is collected as a seriousness criteria and is also collected in other CRFs (e.g study completion, death/survival) in the clinical database.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden*

2. Its relationship to the study treatment

Yes or No

- If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'
- The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single patient

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 10.1.2 for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug temporarily interrupted with continued follow up
- Drug permanently withdrawn

6. Its outcome

- not recovered/not resolved;
- recovered/resolved;
- recovering/resolving,
- recovered/resolved with sequelae;
- fatal;
- unknown.

Conditions that were already present at the time of informed consent should be recorded in medical history of the patient.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 28 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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 must 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 the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Follow the instructions found in the Site Operations Manual and eCRF completion guidelines for data capture methodology regarding AE collection for patients.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical condition(s) which meets any one of the following criteria:

- fatal
- life-threatening

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 (please refer to the ICH-E15D Guidelines 2003).

- 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 of diabetic nephropathy.

- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- 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

- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

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. Such events should be considered as "medically significant". 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.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse event.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective of whether a clinical event has occurred.

10.1.3 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 28 days after the last study visit must be reported to Novartis/ safety immediately, without undue delay, and under no circumstances later than 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

IMPORTANT: To comply with regulations, all suspected, unexpected, serious adverse reactions (SUSARs) occurring in a clinical trial must be reported in an expedited timeframe (7 or 15 days) to competent authorities.

1. Screen Failures (e.g. A patient who is screened but is not treated or randomized): SAEs occurring after the patient has provided informed consent until the time the patient is deemed a Screen Failure must be reported to Novartis
2. Randomized OR Treated patients: SAEs collected until post-study call (contact).

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.

If the SAE is not previously documented in the Investigator's Brochure and is thought to be related to the study treatment, a Chief Medical Officer & Patient Safety (CMO & PS)

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.

Any SAEs experienced after the 28 day period after the last study visit and/or following the last administration of study treatment (in the event of early discontinuation) should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign the pregnancy consent form to allow the Study Doctor to ask about her pregnancy. 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 should be recorded and reported by the investigator to the Novartis Chief Medical Office & Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational/study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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.

The newborn will followed up for at least one year after birth/EDD.

10.1.5 Reporting of study treatment 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.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an AE/SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
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 the, respective sections.

10.2 Additional Safety Monitoring

10.2.1 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 Section 16.2 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Once a participant has been exposed to study treatment, every liver event defined in Section 16.2 should be followed up by the investigator or designated personnel, as summarized below. Additional details on actions required in case of liver events are outlined in Section 16.2 Repeat liver chemistry tests (ALT, AST, TBL, Direct Bilirubin, PT/INR, ALP and γ-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be promptly available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the patient. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
- If the initial elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the discontinuation of study treatment information located in Section 9), if appropriate
- Hospitalization of the patient if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy
- 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.
- 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 liver event CRF.

Refer to the Site Operations Manual for additional details.

10.2.2 Renal safety monitoring

Once a participant has been exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

Serum creatinine increase ≥25% compared to baseline during normal hydration status. Baseline serum creatinine is determined as the mean of two serum creatinine measurements (e.g. at screening and pretreatment).

- Albumin-creatinine ratio (UACR) increase ≥ 2X baseline

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-3 .

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the investigator or designated personnel as summarized in Section 16.3.

10.2.3 Fat soluble vitamin deficiency

Although no histological or laboratory findings of fat soluble vitamin (A, D and E) deficiencies were observed in the chronic toxicology studies, this has not been assessed in humans and is a theoretical risk due to sustained partial suppression of bile acid synthesis in response to nidufexor. The following treatment emergent AEs and laboratory findings should prompt consideration of the corresponding vitamin deficiency:

- Worsening night vision, xerophthalmia and new ichthyosis: Vitamin A deficiency
- Hypocalcemia and symptoms of secondary hyperparathyroidism: Vitamin D deficiency
- Vertical gaze palsy, ataxia and hyporeflexia: Vitamin E deficiency

A vitamin deficiency identified during an AE evaluation should be reported in the Adverse Events CRF and managed according to the local standard of care. Deficiency of one fat soluble vitamin should prompt an assessment of the other two indicated above.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator study staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies by generating appropriate error messages on the eCRFs, which allow modification and/or verification of the entered data by the investigator staff.

The investigator is responsible for assuring that the data entered into the eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

After final 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 (Table 8-1) 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.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator study staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior 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.

