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PLATFORM / ADPT02

Clinical Trial Protocol CADPT02A12001 / NCT04147195

NASH EXploratory Single and COmbination Treatment (NEXSCOT): An open label, multicenter, platform study to evaluate the safety, tolerability, pharmacokinetics and efficacy of various single and combination treatments in patients with non-alcoholic fatty liver disease (NAFLD) who manifest a non-alcoholic steatohepatitis (NASH)-like biomarker phenotype

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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

5'NT	5'nucelotidase (5'riboncleotide phosphohydrolase)
ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
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aPTT	activated partial thromboplastin time
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
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BMI	body mass index
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BUN	blood urea nitrogen
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CDS	Core Data Sheet
CFR	Code of Federal Regulations
CI	confidence interval
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CMO&PS	Chief Medical Office & Patient Safety
CNS	central nervous system
COA	Clinical Outcome Assessment
CRA	clinical research associate
CRF	case report/record form (paper or electronic)
CSR	clinical study report
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria Adverse Event
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	data monitoring committee
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ECG	electrocardiogram
EDC	electronic data capture
EDD	expected delivery date or estimated date of delivery
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency

EOS	End of Study
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FDA	Food and Drug Administration
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FIB4	Fibrosis-4
FIH	first-in-human
FSH	follicle-stimulating hormone
FXR	farnesoid X receptor
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
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h	hour
HA	hyaluronic acid
HbA1c	Hemoglobin A1c (glycated hemoglobin)
HBV	Hepatitis B virus
hCG	human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HGB	hemoglobin
HIV	human immunodeficiency virus
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
hsCRP	High-sensitivity C-reactive Protein
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IB	Investigator's Brochure
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IL	interleukin
IMP	investigational medicinal product
IN	Investigator Notification
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IU	international unit
IUD/S	intrauterine device/system
kPa	kilopascal
LC-MS/MS	liquid chromatography-mass spectrometry
LDH	lactate dehydrogenase
LDL	low-density lipoprotein

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MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram(s)
mL	milliliter(s)
MRE	magnetic resonance elastography
MRI	magnetic resonance imaging
MRP	multidrug resistance protein
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NEXSCOT	NASH EXploratory Single and COmbination Treatment
nM	nanomolar
ng	nanogram
NOAEL	no observed adverse event level
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OCA	obeticholic acid
OHP	off-site healthcare professional
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PBC	primary biliary cholangitis
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic (modelling)
PCR	protein-creatinine ratio
PD	pharmacodynamic(s)
PDFF	proton density fat fraction
pg	picogram
P-gp	P-glycoprotein
PIIINP	amino-terminal pro-peptide of procollagen type III
PK	pharmacokinetic(s)
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PT	prothrombin time
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QD	once a day
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RAP/SAP	Report and Analysis Plan (RAP) or Statistical Analysis Plan (SAP) is a regulatory document which documents preplanned statistical analyses

RoW	Rest of World
R Value	ALT/ALP x ULN
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SAC	Safety Assessment Committee
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SAE	serious adverse event
SD	standard deviation
SE	standard error
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SOM	Site Operations Manual
SOP	standard operating procedure(s)
SSP	Safety Surveillance Plan
SUSAR	suspected unexpected serious adverse reactions
SVR	sustained virologic response
TIMP-1	tissue inhibitor of metalloproteinases
µg	microgram
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ULN	upper limit of normal
US	ultrasound
VAS	Visual Analog Scale
WHO	World Health Organization

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy).
Assessment	A procedure used to generate data required by the study.
Biologic samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A set of one or more treatment arms bundled together for review and execution.
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Core NEXSCOT protocol	Section 1 - Section 16. These are the sections of the NEXSCOT protocol that remain constant over the duration of this platform study.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant 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 source data/documents used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. Also, the action of entering one or more participants into the study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant.
Investigational drug/treatment	The drug whose properties are being tested in the study.
Medication number	A unique identifier on the label of medication kits.

Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study, or the participant allocated to an invalid stratification factor.
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site Healthcare Professional (OHP)	A qualified healthcare professional, such as a nurse, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (e.g., concomitant or rescue therapy).
Participant	An individual with the condition of interest for the study. "Participant" terminology may be used in the protocol whereas term, "Subject" may be used in data collection.
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug.
Personal data	Participant information collected by the investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized patient.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
Remote	Describes any trial activities performed with the participant at a location that is not the investigative site where the investigator will conduct the trial, but is for example the participant's home or another appropriate location.
Screen failure	A participant who did not meet one or more criteria that were required for participation in the study.
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.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant.
Study treatment	Any single drug or combination of drugs or intervention administered to the participant as part of the required study procedures.

Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial.
Treatment arm/group	A single or combination treatment regimen.
Treatment specific information	Section 17. This section contains all the supporting information on the individual treatments to be studied in the NEXSCOT platform study.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent (EoC) / Opposition to use of data/biological samples	Withdrawal of consent from the study occurs when a participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol-required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in countries where collection and processing of personal data is justified by a different legal reason than consent.

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Protocol summary

Protocol number	CADPT02A12001 (NEXSCOT)
Full Title	NASH EXploratory Single and COmbination Treatment (NEXSCOT): An open label, multicenter, platform study to evaluate the safety, tolerability, pharmacokinetics and efficacy of various single and combination treatments in patients with non-alcoholic fatty liver disease (NAFLD) who manifest a non-alcoholic steatohepatitis (NASH)-like biomarker phenotype
Brief title	Study of safety, pharmacokinetics (PK), and efficacy of various single and combination treatments in patients with non-alcoholic fatty liver disease (NAFLD) who have characteristics of non-alcoholic steatohepatitis (NASH)
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This platform study is designed to assess the safety, tolerability, PK, and early efficacy after administration of treatments for 12 weeks in NAFLD patients with a biomarker phenotype consistent with ongoing liver inflammation and fibrosis, and thus, NASH. Data from this study will enable efficient detection of high efficacy single drug and/or drug combinations, which will support the future development of optimal therapies for NASH.
Primary Objective	To determine the safety and tolerability of single or combination therapy during 12 weeks of treatment by monitoring safety endpoints (including vital signs, physical examination, laboratory measurements, electrocardiogram [ECG]) and adverse events.

Secondary Objectives	• Objectives 1-4: To determine the effect of twelve weeks of single or combination therapy on
	  • 1: Circulating markers of ongoing liver fibrosis as measured by the Enhanced Liver Fibrosis (ELF) Test
	  • 2: Intrahepatic lipid content (percent liver fat) by measuring Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF)
	  • 3: Cardiometabolic risk parameters by measuring body weight, waist and hip circumference, waist-to-hip ratio, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1C (HbA1c), fasting glucose, fasting insulin, and fasting lipid profile
	  • 4: Circulating markers of liver and/or systemic inflammation by measuring liver function tests (ALT) and high-sensitivity C-reactive Protein (hsCRP)
	And
	• Objective 5: To evaluate the PK of each individual agent when administered as a single or combination therapy by collecting and analyzing blood samples to obtain plasma concentrations over 12 weeks of treatment.

Study design	This is a non-confirmatory, multicenter, open label, platform study in NAFLD patients with a NASH-like biomarker phenotype to examine the effects of single and combination therapies over 12 weeks of treatment. Commercially Confidential Information Each cohort consists of a 33-day screening period, 27-day baseline period, 12-week treatment period, and a study completion visit (End of Study [EOS] 1) approximately 28 days after the last drug administration. For drugs with longer half-lives, the same study design will be followed, however, an additional post-treatment follow-up visit (EOS2) will occur 56 days after the last drug administration, and study completion evaluations will take place at this visit instead.
Population	The study population will be comprised of adult (18 years or older) male and female NAFLD patients with a NASH-like biomarker phenotype. Approximately 25 participants per arm will be enrolled in the study and 20 per arm are expected to be evaluable. Cohort 1 consists of two treatment arms. Multiple arms/cohorts are planned and future therapies will be introduced in subsequent protocol amendments.

Key Inclusion criteria	These criteria are applicable for all participants across all therapies/arms/ cohorts.
	• Male and female participants 18 years or older (at the time of the screening visit)
	• NAFLD patients with a NASH-like biomarker phenotype are defined based on the presence of ALL FIVE of the following:
	  • ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) **AND**
	  • BMI ≥ 27 kg/m^2 (in participants with a self-identified race other than Asian) or ≥ 23 kg/m^2 (in participants with a self-identified Asian race) **AND**
	  • History of Type 2 diabetes mellitus with HbA1c ≤ 9% at baseline **AND**
	  • ELF Test score ≥ 8.5 and ≤ 10.5 at either screening or baseline **AND**
	  • Liver fat ≥ 8% at baseline as determined by the reading of the central MRI laboratory of locally produced images. The MRI assessment should only be performed after eligibility has been confirmed from all other baseline assessments.
	• Participants must weigh at least 40 kg (88 lbs.) and no more than 150 kg (330 lbs.)

Key Exclusion criteria	These criteria are applicable for all participants across all therapies/arms/cohorts. Please also refer to the cohort-specific eligibility criteria for any additional factors to consider. • Use of other investigational drugs within 5 half-lives of randomization, or within 3 months, whichever is longer; or longer if required by local regulations. • Use of obeticholic acid (OCA) or pharmacologically-active weight loss drugs within 1 month of randomization. • Use of strong CYP3A4/5 inhibitors or strong CYP3A4 inducers within 5 half-lives or 7 days of randomization, whichever is longer. • Participants on treatment with the following medicines UNLESS they are on stable dosing for at least 3 months before randomization: anti-diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control. • Participants on treatment with vitamin E at doses > 200 IU/day and ≤ 800 IU/day UNLESS they are on stable dosing for at least 6 months before randomization, OR any participants on treatment with vitamin E > 800 IU/day regardless of stable dosing. • Pregnant or nursing (lactating) women. • Women of child-bearing potential UNLESS they are using highly effective methods of contraception during dosing and for a duration equal to approximately 5 times the terminal half-life after stopping study medication. • Sexually active males UNLESS they agree to use a condom during intercourse while taking study medication and for a duration equal to approximately 5 times the terminal half-life after stopping study medication, and should not father a child in this period. • History of ongoing drug abuse within the 12 months prior to dosing, or current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as ≥ 21 units of alcohol per week in males and ≥ 14 units of alcohol per week in females; a unit of alcohol is equivalent to 8 grams pure ethanol, 12 ounce (355 mL) beer, 4 ounce (118 mL) glass of wine, or 1 ounce (30 mL) shot of hard liquor). • Type I diabetes or uncontrolled Type II diabetes (defined as HbA1c > 9% at baseline). • Evidence of hepatic decompensation, severe liver impairment, cirrhosis, or severe acute or chronic renal insufficiency. • History or presence of other concomitant liver diseases or liver transplantation; current placement on a liver transplant list. • History or current diagnosis of ECG abnormalities indicating safety concerns for participants. • Participants with contraindications to MRI imaging.

Study treatment	Cohort 1 consists of two treatment arms: • Arm 1: LYS006 CCI • Arm 2: Tropifexor (LJN452) CCI + LYS006 CCI Participants will be randomized into any of the treatment arms open to enrollment for which the participant meets the eligibility criteria. Randomization will be stratified by race and body mass index (BMI). Multiple arms/cohorts are planned and future therapies will be introduced in subsequent protocol amendments.
Efficacy/ Pharmacodynamic (PD) assessments	• Liver function tests and liver and/or systemic inflammation markers • Markers of liver fibrosis (including ELF Test) • Magnetic Resonance Imaging (MRI) • Cardiometabolic risk parameters
Pharmacokinetic assessments	• Plasma concentrations for tropifexor and LYS006 (Cohort 1)
Key safety assessments	• Vital signs • Physical examination • Laboratory measurements • ECG
Other assessments	Commercially Confidential Information
Data analysis	Safety data will be summarized using descriptive statistics. A mixed-effect model for repeated measures (MMRM) analysis will be conducted for log-transformed ratio to baseline ELF Test and ALT. The model will include effects for treatment, visit, treatment by visit interaction, stratification factor (race and BMI group), log-transformed baseline, and log-transformed baseline by visit interaction. An unstructured variance-covariance matrix will be used to account for correlation among multiple measurements from the same participant and variance heterogeneity. If the unstructured covariance causes model convergence issues then other simpler covariance structures will be considered. Least squares mean, the associated 2-sided 80% confidence interval and the p-value will be obtained for each treatment at each visit and back transformed to the original scale. Contrasts assessing trend over time will be constructed for each treatment using various functional forms as needed. Both cohort-wise and combined cohort analysis will be performed as appropriate. % liver fat as well as other secondary PD/biomarker endpoints will be analyzed similarly.
Key words	Non-alcoholic fatty liver disease, NAFLD, non-alcoholic steatohepatitis, NASH, platform design

1 Introduction

1.1 Background

Non-alcoholic steatohepatitis (NASH)

The NASH EXploratory Single and COmbination Treatment (NEXSCOT) study is designed to measure the safety and efficacy of various single and combination drug treatments in patients with non-alcoholic fatty liver disease (NAFLD) who also manifest a non-alcoholic steatohepatitis (NASH)-like biomarker phenotype.

NASH is a severe and often lethal liver disease which is becoming increasingly prevalent throughout the world (Calzadilla and Adams 2016). It is anticipated that by 2024, NASH will become the most common cause of liver failure requiring liver transplant (Zezos and Renner 2014). Three main features of the pathobiology of NASH are increased liver fat, inflammation and fibrosis.

There is no approved pharmaceutical treatment for NASH. This fact underscores the intractable nature of this disease which is in large part due to the contribution of multiple pathobiologic pathways, including increased de novo lipogenesis, inflammation and fibrosis. Based on these multiple contributing pathways it is reasonable to assume that regimens including more than one drug may be necessary to manage this disease effectively. This concept was recently supported by (Friedman et al 2018), who stated that, "...the possibility of drug combinations as a future therapeutic option is increasingly likely because of concern that attacking a single target will not be sufficiently potent..." in NASH.

Treatment specific background

NEXSCOT will study a number of investigational drugs as both single and combination treatment arms, with new treatment arms added during the conduct of the study. The specific background information for these particular treatment arms can be found in Section 17. Cohorts of new treatment arms will be added to Section 17 as amendments.

In contrast, the core parts of this protocol, Section 1 – Section 16, will remain constant over the duration of the NEXSCOT platform study.

1.2 Purpose

This platform study is designed to assess the primary objectives of safety and tolerability, and the secondary objectives of pharmacokinetics (PK) and biomarker efficacy after administration of CCI treatments for 12 weeks in NAFLD patients with a biomarker phenotype consistent with ongoing liver inflammation and fibrosis, and thus, NASH. Data from this study will enable efficient selection of high efficacy, single drug and/or drug combinations, which will support the rapid future development of optimal therapies for NASH.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Primary Objective	**Endpoints**
To determine the safety and tolerability of single or combination therapy during 12 weeks of treatment	Safety endpoints (including vital signs, physical examination, laboratory measurements, ECG); Adverse events
Secondary Objectives	**Endpoints**
To determine the effect of single or combination therapy on circulating markers of ongoing liver fibrosis	Enhanced Liver Fibrosis (ELF) Test
To determine the effect of single or combination therapy on intrahepatic lipid content	Percent (%) liver fat as measured by Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF)
To determine the effect of single or combination therapy on cardiometabolic risk parameters	Body weight, waist and hip circumference, waist-to-hip ratio, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1c (HbA1c), fasting glucose, fasting insulin, fasting lipid profile
To determine the effect of single or combination therapy on circulating markers of liver and/or systemic inflammation	Liver function test (ALT), high-sensitivity C-reactive Protein (hsCRP)
To evaluate the pharmacokinetics (PK) of each individual agent when administered as a single or combination therapy	Plasma concentrations
Exploratory Objectives	**Endpoints**

3 Study design

This is a non-confirmatory, multicenter, open label, platform study in NAFLD patients with a NASH-like biomarker phenotype.

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There is a maximum of five cohorts planned. Each cohort will consist of a 33-day screening period (Day -60 to Day -28), a baseline period of 27 days (Day -27 to Day -1), a treatment period of 12 weeks (Day 1 to Day 85), and a study completion evaluation (End of Study [EOS] 1) approximately 28 days after the last drug administration (Day 113).

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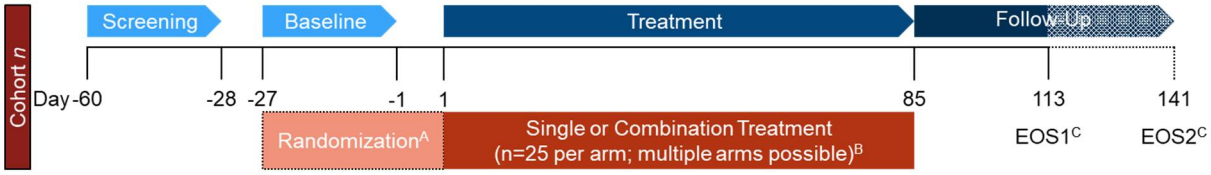
Participants will be advised to maintain their recommended diet for NAFLD during the study. The study design scheme is shown below in Figure 3-1:

Figure 3-1 Study design



EOS = End of Study

[A]Randomization for any patient can occur after informed consent is obtained and eligibility is confirmed, ideally as close to Day 1 as possible. Patients will be randomized into any of the treatment arms open to enrolment for which the patient meets the eligibility criteria.
[B]Treatment arm(s) will be defined for each cohort.
[C]EOS2 visit only required for treatments with an extended half-life. For all other treatments, EOS1 will serve as the EOS visit.

Participants who meet the eligibility criteria at screening will have baseline assessments performed, including determination of the percent liver fat content by MRI.

Once eligibility has been confirmed from screening and baseline assessments, participants will be randomized into any of the treatment arms open to enrollment for which the participant meets the eligibility criteria using an Interactive Response Technology (IRT) system. If a participant does not meet the specific eligibility criteria of a particular treatment arm, the participant will be randomized to any open and actively enrolling arms for which the participant is eligible. Randomization will be stratified by race and BMI (refer to Section 6.3.2). In the event that there

is only one open treatment arm in a cohort or if participants are only deemed eligible for one treatment arm, participants will be enrolled using the same IRT system, but without randomization.

The first dose of study medications will be administered to participants during the visit on Day 1, and scheduled assessments will be performed as defined in the Assessment schedule.

For orally-administered study medications, the first dose will be administered under fasted conditions at the visit on Day 1. Also, participants will be provided with a supply for -self administration during the treatment period on non-visit days. On visit days, study medication will be administered by study staff. In the event that multiple doses are needed per day, the participant can also self-administer subsequent doses after the initial dose is administered by study staff. For other types of study medications, such as injectable monoclonal antibodies, dose administration will be managed by study staff on designated visit days. Detailed instructions for taking/administering study treatment will be provided in the cohort-specific sections and/or the SOM.

If adverse events or significant laboratory abnormalities are noted, in addition to dose reduction or interruption of the investigational drug(s), the investigator may choose to place the participant under a period of close observation until the participant is deemed to have returned to a satisfactory state of health in the opinion of the investigator. In the case of liver or renal laboratory abnormalities, please see Section 16.1 and Section 16.2, respectively, for additional information.

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, biomarker and PD assessments.

Please refer to Section 9.3 for details regarding the end of the study.

Remote procedures

At the investigator's discretion, and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures according to Table 8-1 performed at a remote location. Procedures may 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 an off-site healthcare professional (OHP). In addition to procedures performed by the OHP, the on-site staff may support certain assessments using tele-visits.

The remote procedures will only be offered in certain countries and sites as determined by Novartis based on national and local regulations. The OHPs will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHPs that are not provided by Novartis, this must be agreed upon with Novartis prior to use.

4 Rationale

4.1 Rationale for study design

The NEXSCOT study is designed to safely allow rapid and efficient determination of potential high efficacy drugs and drug combinations in participants with NAFLD and a NASH-like (biomarker) phenotype. Rationale for key aspects of this design are provided below.

4.1.1 Platform study

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The cohort-specific modules (Section 17) will contain the mechanism of action, non-clinical information, proposed dose and dosing regimen, and rationale for each treatment arm including anticipated safety, potential drug-drug interactions, unique inclusion or exclusion criteria, unique stopping rules or dose reduction criteria and other treatment specific information.

4.1.2 Study population

The study enrolls NAFLD patients with characteristics consistent with NASH:

- Two risk factors for NASH: elevated BMI and history of Type II diabetes mellitus, and
- Three phenotypic biomarkers for NASH as shown in Table 4-1: elevated liver fat content diagnostic of NAFLD as measured by MRI-PDFF, liver inflammation as measured by ALT, and liver fibrosis as measured by ELF Test. These phenotypic biomarkers are consistent with the pathobiology of NASH and recent studies have supported these biomarkers as being highly predictive of NASH (Harrison et al 2018a; Sanyal et al 2017).