Randomization codes and data about all study treatment(s) dispensed to the patient will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

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.

11.3 Site monitoring

Before study initiation, at a site initiation visit, virtual training event, or at an investigator's meeting, a Novartis delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) 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 field monitor will check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data to identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary 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.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

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

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

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

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

12.2 Patient demographics and other baseline characteristics

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

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

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

12.3 Treatments

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

12.4 Analysis of the primary endpoint(s)

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

12.4.1 Definition of primary endpoint(s)

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

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

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Safety endpoints

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

Adverse events

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

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

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

Separate summaries will be provided for study medication related AEs, death, SAEs, other significant AEs and AEs leading to discontinuation.

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

Vital signs

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

12-lead ECG

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

Clinical laboratory evaluations

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

12.4.2.2 Efficacy and/or Pharmacodynamic Endpoints

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

A repeated measures Analysis of Covariance (ANCOVA) will be performed for log-transformed ratio to baseline UACR measured at each visit. The model will include effects for log-transformed baseline, treatment, visit, treatment by visit interaction and visit by log-transformed baseline interaction. An unstructured variance-covariance matrix will be used to account for correlation among multiple measurements from the same patient and variance heterogeneity.

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

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

12.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

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.

12.4.4 Sensitivity and Supportive analyses

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12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Log-transformed ratio to baseline for eGFR, free water clearance, HbA1c and fasting lipid profiles (total cholesterol, HDL, LDL, triglycerides and Lp(a)) as well as change from baseline in weight, BMI and WTH ratio will be analyzed using the same repeated measures ANCOVA described in Section 12.4.2 with baseline in lieu of log-transformed baseline as a covariate for change from baseline analysis. For parameters with only one post-treatment measurement an ANCOVA with treatment as a classification factor and baseline (or log-transformed baseline if applicable) as a covariate will be employed.

12.5.2 Pharmacokinetics

Nidufexor 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 8.5.2 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, and AUClast from the plasma concentration-time data. The linear trapezoidal rule will be used for AUC calculation.

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12.5.5 PK/PD relationships

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

12.5.6 Patient reported outcomes

Change from baseline itch VAS measurements will be analyzed using the same repeated measures ANCOVA described in Section 12.4.2.

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Data from 50 patients per arm will provide 72% power to detect the combination of a drug effect on UACR at Week 24 that is both clinically significant (defined as an estimated relative reduction of at least 25% compared to placebo) and statistically significant (defined as ≥90% probability of a > 0% reduction relative to placebo) if the true placebo adjusted reduction is 30%. The figure below shows the probability of decision making for various true drug effects at a sample size of 50 patients per arm. A "Go" decision will be made if both the clinical significance and the statistical significance criteria are met while a "No Go" decision will be made if neither the clinical significance nor the statistical significance criterion is met. Otherwise it will be an indeterminate situation requiring further information to be obtained before a decision can be made.

The power calculations were performed using simulations based on log-transformed ratio to baseline analysis. The standard deviation was assumed to be 0.6, estimated from published studies in the literature (Hanes et al 2018). Treatment comparison was based on a one-sided two sample t-test.

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13 Ethical considerations and administrative procedures

13.1 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 CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible databases such as clinicaltrials.gov and as required in EudraCT and/or as required by local country registries. In addition, after study completion *(defined as last patient last visit)* and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 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 including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study.** If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators 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.

14.1 Protocol Amendments

Any change or addition 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.

Only amendments that are required for patient safety 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, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Please refer to the Central Laboratory Manual for a list of clinically significant laboratory values.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × 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

Chalasani and Regev 2016

Table 16-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γ-GT until resolution[c] (frequency at investigator discretion)
ALT or AST		
for patients with normal baseline: > 8 × ULN For patients with elevated baseline> 8 X ULN or > 500 U/L whichever comes first	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
For patients with normal baseline: > 5 to ≤ 8 × ULN For patients with elevated baseline: >5 to ≤ 8 x ULN or >5X ULN to ≤ 500 U/L whichever comes first	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		

Criteria	Actions required	Follow-up monitoring
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated 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
[c]Resolution 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.
Chalasani and Regev 2016

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
Albumin-creatinine ratio increase ≥2 fold from baseline value	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
	Blood glucose (fasting) Perform serum creatinine, UACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, UACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or albumin-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or albumin-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

Bakris et al 2015, de Zeeuw et al 2014