Table 4-1 Biomarker inclusion criteria compared to normal range

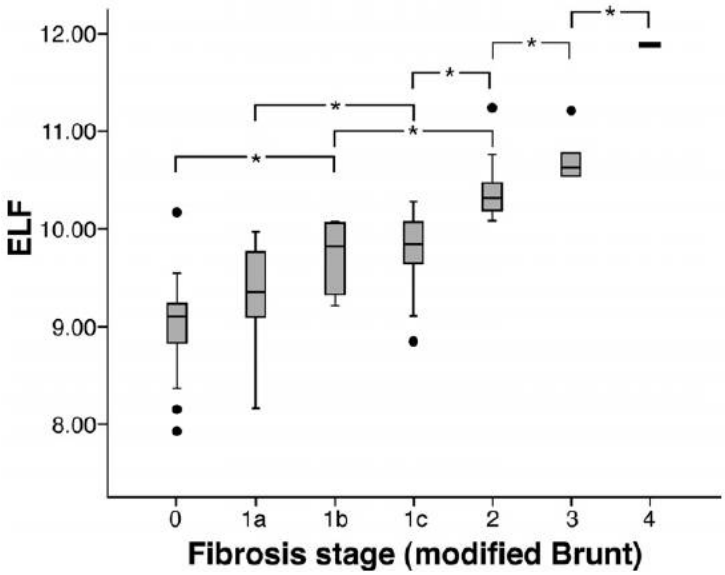
	ALT	Liver fat content (MRI-PDFF)	ELF Test
Normal value	29-33 IU/L (males) 19-25 IU/l (females)	< 5%	< 7.7
NEXSCOT inclusion criteria	≥ 43 IU/L and ≤ 5x ULN (males) ≥ 28 IU/L and ≤ 5x ULN (females)	≥ 8%	8.5-10.5
Reference	Kwo et al 2017	Petäjä and Yki-Järvinen 2016	Lichtinghagen et al 2013, Vilar-Gomez and Chalasani 2018

In this study, ELF Test measurement will be conducted at screening (see Section 5.1 Inclusion criteria), and participants with an ELF Test result within the range of 8.5-10.5 will be

eligible for participation in the study. The goal of using these ELF Test inclusion criteria is to enrich the study population for those subjects with a high likelihood of an ongoing fibrotic process in the liver (disease stage F1-F3) but do not yet have severe fibrosis or cirrhosis (stage F4). This ELF Test inclusion range is based on a weight-of-evidence analysis of the following reports:

- In their review of the current state-of-the-art of soluble liver fibrosis biomarkers, (Vilar-Gomez and Chalasani 2018) noted that the area under the receiver operating characteristic curve (AUROC) for ELF Test using 8.5-10.18 cut-off values to detect liver fibrosis (F≥2) was 0.82 in a meta-analysis of adult and pediatric patients (n=1329) with chronic liver disease, including NAFLD.
- (Lichtinghagen et al 2013) proposed the following ELF Test cut-off values based on the results of this test in healthy volunteers (n=400) and the relationship of this test with liver biopsy staged fibrosis in patients with hepatitis C (n=39):
  - ≤7.7 excluded fibrosis with high sensitivity
  - ≥9.8 had high specificity for identification of fibrosis
  - ≥11.3 discriminated cirrhosis
- (The National Institute for Health and Care Excellence 2016) proposed that NAFLD patients should have ELF Test as a measure of advanced liver fibrosis and proposed that a value of ≥10.51 was consistent with advanced liver fibrosis.
- (Gungoren et al 2018) showed that using an ELF Test cut-off of ≥8.84 was associated with a liver fibrosis score of F≥2 at an AUROC of 0.89 in 46 patients with auto-immune hepatitis who have liver biopsy.
- As shown in Figure 4-1, (Nobili et al 2009) reported a step-wise relationship of liver biopsy measured fibrosis stage to ELF Test result in 121 patients with NAFLD.

Figure 4-1 Relationship of fibrosis state and ELF Test result



Source: (Nobili et al 2009).

This study does not require the invasive procedure of liver biopsy in order to confirm NASH. However, based on the biomarkers evaluated at screening and respective inclusion criteria, in particular ELF Test scores, it can be reasonably assumed that a large proportion of participants enrolled in this study will indeed have NASH (Lopez et al 2017). Patients with ELF Test > 10.5 and ALT > 5x ULN will not be enrolled given that these highly elevated values are consistent with severe and potentially intractable liver fibrosis / cirrhosis and/or inflammation.

4.1.3 Objectives (Endpoints)

Given that NEXSCOT will be studying investigational drugs used in combination for the first time, safety and tolerability will be the paramount and primary objective, assessed by safety endpoints (including vital signs, physical examination, laboratory measurements, ECG) and adverse events (see Section 12.4).

Secondary objectives are included in Table 2-1. The secondary endpoints are (see Section 12.5):

- ALT, % liver fat (MRI-PDFF), and ELF Test: These biomarkers will provide evidence of efficacy and are further described below.
- Cardiometabolic risk factors: NAFLD and NASH patients are at high risk for cardiovascular morbidity and mortality. Therefore, it is important to characterize any negative or positive effects of single drugs or drug combinations on cardiometabolic risk factors including body weight, waist and hip circumference, waist-to-hip ratio, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1C (HbA1c), fasting glucose, fasting insulin, and fasting lipid profile.
- Pharmacokinetics: The potential pharmacokinetic interactions of drugs used in combination will be measured.

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Currently, there are no approved treatments for NASH. However, over the last five years, the results of a number of studies in this indication have been reported in the medical literature (Sanyal et al 2017; Harrison et al 2018a; Harrison et al 2018b). Based on these results, considerable knowledge of the magnitude of both placebo and active treatment effects in NASH studies now exists.

The placebo effects reported in four relatively short-term (≤ 16 week) NASH studies for three main efficacy endpoints, ALT, % liver fat (MRI-PDFF), and ELF Test, are summarized in Table 4-2.

Table 4-2 Examples of placebo effect in published studies in NASH and NASH-like patient populations

Investigational drug	Obeticholic acid (n=23)	Obeticholic acid (n=142)	NGM282 (n=27)	MGL3196 (n=42)	BMS986036 (n=26)
Duration (weeks)	6	12	12	12	16
%Δ ALT from baseline	35.5	-13.4	-2.2	-	-4.5
Relative %Δ liver fat from baseline	-	-	-3.0	-9.6	-
Δ ELF Test from baseline	0.3	-	0	0.1	-
Reference	Mudaliar et al 2013	Neuschwander-Tetri et al 2015	Harrison et al 2018a	Harrison et al 2018b, Abstract GS-009	Sanyal et al 2017

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Conversely, a review of multiple, recent studies in patients with NASH or a NASH-like (biomarker) phenotype shows that high efficacy, active treatment is associated with relative percent decreases in % liver fat (MRI-PDFF) and ALT of ≥ 30% (Sanyal et al 2017; Harrison et al 2018a; Harrison et al 2018b). Similarly, a decrease in ELF Test by ≥ 0.3 units or 3% can be considered evidence of a substantive, beneficial reversal in the ongoing liver fibrotic process (Harrison et al 2018a).

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4.1.5 Follow-up period

All participants receiving treatment in the NEXSCOT study should have safety evaluations and collection of concomitant treatments and/or adverse event data until at least approximately 28 days (Day 113) or, if applicable, until at least approximately 56 days (Day 141) after the last dose of study treatment. Please refer to Section 9.1.1 for details pertaining to early study discontinuation and associated safety follow-up.

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4.2 Rationale for dose/regimen and duration of treatment

Please refer to Section 17 (cohort-specific information) for a detailed rationale of each drug or drug combination treatment.

In general, the dose(s) of the drug(s) to be studied will be chosen based on an evaluation of all available preclinical and/or clinical data to ensure 1) a high likelihood of target or pathway modulation and 2) reasonable safety and tolerability.

Over the last five years, many exploratory studies in NASH have used a twelve-week duration of treatment, for example, (Mudaliar et al 2013) and (Neuschwander-Tetri et al 2015). Twelve weeks is considered the shortest treatment period that will allow measurable changes in improvement of endpoints such as liver inflammation, liver fat content and liver fibrosis.

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

There is currently no appropriate comparator for use in the NASH/NAFLD patients.

While the primary purpose of NEXSCOT is to detect high efficacy drug combinations, single drug treatment arms may also be studied in those situations where the efficacy of the particular drug on the relevant endpoint biomarkers in the relevant patient population has not been previously measured. In this case, the treatment effects of the single drug treatment arm would be compared to both the combination drug effects and the historical placebo effects.

4.4 Purpose and timing of interim analyses

Please refer to Section 12.7.

4.5 Risks and benefits

Detailed descriptions of the expected safety, tolerability and efficacy characteristics of each of the proposed individual treatment arms can be found in Section 17.

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Based on CCI risk considerations, additional safety measures employed in NEXSCOT include, but are not limited to:

- The study employs safety management measures which are considered relevant and appropriate for this patient population and protocol to facilitate safe conduct of the study.
- The study will only be conducted by investigators who have broad experience with patients who have multiple metabolic and/or liver comorbidities.
- Patients with advanced liver disease, for example cirrhosis or more severe hepatitis, will not be enrolled.
- Patients with evidence of ECG abnormalities consistent with significant cardiovascular risk will not be enrolled.
- Participants will have a visit every two weeks during the first two months of treatment for safety assessments, including ECGs and laboratory tests. Halfway through the final month of treatment (Month 3), study staff will contact the participant by phone to inquire about tolerability and safety.
- This protocol pre-specifies both liver and renal events requiring intervention (Section 16.1 and Section 16.2, respectively).
- The study will be also monitored by an internal Safety Assessment Committee (SAC), which will provide an additional layer of oversight for safety events. For further details, please refer to Section 10.2.1 and the standalone Safety Surveillance Plan (SSP).
- Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

Benefits

The key, potential benefits expected to be associated with participation in the NEXSCOT protocol include:

1. Participants will receive a potentially efficacious treatment where currently no approved treatment is available. Over the duration of the study, patients may have the clinical benefit of reductions in hepatic fat, inflammation and/or the ongoing fibrotic process.
2. The severity of the participant's NAFLD will be staged by liver fat, ELF Test and liver transaminases. Knowledge of these parameters may guide future treatment and behavior modification for the particular participant.
3. Participants will contribute to the potential identification of high efficacy, combination regimens for NASH treatment, where an unmet medical need exists.

Benefit:risk associated with the COVID-19 pandemic

The assessment of the benefit:risk for the study in the context of the COVID-19 pandemic concluded the absence of additional risks for the study population and/or related to the investigational medicinal product. As the COVID-19 situation evolves, investigators must use their best judgment to minimize risk to participants during the conduct of the study.

4.5.1 Blood sample volume

A volume of approximately 625 mL is planned to be collected over a period of up to approximately seven to eight months from each participant as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Table 8-1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and the central laboratory manual.

See Section 8.5.4.1 on the potential use of residual samples.

4.6 Rationale for public health emergency mitigation procedures

Remote procedures are planned in this study to minimize burden on participants, and offer them increased flexibility to participate in the study from a remote location (as described in Section 3 and defined in Section 8). During a public health emergency as declared by local or regional authorities (e.g., pandemic, epidemic, natural disaster), additional mitigation procedures to ensure participant safety and trial integrity may be considered. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population will be comprised of male and female NAFLD patients with a NASH-like biomarker phenotype.

Approximately 25 participants per arm will be enrolled in the study, and around 20 participants per arm are expected to be evaluable. Based on the results of the ongoing data review, the sample size may be increased to an enrollment target up to approximately 50 total for a specific arm; for example, due to higher than anticipated variability of the biomarker data.

Please refer to Section 17 (cohort-specific information) for eligibility criteria specific to each treatment arm.

The investigator must ensure that all participants enrolled into the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order for the study population to be representative of all eligible patients.

Participant selection is to be established by checking through all eligibility criteria at both screening and baseline, unless otherwise specified. Please also refer to the Assessment Schedule for the exact tests to be performed at either visit, but note that certain eligibility criteria may only need to be confirmed to be within the ranges specified at one of the two visits. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a participant from enrollment/randomization into the study.

Reference ranges for laboratory assessments are located in the standalone laboratory manual.

If any parameters are found to be outside of the range specified in the inclusion or exclusion criteria (where relevant) at screening or baseline, the assessment can be repeated once to rule-out laboratory error or anomaly.

Refer to Section 8.1 (Screening) for information regarding re-screening.

5.1 Inclusion criteria

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

1. Signed informed consent(s) must be obtained prior to participation in the study.
2. Male and female participants 18 years or older (at the time of the screening visit).
3. NAFLD patients with a NASH-like biomarker phenotype are defined based on the presence of ALL FIVE of the following:
   a. ALT $\geq$ 43 IU/L (males) or $\geq$ 28 IU/L (females)* **AND**
   b. BMI $\geq$ 27 kg/m^2 (in participants with a self-identified race other than Asian) or $\geq$ 23 kg/m^2 (in participants with a self-identified Asian race) **AND**
   c. History of Type 2 diabetes mellitus with HbA1c $\leq$ 9% at baseline **AND**
   d. ELF Test score $\geq$ 8.5 and $\leq$ 10.5 at either screening or baseline **AND**
   e. Liver fat $\geq$ 8% at baseline as determined by the reading of the central MRI laboratory of locally produced images. The MRI assessment should only be performed after eligibility has been confirmed from all other baseline assessments.
4. Participants must weigh at least 40 kg (88 lbs.) and no more than 150 kg (330 lbs.).
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

*Average of two independent results obtained approximately four weeks apart (e.g., once at screening and once at baseline) must be in this range AND both results must be within 30% of one another. Should the initial variance between the two baseline measures be > 30%, a third measure may be obtained 2 weeks after the second measurement. Such participants would be eligible for enrollment provided the variability between any two of these three samples is ≤ 30%.

5.2 Exclusion criteria

IMPORTANT

The exclusion criteria for the core protocol are located in this section (Section 5.2). These exclusion criteria apply to all participants enrolled into this study. However, there may also be additional treatment specific exclusion criteria which are provided in Section 17 for the individual treatment arms.

Participants meeting any of the following criteria and any criteria detailed in the cohort-specific information (Section 17) are not eligible for inclusion in this study.

1. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
2. Use of other investigational drugs within 5 half-lives of randomization, or within 3 months, whichever is longer; or longer if required by local regulations.
3. Use of obeticholic acid (OCA) within 1 month of randomization.
4. Participants on treatment with the following medicines UNLESS they are on stable dosing for at least 3 months before randomization: anti-diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control.
5. Participants on treatment with vitamin E at doses > 200 IU/day and ≤ 800 IU/day UNLESS they are on stable dosing for at least 6 months before randomization, OR any participants on treatment with vitamin E > 800 IU/day regardless of stable dosing.
6. Use of pharmacologically-active weight loss drugs such as lorcaserin, phentermine/topiramate, bupropion-naltrexone HCl, or orlistat within 1 month of randomization.
7. Use of strong inhibitors of CYP3A4/5 (for example; boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir, fazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole) within 5 half-lives or 7 days of randomization, whichever is longer.
8. Use of strong CYP3A inducers (for example; avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort) within 5 half-lives or 7 days of randomization, whichever is longer.
9. Participants taking medications prohibited by the protocol, including cohort-specific guidance. See the 'Prohibited Treatment' sections in the core (Section 6.2.2) and cohort-specific portions (Section 17) of the protocol for further details.
10. History of malignancy for which, based on the investigator assessment, would be reasonable grounds for exclusion.

11. 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.
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception during dosing and for a duration equal to approximately 5 times the terminal half-life after stopping study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). 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), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment;
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant;
    - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception, or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception.

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

    If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
13. Sexually active males will be excluded UNLESS they agree to use a condom during intercourse while taking study medication and for a duration equal to approximately 5 times the terminal half-life after stopping study medication, and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. In addition, male participants must not donate sperm for the time period specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.
14. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening. Significant alcohol consumption is defined as ≥ 21 units of alcohol per week in males and ≥ 14 units of alcohol per week in

females; a unit of alcohol is equivalent to 8 grams pure ethanol, 12 ounce (355 mL) beer, 4 ounce (118 mL) glass of wine, or 1 ounce (30 mL) shot of hard liquor.

15. Inability to reliably quantify alcohol consumption based upon local study physician judgment.
16. History of ongoing drug abuse within the 12 months prior to dosing.
17. Prior or planned (during the study period) bariatric surgery (e.g., gastroplasty, roux-en-Y gastric bypass).
18. Type I diabetes or uncontrolled Type II diabetes (defined as HbAlc > 9% at baseline).
19. Evidence of severe acute or chronic renal insufficiency, such as participants with eGFR < 60 mL/min/1.73m^2.
20. Suspected or confirmed Gilbert's syndrome.
21. Evidence of hepatic decompensation or severe liver impairment or cirrhosis, as defined by the presence of any of the following abnormalities (reminder that all lab ranges below must be confirmed at both screening and baseline):
    - Serum albumin < 3.2 g/dL
    - INR > ULN
    - Total bilirubin > ULN
    - ALT or AST > 5x ULN*
    - Alkaline phosphatase > ULN
    - Platelets outside of normal reference range
    - History of esophageal varices, ascites, or hepatic encephalopathy
    - Splenomegaly

*Average of two independent results obtained approximately four weeks apart (e.g., once at screening and once at baseline) in this range AND both results within 30% of one another. Should the initial variance between the two baseline measures be > 30%, a third measure may be obtained 2 weeks after the second measurement. Since this is an exclusion criterion, in order for the participant to qualify, he/she must demonstrate an average ALT and AST ≤ 5x ULN where the two individual measurements are ≤ 30% variable from one another.

22. History or presence of other concomitant liver diseases including, but not limited to:
    - Hepatitis B or C virus (HCV, HBV) infection, confirmed using standard laboratory assays. Participants with a history of HCV who have appropriate documentation of curative therapy per Investigator's discretion (e.g., biopsy, sustained virologic response [SVR] for more than 3 years prior to screening) are not excluded.
    - Primary biliary cholangitis (PBC)
    - Primary sclerosing cholangitis (PSC)
    - Alcoholic liver disease
    - Definite autoimmune liver disease or overlap hepatitis
    - Hemochromatosis
    - Known bile duct obstruction
    - Suspected or proven liver cancer
23. History of liver transplantation or current placement on a liver transplant list.

24. Known positivity for Human Immunodeficiency Virus (HIV) infection, confirmed using standard laboratory assays.
25. History of non-adherence to medical regimens, or participants who are considered by the investigator to be unable to reliably comply with the requirements of the study.
26. History or current diagnosis of ECG abnormalities indicating safety concerns for participants such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
27. Donation or loss of 400 mL or more of blood within eight (8) weeks prior to initial dosing, or longer if required by local regulation.
28. Participants with contraindications to MRI imaging, including but not limited to:
    - Brain aneurysm clip
    - Implanted neural stimulator
    - Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires
    - Prosthetic heart valves
    - Cochlear implant
    - Ocular foreign bodies that might be ferromagnetic (e.g., metal shavings)
    - Other implanted medical devices (e.g., insulin pumps)
    - Metal shrapnel or bullets still in the body
    - Severe claustrophobia
    - Piercings or tattoos (as determined by the investigator and imager)
    - Weight in excess of MRI machine capacity
29. Signs or symptoms, in the judgment of the investigator, of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to screening.
    - COVID-19 specific: It is highly recommended that PCR or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, a positive test result would exclude a participant from enrollment into the study. Additional testing may occur at the discretion of the investigating physician. COVID-19 testing should be completed via nasal or throat swabs if available. If testing is not performed, the investigator must document their discussion with the subject regarding testing, and the rationale for not testing, in the source documentation. This requirement may be ignored if the pandemic is declared ended by the country where the site is located, and resumed if the pandemic recurs.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Refer to cohort-specific information in Section 17.

6.1.2 Additional study treatments

No other treatment beyond the investigational drug(s) are included in this trial.

6.1.3 Treatment arms/group

Refer to cohort-specific information in Section 17.

6.2 Other treatment(s)

Refer to Section 17 for guidance for other treatments based on the specific treatment arm/cohort.

6.2.1 Concomitant therapy

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Use of the treatments displayed in the below table is allowed for all treatment arms as long as the required minimum period of stable dosing is observed. However, if the minimum period of stable dosing cannot be observed, then these treatments are NOT allowed from randomization until the end-of-study visit. New initiation of these treatments during the study are not allowed.

Table 6-1 Permitted concomitant medications

Medication	Minimum period of stable dosing prior to randomization
Anti-diabetic medications	3 months
Insulin	3 months
Beta-blockers	3 months
Thiazide diuretics	3 months
Fibrates	3 months
Statins	3 months
Niacin	3 months

Medication	Minimum period of stable dosing prior to randomization
Ezetimibe	3 months
Thyroid hormone	3 months
Psychotropic medications	3 months
Estrogen or estrogen containing birth control	3 months
Vitamin E at doses < 800 IU/day	6 months

6.2.2 Prohibited medication

IMPORTANT

The prohibited medications for the core protocol are located in this section. These apply to all participants enrolled into this study. However, there may also be additional treatment specific prohibited medications which are provided in Section 17 for the individual treatment arms.

Use of the treatments displayed in the below table is not allowed for all treatment arms for the duration of the prohibited period defined below:

Table 6-2 Prohibited medication

Medication	Prohibition period start	Prohibition period end
Other investigational drugs	Within 5 half-lives of randomization, or within 3 months, whichever is longer; or longer if required by local regulations	End-of-study visit
Obeticholic acid	Within 1 month of randomization	End-of-study visit
Anti-diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control†	Randomization	End-of-study visit
Vitamin E at doses > 200 IU/day and ≤ 800 IU/day‡	Randomization	End-of-study visit
Vitamin E at doses > 800 IU/day	Randomization	End-of-study visit
Pharmacologically-active weight loss medications (for example; lorcaserin, phentermine/topiramate, bupropion-naltrexone HCl, orlistat)	Within 1 month of randomization	End-of-study visit
Strong inhibitors of CYP3A4/5 (for example; boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole,	Within 5 half-lives or 7 days of randomization, whichever is longer	End-of-study visit

Medication	Prohibition period start	Prohibition period end
lopinavir, fazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole)		
Strong CYP3A inducers (for example; avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort)	Within 5 half-lives or 7 days of randomization, whichever is longer	End-of-study visit

†These medications are prohibited UNLESS the participant has been on stable dosing for at least 3 months prior to randomization. New initiations of these medications during the study are prohibited.

‡This medication is prohibited UNLESS the participant has been on stable dosing for at least 6 months prior to randomization. New initiations of this medication during the study are prohibited.

Please refer to the respective cohort-specific information (Section 17) prohibited medication section for additional restrictions, as applicable.

6.2.3 Restriction for study participants

For the duration of the study, the participants should be informed and reminded of the restrictions outlined in this section.

6.2.3.1 Dietary restrictions

On Day 1 and Day 85, all participants must fast (i.e., no food or liquid except water) for at least 8 hours prior to administration of study treatment. Fasting is a requirement for certain samples (e.g., biomarkers) that are collected at these visits.

It is recommended that participants fast for at least 4 hours prior to any MRI or Fibroscan assessment. Please refer to the SOM for more details.

During the entire treatment period, it is recommended that study treatment should be administered with a light meal unless stated otherwise in the respective cohort-specific Section 17.

Participants can drink water *ad libitum* however, to ensure adequate hydration for urine collection (if applicable), participants should be encouraged to have a fluid intake of at least 240 mL every 4 hours during waking hours in addition to fluid taken with meals and medication.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Upon signing the informed consent form, each participant is uniquely identified by a participant number. The participant number assigned to a participant at screening remains the unique identifier for the participant throughout the study. For additional details on participant numbering, please see the 'Participant numbering' section in the SOM.

6.3.2 Treatment assignment, randomization

Once eligibility is confirmed from baseline assessments, all eligible participant will be randomized via Interactive Response Technology (IRT) to one of the treatment arms.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased: a participant randomization list will be produced by the IRT provider, or by a delegate under Novartis supervision, using a validated system that automates the random assignment of treatment arms to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by race and BMI at baseline (Asian race with BMI < 30 kg/m^2, or Asian race with BMI ≥ 30 kg/m^2, or non-Asian race with BMI < 35 kg/m^2, or non-Asian race with BMI ≥ 35 kg/m^2). The race will be based on the race the participant self-reports as captured on the demography eCRF.

Participants will be enrolled without randomization if there is only one open treatment arm in a cohort, or if they are only deemed eligible for one treatment arm.

Please refer to the SOM for further details regarding the process of treatment assignment and randomization of participants.

6.4 Treatment blinding

This is an open label study. Treatment blinding is not applicable.

6.5 Dose escalation and dose modification

6.5.1 Permitted dose adjustments and interruptions of study treatment

The NEXSCOT study will start all participants on the initial, planned dose(s) of either the single or combination of drug(s). Change and/or interruption of dose is permitted based upon safety considerations. Dose adjustment for any reason other than for safety will be subject of a protocol amendment.

Safety and tolerability

If the treatment is not tolerated, the protocol allows reduction/interruption of dose(s), unless otherwise specified in the cohort-specific treatment information in Section 17. Please refer to Section 17 for the exact reduced dose(s) and the guidance below for more details.

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At the end of two weeks of reduced dosing, the investigator, weighing all the evidence, may consider increasing the dose(s) of the drugs in the regimen back to the starting dose(s). However, if the intolerability returns, the investigator should again decrease the dose(s) as before and

maintain the participant on these reduced dose(s) for the remainder of the study. If the participant cannot tolerate the reduced dose(s), then the investigator should consider stopping the experimental treatment.

Table 6-3 Dosing response to safety/tolerability events

First Action	Result	2nd Action	Result	3rd Action
Interrupt dosing for up to two days and/or decrease dose to approximately one-half of the original starting dose for 2 weeks*†	Reduced dose tolerated	Consider increasing the dose back to the starting dose	Starting dose tolerated	**Continue at starting dose until study completion**
			Starting dose NOT tolerated	Decrease dose back to approximately one-half of starting dose and remain at this dose until study completion†
	Reduced dose NOT tolerated	**Discontinue study treatment**		

*If the causative drug is unknown, the dose of all drugs in the combination should be reduced. If the event is believed to be causally-related to one specific drug, only the dose of that drug may need to be reduced while the other drug(s) in the combination may remain at the starting dose.
†Please refer to cohort-specific treatment information in Section 17 for the exact reduced dose(s).

For some drugs that may be used in the NEXSCOT study, adverse events thought to be related to treatment are included in their reference safety information as listed in their respective IBs. Cohort-specific information (Section 17) for that particular drug should be used to determine if the individual drug could be dose interrupted and/or reduced. An example would be "Drug A" for which diarrhea is a commonly reported adverse event. In this example, in the setting of new onset diarrhea with a drug combination which includes Drug A, it may be reasonable to only dose reduce Drug A, rather than reduce the dose of all drugs in the combination.

Liver and renal events

Certain liver and renal events as defined in Section 16.1 and Section 16.2, respectively, may necessitate dose modifications. The recommendations for the timing and duration of treatment discontinuation, adjustment and/or interruption, are also provided in Section 16.1 and Section 16.2. In the event that dose reduction is needed, please refer to cohort-specific treatment information in Section 17 for the exact reduced dose(s) to be used.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. 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.

Where applicable, remote treatment administration compliance will be assessed by the OHP and information will be provided to the Investigator and/or study personnel.

6.7 Preparation, dispensation, and management of investigational drug

6.7.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Unless specifically instructed by Novartis, the investigator must not destroy any drug labels, or any partly used or unused drug supply. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Further details regarding the handling of study treatment are provided in the SOM; information will also be provided in Section 17 if the study treatment requires special handling (e.g., biologics, injectables).

6.7.2 Accountability and monitoring

The investigator must maintain an accurate record of the receipt and of dispensing of study treatment in a drug accountability log. Further details regarding accountability and monitoring are provided in the SOM.

6.7.3 Preparation and dispensation

Clinical supplies are to be dispensed only in accordance with the protocol. Medication labels will be in the local language and comply with the legal requirements of each country. Each study site will be supplied with study drug in packaging as described under the cohort-specific treatment information in Section 17.

Further details regarding the preparation of study treatment are provided in the SOM; information will also be provided in Section 17 if the study treatment requires special preparation (e.g., biologics, injectables).

6.7.4 Instructions for administration

Study medication will be administered throughout the 12-week treatment period.

As study treatments may vary depending on the specific arm, please refer to the respective cohort-specific information (Section 17) for further details on administering study treatment.

6.7.5 Remote delivery

For remote visits, where delivery of study treatment directly to a participant's remote location (e.g., home) is permitted by national and local governing regulations, dispatch of IMP from the site (or depot/pharmacy) to the participant will be performed under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month's supply.

Regular contact with the site and/or OHP will occur for instructional purposes, safety monitoring, and discussion of the participant´s health status until the next scheduled visit, as required.

Study treatment for remote administration will be handled and shipped in line with the SOM and required procedures for shipping.

7 Informed consent procedures

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

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 participant 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 to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB or CDS for marketed drugs. This information will be included in the participant informed consent and should be discussed with the participant 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 participant.

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 participants 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.

The study includes the option for the participant to have certain study procedures performed off-site by an OHP instead of at the study site, for which a separate signature is required if the participant agrees. The Investigator may present this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the Assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Please refer to the SOM for guidance regarding visit/assessment windows and other changes to scheduled visits/assessments.

Participants who discontinue from the study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit (i.e., EOS1 or EOS2) if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

All assessments, except those marked with a "NR" footnote, may be performed remotely by an OHP in certain countries and sites, as allowed by national and local regulations.

Table 8-1 Assessment Schedule

Epoch	**Screening**		**Treatment**																**Post-Treatment Follow-Up 1**[1,2]	**Post-Treatment Follow-Up 2**[1,2]
Visit Name	**Screening**	**Baseline**	**Treatment**																**EOS1**	**EOS2**
Days	**-60 to -28**	**-27 to -1**	**1**[3,4]	**8**[5]	**15**[3]	**22**[5]	**29**[3]					**43**[3]	**57**[3]					**71**[5]	**85**[3,4]	**113**	**141**
Weeks	**-9 to -4**	**-4 to -1**	**1**	**2**	**3**	**4**	**5**					**7**	**9**					**11**	**13**	**17**	**21**
Time (post-dose)	**-**	**-**	**-**	**-**	**-**	**-**	**0h**[3]	**1h**	**2h**	**3h**	**4h**	**-**	**0h**[3]	**1h**	**2h**	**3h**	**4h**	**-**	**-**	**-**	**-**
Informed consent[6]	X																				

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Inclusion / Exclusion criteria	X	X																		
Medical history/current medical conditions	X	X																		

Epoch	Screening		Treatment																Post-Treatment Follow-Up 1[1,2]	Post-Treatment Follow-Up 2[1,2]
Visit Name	Screening	Baseline	Treatment																EOS1	EOS2
Days	-60 to -28	-27 to -1	1[3,4]	8[5]	15[3]	22[5]	29[3]					43[3]	57[3]					71[5]	85[3,4]	113	141
Weeks	-9 to -4	-4 to -1	1	2	3	4	5					7	9					11	13	17	21
Time (post-dose)	-	-	-	-	-	-	0h[3]	1h	2h	3h	4h	-	0h[3]	1h	2h	3h	4h	-	-	-	-
Demography	X																				
Hepatitis and HIV Screen[8]	S																				
COVID-19 Test[8a]		S																			
Pregnancy and assessments of fertility[9]	X	X	X				X						X						X	X	X
Physical examination[10]	S	S	S		S		S						S						S	S	S
Vital signs and body measurements[11]	X	X	X		X		X					X	X						X	X	X
ECG evaluation	X	X	X		X														X	X	X
Hematology	X	X	X		X		X					X	X						X	X	X
Blood chemistry	X	X	X		X		X					X	X						X	X	X
Urinalysis	X	X	X		X		X					X	X						X	X	X
Coagulation panel[12]	X	X	X		X		X					X	X						X	X	X
Fasting glucose, insulin, and lipids[13]			X																X		
PK blood collection[14]			X		X		X	X	X	X	X	X	X	X	X	X	X		X	X[15]	X[15]
Conditional biomarker RNA[16]		X	X										X						X	X	X
Central lab biomarkers [17]	X[18]	X	X										X						X	X	X

Epoch	Screening		Treatment																Post-Treatment Follow-Up 1[1,2]	Post-Treatment Follow-Up 2[1,2]
Visit Name	Screening	Baseline	Treatment																EOS1	EOS2
Days	-60 to -28	-27 to -1	1[3,4]	8[5]	15[3]	22[5]	29[3]					43[3]	57[3]					71[5]	85[3,4]	113	141
Weeks	-9 to -4	-4 to -1	1	2	3	4	5					7	9					11	13	17	21
Time (post-dose)	-	-	-	-	-	-	0h[3]	1h	2h	3h	4h	-	0h[3]	1h	2h	3h	4h	-	-	-	-
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Dose administration[22]			X	X[23]	X[23]	X[23]	X					X[23]	X					X[23]	X[23]		
Fibroscan[24,25,NR]		X																	X	X[26]	
MRI/MRE[27,NR]		X																	X	X[26]	
VAS (Visual Analog Scale)[28]		X																	X		
Telephone follow-up				X		X												X			
Concomitant therapies[29]	X																				
Adverse events	As required																				
Serious adverse events	As required																				
Comments	As required																				
Study completion information																				X	X

[X] Assessment to be recorded in the clinical database
[S] Assessment to be recorded in the source documentation only
[NR] Non-remote, i.e. this assessment may not be performed remotely (i.e., must be performed at the originally qualified facilities).

[1] For treatments with an extended half-life, EOS1 will be required as a standard, non-EOS post-treatment follow up visit, and EOS2 will serve as the EOS visit. For all other treatments, EOS1 will serve as the EOS visit.
[2] If a participant discontinues study treatment early, the participant should be scheduled for a subsequent visit at which time all assessments at the EOS1 visit should be performed. For treatments with an extended half-life, if a participant discontinues early after EOS1, then the participant should be scheduled for a subsequent visit at which time all assessments at the EOS2 visit should be performed.
[3] Assessments to be performed pre-dose.
[4] All participants must fast for at least 8 hours prior to administration of study treatment.
[5] Visit will be conducted via telephone only. Participants are not required to present to the study site for assessments.

[6] Informed consent must be provided by all participants before any screening procedures are performed. The DNA assessment is optional and requires a separate informed consent to be signed.

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[8] Standard laboratory assays to be used for screening.

[8a]COVID-19 test highly recommended to be completed within 1 week prior to first dosing, as defined in Exclusion Criterion #29.

[9] Serum pregnancy tests will be performed at Screening and EOS; urine tests may be used at other time points.

[10] A complete physical examination is required at Screening, Day 1, Day 85, and at the study completion visit. A focused physical examination can be performed at all other visits where a physical examination is required. Please see protocol Section 8.4 for more details.

[11] Body height only measured at Screening. Waist and hip circumference (for waist-to-hip ratio calculation) only measured at Baseline and Day 85. Blood pressure and pulse rate will be measured in a sitting position at all marked visits.

[12] Coagulation panel includes PT/INR and aPTT.

[13] Fasting glucose and insulin used for Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) calculation. Fasting lipid panel includes total cholesterol, LDL, HDL, and triglycerides. Additional analyses of HDL and LDL sub-fractions, ApoC3, and lipoprotein(a) at these timepoints may be performed depending on the compound under investigation.

[14] Trough PK samples will be collected at all visits during the treatment period (Day 1 to Day 85). On Day 29 and Day 57, additional samples will be obtained as marked.

[15] Assessment is only to be performed at EOS if a participant discontinues study treatment and from the study early.

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[17] Assessment may include (CCI CRP, CCI ELF Test).

[18] ELF Test only.

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[22] For orally-administered study medications, participants will be provided with a supply to self-administer for 12 weeks (Day 2 to Day 84).
Study medication will be administered by study staff on marked visit days. Participants should bring all used and unused medications, and diaries, to each visit. For other types of study medications, such as injectable monoclonal antibodies, dose administration will be managed by study staff on marked visit days.

[23] Orally-administered study medications only.

[24] Optional assessment.

[25] If Fibroscan is unavailable, alternative technology to assess liver stiffness may be considered upon consultation with the sponsor.

[26] Assessment is only to be performed at this visit if a participant discontinues study treatment early on or after Week 8 for any reason and should be scheduled as closely to the last dose of treatment as possible.

[27] Assessment should be performed after eligibility is confirmed from all other screening/baseline assessments wherever possible. MRE is an optional

assessment. See Imaging Subject Scanning Guide for further instructions.
[28] VAS assessments for itching of the skin.
[29] A thorough review of any concomitant medications (including medication name, dose, unit, frequency, and route) should be performed at every visit.

8.1 Screening

In general, it is permissible to re-screen a participant once if he/she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. A participant may not be enrolled in more than one treatment arm.

Further information on re-screening is outlined in the SOM.

8.1.1 Information to be collected on screening failures

Certain limited data on screening failures will be collected. Further information on what data must be collected and further information on re-screening is outlined in the SOM.

8.1.2 Pre-screening

Prior to the screening visit, optional pre-screening assessments may be conducted, including laboratory tests for serum albumin, ALT, AST, ALP, bilirubin, creatinine, ELF (or one of its component measures such as hyaluronic acid), HbA1c, INR, and platelets, in order to assess participant eligibility for inclusion. Prior to any assessments being conducted, the pre-screening informed consent form must be signed by the participant.

Only data related to SAEs causally related to study procedures (i.e., blood sampling) will be reported. All other data related to pre-screening will be recorded only in the source documentation.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF.

Participant demographic and baseline characteristic data are to be collected on all participants. Relevant medical history/current medical condition present before signing the informed consent will be recorded. Investigators will have the discretion to record abnormal test findings on the appropriate CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.3 Efficacy/Pharmacodynamics

Efficacy of the single or combination drug regimens will be assessed based on the following three general classes of assessments:

- Liver function tests and liver and/or systemic inflammation markers (including ALT)
- Markers of liver fibrosis (including ELF Test)
- Magnetic Resonance Imaging (including MRI-PDFF)

In addition, the impact of treatment on cardiometabolic risk parameters including body weight, waist and hip circumference, waist-to-hip ratio, Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1C (HbA1c), fasting glucose, fasting insulin, and fasting lipid profile will be assessed.

Pharmacodynamic (PD) samples will be collected at the timepoints defined in the Assessment schedule (Table 8-1). Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. PD samples will be obtained and evaluated in all participants at all dose levels.

8.3.1 Liver function tests and liver and/or systemic inflammation markers

ALT, AST, GGT, ALP (total), total bilirubin, albumin, and high-sensitivity C-reactive Protein (hsCRP) will be assessed as indicated in the Assessment schedule. The methods for assessment and recording are specified in the laboratory manual.

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

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

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

8.3.2 Markers of Liver Fibrosis

- Enhanced liver fibrosis Test (ELF Test™) will assess: hyaluronic acid (HA), tissue inhibitor of metalloproteinases (TIMP-1), and amino-terminal pro-peptide of procollagen type III (PIIINP).
- Fibroscan® (optional) to assess liver stiffness (in kPa) will be performed where available. If Fibroscan is unavailable, alternative technologies to assess liver stiffness may be considered upon consultation with the sponsor.
- Fibrosis biomarker test (originally called Fibrotest®/ Fibrosure®) will assess: α2-macroglobulin, apolipoprotein A1, total bilirubin, haptoglobin, GGT, and ALT.
- Additional fibrosis markers may be assessed, including but not limited to FIB4 score, APRI score, and NAFLD score.

Additional information is provided in the central laboratory manual. These markers will be assessed as indicated in Table 8-1 (Assessment schedule).

8.3.3 Magnetic Resonance Imaging (MRI)

Participants will undergo magnetic resonance imaging twice during the course of the study (at Baseline and End of Treatment) to quantitate liver fat. Optional exploratory MRI-based assessments will be performed in a subset of participants to evaluate the effect of treatment on exploratory MRI related endpoints as outlined in Table 2-1 (Objectives and related endpoints).

All participants who discontinue prematurely on or after Week 8 must have an end of treatment MRI assessment scheduled as close to the last dose of treatment as possible.

8.3.4 Anthropometric assessments

Height in centimeters (cm), waist and hip circumference (cm), and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes), will be measured as indicated in Table 8-1 (Assessment schedule). Additional details of these assessments will be provided in the SOM.

8.3.5 Cardiometabolic risk parameters

Blood samples will be collected for Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), hemoglobin A1c (HbA1c), fasting glucose, fasting insulin, and fasting lipid profile including total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and lipoprotein A as per Table 8-1. Glucose and lipid measurements should be collected under fasted conditions. Detailed information will be provided in the central laboratory manual.

Note: Body weight, waist and hip circumference, and waist-to-hip ratio are also considered cardiometabolic risk parameters.

8.3.6 Appropriateness of biomarker assessments

As described in Section 4.1, the three biomarkers supporting the secondary objectives of this study, liver fat content using MRI-PDFF, ALT and ELF Test are well established, platform technologies which are frequently used in both clinical practice and research in liver disease. Multiple studies in NAFLD and NASH conducted over the last five years have used some or all of these biomarkers as endpoints (Sanyal et al 2017; Harrison et al 2018a; Harrison et al 2018b).

8.4 Safety

Safety assessments are specified below with the Assessment schedule (Table 8-1) detailing when each assessment is to be performed.

The methods for each assessment and data recording details are located in the SOM.

For details on AE collection and reporting, refer to the AE Section 10.1.1.

Table 8-2 Physical Assessments

Assessment	Specification
Physical examination	Complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed. Focused physical examination will include the examination of general appearance, skin, throat, lungs, heart, abdomen, and extremities.
Vital signs	Includes body temperature, pulse, and blood pressure.

8.4.1 Safety-related laboratory evaluations

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory

until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-3 Safety-related Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin (HGB), Ery. Mean Corpuscular Hemoglobin (MCH), Ery. Mean Corpuscular HGB Concentration (MCHC), Ery. Mean Corpuscular Volume (MCV), Platelets, Erythrocytes, Leukocytes, Erythrocyte Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, HbA1c, Glucose
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (aPTT)
Pregnancy Test	Serum / Urine pregnancy test

8.4.2 Electrocardiogram (ECG)

Single 12 lead ECGs will be collected at the time points indicated in the Assessment schedule (Table 8-1).

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

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated by study staff, unless auto-calculated by the ECG machine.

Clinically significant abnormalities must be reported as adverse events.

Additional details pertaining to ECG collection and reporting are included in the SOM.

8.4.3 Pregnancy and assessments of fertility

Pregnancy testing

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 urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 10.1.4 for details on Pregnancy reporting.

Assessments of Fertility

Refer to Section 5.2 for criteria to determine a female participant's childbearing potential status.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female participant, regardless of reported reproductive/menopausal status at screening/baseline.

Vasectomized partners of female participants should provide supporting documentation, which is to be kept as source, as applicable per local Health Authority regulations.

8.4.4 Appropriateness of safety measurements

Other than possible treatment specific safety measures (Section 17), the safety assessments selected are standard for this indication/ participant population.

8.5 Additional assessments

No additional tests will be performed on patients entered into this study.

8.5.1 Clinical Outcome Assessments (COAs)

8.5.1.1 Visual Analog Scale (VAS)

A 100 mm visual analogue scale (VAS) will be used to assess the severity of participants' itch (ranging from 0 = no itch at all to 100 = the worst imaginable itch). The score (distance from left) on the VAS will be recorded by the participant marking with a line.

The scale will be completed by participants as indicated in Table 8-1 (Assessment schedule).

8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the Assessment schedule (Table 8-1). Follow instructions outlined in the central laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data and the expected PK for the drug(s) being tested.

Pharmacokinetic (PK) samples will be collected in all participants.

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Concentrations will be expressed in mass per volume units and will refer to the free base.

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8.5.4.1 Use of residual biological samples

Residual blood samples may be used for another protocol specified endpoint.

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8.5.5 Imaging

Magnetic resonance imaging (MRI) and magnetic resonance elastography (MRE)

Participants will undergo magnetic resonance imaging twice during the course of the study (Baseline and End of Treatment) to quantitate liver fat. Optional exploratory MRI-based assessments (including MRE) will be performed in a subset of participants to evaluate the effect of treatment on exploratory MRI related endpoints as outlined in Table 2-1 (Objectives and related endpoints).

All participants who discontinue prematurely on or after Week 8 must have an end of treatment MRI assessment.

MRI acquisition sequences, including MRE, are described in MRI Participant Scanning Guide.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment in individual participants

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration) and can be decided by either the participant or the investigator.

Study treatment must be discontinued under the following circumstances:

1. Participant decision
2. Pregnancy
3. Use of prohibited treatment(s)
4. Any situation in which study participation might result in a safety risk to the participant
5. The investigator believes that continuation would negatively impact the safety of the participant or the risk/benefit ratio of trial participation

6. Hypersensitivity (CTCAE Grade 2 or higher) reaction to study medication
7. An adverse event that is CTCAE Grade 4 or higher, regardless of whether the event is suspected to be related to study drug(s)
8. An adverse event that is CTCAE Grade 3 and suspected to be related to study drug(s) (apart from liver and renal events - see below)
    - If a liver or renal event occurs, follow guidelines outlined in Section 16.1 and Section 16.2, respectively, regarding discontinuation of study treatment
9. Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment assessments (i.e., EOS1 or EOS2) indicated in the Assessment schedule (Table 8-1; and refer to Section 8).

If the participant cannot or is unwilling to attend any visit(s), the study staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

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

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

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

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation occurs should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples), and
- No longer wishes to receive study treatment, and
- Does not want any further visits or assessments (including further study-related contacts)

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the Assessment schedule (please also refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at the time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.2.1 Study stopping rules

Treatment arm stopping rules

If any of the following events occur, all ongoing treatment arms sharing the same suspect drug(s) will be placed on hold to further enrollment, and no new participants may be dosed, however dosing of those without safety concerns may continue. In addition, a full review of all available clinical safety data and discussion with the investigators will take place.

- One participant on study drug experiences any adverse event that is CTCAE Grade 4 or higher that is suspected to be related to study drug(s)
- Two participants on study drug experience a similar adverse event that is a CTCAE Grade 3 or higher other than ALT elevation regardless of whether the events are suspected to be related to study drug(s)
- Two participants are discontinued due to a liver event as defined in Section 16.1
- Two participants are discontinued due to a renal event as defined in Section 16.2

- Two participants meet the same individual participant stopping rule 6, 7, or 8 (Section 9.1.1)
- One participant experiences any adverse event that is CTCAE Grade 5 regardless of whether the event is suspected to be related to study drug(s)
- One participant experiences an SAE that is suspected to be related to study drug(s)
- The Principal Investigator and Sponsor consider that the number and/or severity of adverse events justify discontinuation of the suspect drug(s)
- The Sponsor unilaterally requests it

Safety reviews for treatment arm stopping will be conducted cooperatively between medically qualified representatives of the sponsor and investigator and a joint decision will be made. The treatment arm may resume following the safety review, if the investigator and sponsor agree it is safe to proceed.

9.2.2 Early study termination by the sponsor

The study can be paused or terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant's welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. 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 participant'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.

9.3 Study completion and post-study treatment

Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

For participants who discontinue the study early and do not return for a study completion visit, a safety follow-up call will be conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and the SOM. Documentation of attempts to contact the participant should be recorded in the source documentation.

Trial-level study completion is defined as when final data analysis and reporting, and appropriate closeout activities are completed, following either triggering event:

1. When the final participant in the fifth cohort finishes his/her Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or
2. When an early study termination decision is finalized.

10 Safety monitoring, reporting, and committees

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 clinical investigation participant 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 participant 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 participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded 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. the Common Toxicity Criteria (CTC) AE grade (version 5.0 or higher) for the adverse event. If CTC-AE grading does not exist for an adverse event, use:
   - 1 = mild
   - 2 = moderate
   - 3 = severe
   - 4 = life threatening* (see Section 10.1.2 for definition of a serious adverse event [SAE])
     *Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g., certain laboratory abnormalities in the absence of meeting other seriousness criteria).
   - 5 = death
2. its relationship to the study treatment
3. its duration (start and end dates or ongoing) and the outcome 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
6. its outcome i.e., its recovery status or whether it was fatal

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

- Dose not changed

- Dose reduced/increased
- Drug interrupted/permanently discontinued

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

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 5 half-lives following the last dose of study treatment or until the final study visit, whichever is longer.

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 participants with the underlying disease.

Follow the instructions found in the SOM for data capture methodology regarding AE collection for participants that fail screening.

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 conditions[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 participant 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-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- social reasons and respite care in the absence of any deterioration in the participant'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 participant 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 participant 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 reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred. Please see Section 10.1.5 for more details.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 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. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

For patients who sign the pre-screening informed consent form, SAEs which occur after signature of this consent will only be captured if they are reported to be causally related to study procedures (i.e., blood sampling).

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a screen failure must be reported to Novartis.

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 or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office and Patient Safety (CMO&PS) 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 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment must be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review, and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy.

To ensure participant 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 CMO&PS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery (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, participant, 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 recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an 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 Dosing CRF (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

Refer to Section 16.1 for liver safety monitoring, and Section 16.2 for renal safety monitoring.

10.2.1 Safety Assessment Committee

As described in the FDA Draft Guidance for Industry: Safety Assessment for IND Safety Reporting (CDER 2015), this study will include a Safety Assessment Committee (SAC) which will include both study team members and also members not directly related to the conduct of the study. The SAC will function independently of site investigators participating in the study. The SAC will assess at frequent intervals the progress of the NEXSCOT treatment arms and the safety data and will continue, modify or terminate treatment arms based on these reviews.

The rationale for using a SAC rather than an external DMC and specific details regarding composition, responsibilities, data monitoring, meeting frequency, and documentation of SAC reports, minutes, and recommendations is described in the Safety Surveillance Plan.

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, and study staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

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 study staff via the EDC system. Designated 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 World Health Organization (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 will be tracked using 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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit 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 visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, 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 & identify risks & 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 participant 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 participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 participants 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.

All data will be listed, summarized and analyzed by cohort and treatment. Combined cohort analysis will be performed as appropriate.

12.1 Analysis sets

The safety analysis set will include all participants that received any study drug.

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

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

For all analysis sets, participants will be analyzed according to the study treatment(s) received.

12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, sample size (n), mean (arithmetic), standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} (Q1) and 75th (Q3) percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by treatment, participant, system organ class (SOC) and preferred term (PT).

12.3 Treatments

The safety analysis set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by treatment, participant and the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis of the primary endpoint(s)

The primary objective of the study is to evaluate the safety and tolerability of single or combination therapy during 12 weeks of treatment. Safety and tolerability data will be summarized using descriptive statistics. Details are provided in Section 12.4.2.

12.4.1 Definition of primary endpoint(s)

All safety data collected, including laboratory measurements, vital signs, adverse events and ECG, represent the primary endpoints of this study and will be used to support the assessment of the primary objective.

12.4.2 Statistical model, hypothesis, and method of analysis

Formal statistical analysis will not be performed on the safety and tolerability data.

Adverse events

All information obtained on adverse events will be displayed by treatment and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication, or present prior to start of treatment but increased in severity based on preferred term, or changed from being not suspected to being suspected of study drug relationship, or developed into SAEs after the start of the treatment period) 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 adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A participant with multiple adverse events 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, participant, 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 and will include sample size (n), mean (arithmetic), SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum.

Standard 12-lead ECG

All ECG data will be listed by treatment, participant and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time and will include sample size (n), mean (arithmetic), SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, participant, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing will be provided presenting all parameters in a participant with any abnormal values. Summary statistics will be provided by treatment and visit/time and will include sample size (n), mean (arithmetic), SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum and maximum.

12.4.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

12.4.4 Sensitivity and Supportive analyses

Not applicable.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

A mixed-effect model for repeated measures analysis (MMRM) will be conducted for log-transformed ratio to baseline ELF Test and ALT. Commercially Confidential Information

An unstructured variance-covariance matrix will be used to account for correlation among multiple measurements from the same participant and variance heterogeneity. If the unstructured covariance causes model convergence issues, then other simpler covariance structures will be considered. Least squares mean, the associated 2-sided 80% confidence interval and the p-value will be obtained for each treatment at each visit and back transformed to the original scale. Contrasts assessing trend over time will be constructed for each treatment using various functional forms as needed. Both cohort-wise and combined cohort analysis will be performed as appropriate.

Log-transformed ratio to baseline % liver fat, hsCRP, HOMA-IR, HbA1c, fasting glucose, fasting insulin, and fasting lipid profile, as well as change from baseline ELF Test, ALT, % liver fat, waist circumference, hip circumference, waist-to-hip ratio, and % change from baseline weight will also be analyzed. Parameters with more than one post-treatment measurement will be subjected to the same MMRM analysis described above for ELF Test and ALT using untransformed baseline in lieu of log-transformed baseline as a covariate for the untransformed data analysis. For parameters with only one post-treatment measurement such as % liver fat, an ANCOVA with treatment and stratification factor (race and BMI group) as classification factors and baseline (or log-transformed baseline if applicable) as a covariate will be employed.

Additionally, a multivariate ANCOVA will be done for the three-dimensional endpoint: log-transformed ratio to baseline ELF Test, ALT and % liver fat at Week 12. The model will include treatment and stratification factor (race and BMI group) as classification factors and log-transformed baseline as a covariate. An arbitrary 3 by 3 covariance matrix will be assumed for the three-dimensional endpoint.

Proportion of participants with at least 30% relative reduction and 5% absolute reduction in % liver fat will be tabulated separately by treatment. If there are sufficient data, then a subgroup analysis (ANCOVA) in participants with baseline liver fat ≥10% will be performed to compare % liver fat between treatments.

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Baseline participant characteristics will be monitored closely and compared across cohorts to assess population drift which may occur because of improved general care and enrollment of either less or more healthy participants over time. The population drift, if present, will be accounted for using a modeling approach as appropriate.

Missing data will not be imputed in the MMRM analysis. Assuming data is missing at random, a participant with missing value at a visit will still contribute to the estimation of the treatment effect at that particular visit as the likelihood-based MMRM borrows information from non-missing values of this participant and other participants. For the Week 12 multivariate ANCOVA, an additional analysis with the last post-treatment observation carried forward for missing ELF Test and ALT values may be performed.

12.5.2 Pharmacokinetics

Plasma concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point,

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Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Commercially Confidential Information

Summary statistics (mean, SD, geometric mean, CV, median, min and max) per analyte, per time point will be reported. The concentration data may be integrated with data from other studies for population PK analysis in the future and will be reported separately.

12.5.3 PK/PD relationships

The relationships between individual PK profiles or derived PK parameters and various efficacy/PD measurements or derived variables (including, but not limited to ELF Test, ALT and % liver fat) may be explored using graphical approaches (e.g., scatter plots) and regression analysis as appropriate. Similarly, the relationship between % liver fat reduction and ALT reduction vs. weight loss as well as ALT decrease vs. % liver fat reduction may be explored as needed.

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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, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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 database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as the global last participant 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). For details on the Novartis publication policy including authorship criteria, the Investigators are requested to refer to the Novartis publication policy training materials provided at the trial investigator/initiation 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 participants 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 ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

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.

New cohorts will be added to the protocol using substantial amendments.

Urgent safety measures that are required for participant safety may be implemented immediately provided that 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 participant 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.

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16 Appendices

16.1 Appendix 1: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a process for identification, monitoring and evaluation of liver events has to be followed. For this study in participants likely to have altered liver function at baseline, an adapted monitoring process will be followed.

Participants who develop elevations in liver-related laboratory parameters and/or clinical signs and symptoms suggestive of liver disease, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (< 5%), should be managed according to Table 16-1.

- If ALP, ALT, AST, or bilirubin elevations reach the specified thresholds listed below and outlined in Table 16-1, the participant must be re-evaluated within 48-72 hours after the laboratory results becoming available, at which time confirmatory laboratory testing will be performed. This includes ALP, ALT, AST, total and direct bilirubin and INR.
- At the same time repeat clinical laboratory samples are drawn, an ad-hoc PK sample should be taken. The date and time of the PK draw and the last study medication administration over at least the preceding 2 days shall be recorded in the eCRF.
- If prompt evaluation is not possible within 48-72 hours following receipt of abnormal laboratory results, study drug should be interrupted immediately (date of last study drug dose must be recorded in the eCRF) and the participant must be re-evaluated as soon as possible.
- The sponsor should be notified of laboratory abnormalities and any clinical symptoms within 48 hours of available laboratory results and/or assessment of clinical symptoms.

Liver chemistry repeats should be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. Should this occur, a sample should also be sent to the central laboratory for analysis. Any local liver chemistry tests previously conducted that are associated with this event should have results maintained in source documents. The result from the central laboratory will be provided via the standard electronic transfer.

If the elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption or discontinuation (as described in Table 16-1) if deemed appropriate, close monitoring, causality and clinical evaluation should be performed as below:

- Repeating the liver tests to confirm elevation as described in Table 16-1.
- Discontinuation of the investigational drug, if appropriate. Note that discontinuation is mandatory in the case of decompensated cirrhosis as defined by ascites, bleeding esophageal varices, hepatic encephalopathy, jaundice or any other liver decompensation related symptom.
- Hospitalization of the participant, if appropriate.
- An investigation of the liver event which needs to be followed until resolution, such as by:
  - Obtaining a more detailed history of symptoms and prior or concomitant diseases.
  - Obtaining a history of concomitant drug use (including nonprescription or over-the-counter medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Excluding acute viral hepatitis Types A, B, C, D, and alcoholic hepatitis; hypoxic/ischemic hepatopathy; autoimmune hepatitis and biliary tract disease.
  - Imaging such as abdominal US, CT or MRI, as appropriate.
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.
  - Conducting pathology and serology tests, and/or liver biopsy, based on investigator's discretion.

Participants who permanently discontinue study drug due to potential liver toxicity must be followed for close monitoring until abnormalities stabilize to baseline levels or baseline grade of abnormality and the participant is asymptomatic.

All follow-up information, and the procedures performed must be recorded on the appropriate CRFs, including SAE forms when appropriate.

The baseline value will be calculated as the mean of the last two assessments before first administration of the study drug.

Table 16-1 Management of Participants with Confirmed ALP, ALT, AST, or Bilirubin Elevations With or Without Liver Related Clinical Symptoms

Baseline	Treatment-Emergent (Confirmed[a])	Liver-Related Clinical Symptoms[b]	Action taken	
			Monitoring[c]	Study Drug
ALT and/or AST				
Baseline ALT and/or AST < 2 × ULN	ALT and/or AST > 3 × ULN but ≤ 5 × baseline	None	Laboratory monitoring and causality evaluation	Continue dosing
		Present	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALT and/or AST > 3 × ULN but ≤ 5 × ULN AND total bilirubin > 2 × ULN (in Gilbert's syndrome, see footnote[f])	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALT and/or AST > 3 × ULN and > 5 × baseline	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Permanently discontinue
Baseline ALT and/or AST ≥ 2 × ULN	ALT and/or AST > 2 × baseline but ≤ 3 × baseline	None	Laboratory monitoring and causality evaluation	Continue dosing
		Present	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALT and/or AST > 2 × baseline but ≤ 3 × baseline AND total bilirubin > 2 × ULN[f]	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALT and/or AST > 3 × baseline	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Permanently discontinue
Baseline normal or elevated ALT and/or AST values	ALT and/or AST > 3 × ULN and > 2 × baseline AND either total bilirubin > 2 × baseline OR INR increase by >0.3 to a value >1.5	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
ALP				

Baseline	Treatment-Emergent (Confirmed[a])	Liver-Related Clinical Symptoms[b]	Action taken	
			Monitoring[c]	Study Drug
Baseline ALP ≤ ULN	ALP > 1.5 × ULN (not due to known bone pathology)	None	Laboratory monitoring and causality evaluation[c]	Continue dosing
		Present	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALP > 1.5 × ULN (not due to known bone pathology) AND total bilirubin > 2 × ULN[f]	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
Baseline ALP > ULN	ALP > 2 × baseline (not due to known bone pathology)	None	Laboratory monitoring and causality evaluation[c]	Continue dosing
		Present	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
	ALP > 2 × baseline (not due to known bone pathology) AND total bilirubin > 2 × ULN[f]	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]

Baseline	Treatment-Emergent (Confirmed[a])	Liver-Related Clinical Symptoms[b]	Action taken	
			Monitoring[c]	Study Drug
Total or Direct Bilirubin				
Baseline total bilirubin ≤ ULN	Total bilirubin > 2 × ULN[f]	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
Baseline total bilirubin > ULN	Total bilirubin > 1.5 × baseline[f]	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
Baseline normal or elevated direct bilirubin	Direct bilirubin > 1.5 mg/dL	With or without liver-related clinical symptoms	Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], and PK sampling	Interrupt dosing[e]
ALT, AST, ALP and Total Bilirubin				
Baseline normal or elevated values	Normal or elevated values	Present	Laboratory monitoring and causality evaluation[c]	Continue or Interrupt dosing as appropriate[g]

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eCRF = electronic case report form; INR = international normalized ratio; PK = pharmacokinetics; ULN = upper limit of normal

[a] The required confirmatory measurement should be obtained within 48-72 hours after the laboratory results become available. If prompt evaluation is not possible, study drug should be interrupted immediately (date of last study drug dose must be recorded in the eCRF).

[b] Combination of clinical signs and symptoms of right upper quadrant pain or tenderness, worsening or new fatigue, anorexia, nausea, rash, vomiting, diarrhea, fever, pruritus, and/or eosinophilia (> 5%).

[c] Frequent hepatic laboratory testing and clinical assessments, including a thorough causality evaluation, should be performed every other week at minimum, in consultation with the sponsor, until resolution of clinical symptoms and/or stabilization of liver biochemistries to baseline levels or baseline grade of abnormality.

[d] The sponsor should be notified of laboratory abnormalities and any clinical symptoms, and participants should be closely monitored until resolution of clinical symptoms/stabilization of liver biochemistries to baseline levels or baseline grade of abnormality.

[e] Study drug must be interrupted (date of last study drug dose must be recorded in the eCRF). The sponsor should be notified of laboratory abnormalities and any clinical symptoms, and participants should be closely monitored until resolution of clinical symptoms/stabilization of liver biochemistries to baseline levels or baseline grade of abnormality. In participants with elevations in liver biochemistry but who do not meet permanent drug discontinuation criteria, study drug may be resumed if it is determined that complete resolution to normal or clinically comparable to baseline levels or baseline grade of abnormality (baseline value will be calculated as the mean of the last two assessments before first administration of the study drug) has occurred and it is not considered that the deterioration in liver function was related to study drug. This must be documented based on biochemical parameters and clinical symptoms, per the discretion of the investigator and in consultation with the sponsor. Restarting study drug is only permitted following an interruption of less than 10 days. The investigator should consider restarting study drug treatment at a reduced dose if possible. If significant liver abnormalities recur at any time after restarting study drug, then study drug must be permanently discontinued.

[f] In participants with emerging evidence of Gilbert's syndrome, in place of the <u>total</u> bilirubin criterion, use <u>direct</u> bilirubin > 2 × baseline.

[g] Development of liver-related clinical symptoms in absence of biochemical abnormalities is an indication for prompt biochemical and physical evaluation to decide whether continued dosing is appropriate. If prompt evaluation is not possible, study drug should be interrupted and participant followed for laboratory monitoring and causality evaluation.

16.2 Appendix 2: Renal safety monitoring

Recommended actions and follow-up assessments regarding renal function data are shown in Table 16-2. If evaluation of a renal event reveals a reversible etiology not related to study drug, the study drug may be restarted as long as the period of interruption is less than 10 days.

Note that the day to day variability of a particular participant's serum creatinine is reflected in the different values measured at screening versus baseline. Because of this, the investigator should use the higher of these two values as the reference against which to compare on-treatment serum creatinines.

Table 16-2 Specific renal alert criteria and actions

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to screening or baseline (whichever is higher)	Confirm 25% increase after 2-5 days. If creatinine does not increase to ≥ 50% compared to screening or baseline, revert to original scheduled sampling schedule. Collect urinalysis. Follow up within 2-5 days thereafter.
Serum creatinine increase ≥ 50 % compared to screening or baseline (whichever is higher)	Confirm > 50 % within 2-5 days after receipt of the abnormal value. If confirmation of abnormal value is not possible in this timeframe, study drug must be withheld until further evaluation is possible. Collect urinalysis. Consider drug interruption. Assess participant for other causes of increased serum creatinine including: starting an ACEI or ARB, starting a nonsteroidal anti-inflammatory, new onset hypovolemia and new onset low blood pressure. Consider participant hospitalization / specialized treatment.
New onset dipstick proteinuria, typically +3 or +4, with a protein-creatinine ratio (PCR) ≥ 1g/g or ≥ 90 mg/mmol	Confirm value after 2-5 days. Collect urinalysis. Assess participant for other causes of increased urine protein including: urinary tract infection, diabetes, strenuous exercise. Consider drug interruption / discontinuation.

17 Cohort-specific information

This section contains details that pertain to specific cohorts and treatment arms and should be considered as supplementary to information presented in the preceding core protocol sections and respective Investigator's Brochures. If there are no cohort- or treatment-specific details presented for a given topic (e.g., cohort- or treatment-specific eligibility criteria, study restrictions, dose adjustment rules), then the information in the corresponding section in the core protocol for that topic should be implemented without further adjustment.

17.1 Cohort 1

Cohort 1 will evaluate the use of LYS006 alone and tropifexor (LJN452) in combination with LYS006 for the treatment of elevated liver fat, liver inflammation and liver fibrosis in NAFLD participants who manifest a NASH-like biomarker phenotype. The drug combination of LYS006 and tropifexor (LJN452) may provide clinical benefit beyond that of either drug alone, considering different, complementary mechanisms of action of these drugs.

Approximately 50 participants will be randomized in a 1:1 ratio to one of the following treatment arms:

- Arm 1: LYS006 Commercially Confidential Information
- Arm 2: Tropifexor (LJN452) Commercially Confidential Information + LYS006 CCI

17.1.1 Cohort 1, Arm 1: LYS006

17.1.1.1 Introduction

This treatment arm will evaluate LYS006 alone.

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17.1.1.3 Rationale for the single treatment

The LYS006 CCI single treatment arm will allow assessment of LYS006 safety, tolerability and efficacy and comparison of data to LYS006 combination in order to determine whether the single agent effects are additive, synergistic or antagonistic.

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17.1.1.6 Drug-drug interaction

Not applicable for this treatment arm.

17.1.1.7 Specific restrictions for study participants

17.1.1.7.1 Prohibited medications

Use of the treatments displayed in Table 17-3 is NOT allowed for this treatment arm for the duration of the prohibited period defined below.

Table 17-3 Prohibited medications Commercially Confidential Information

Medication		Prohibited period start	Prohibited period end
OAT3 inhibitors	CCI	Within 5 half-lives or 7 days of randomization, whichever is longer	End-of-study visit

17.1.1.7.2 Dietary restrictions

There are no specific dietary restrictions.

17.1.1.7.3 Other restrictions

Not applicable.

17.1.1.8 Specific safety stopping rules

Not applicable.

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17.1.1.10 Specific study design considerations

As this treatment does not have an extended half-life, the EOS1 visit will serve as the end-of-study visit for participants randomized to this treatment arm.

17.1.2 Cohort 1, Arm 2: LYS006 and tropifexor

17.1.2.1 Introduction

This treatment arm will evaluate a free combination of LYS006 and tropifexor.

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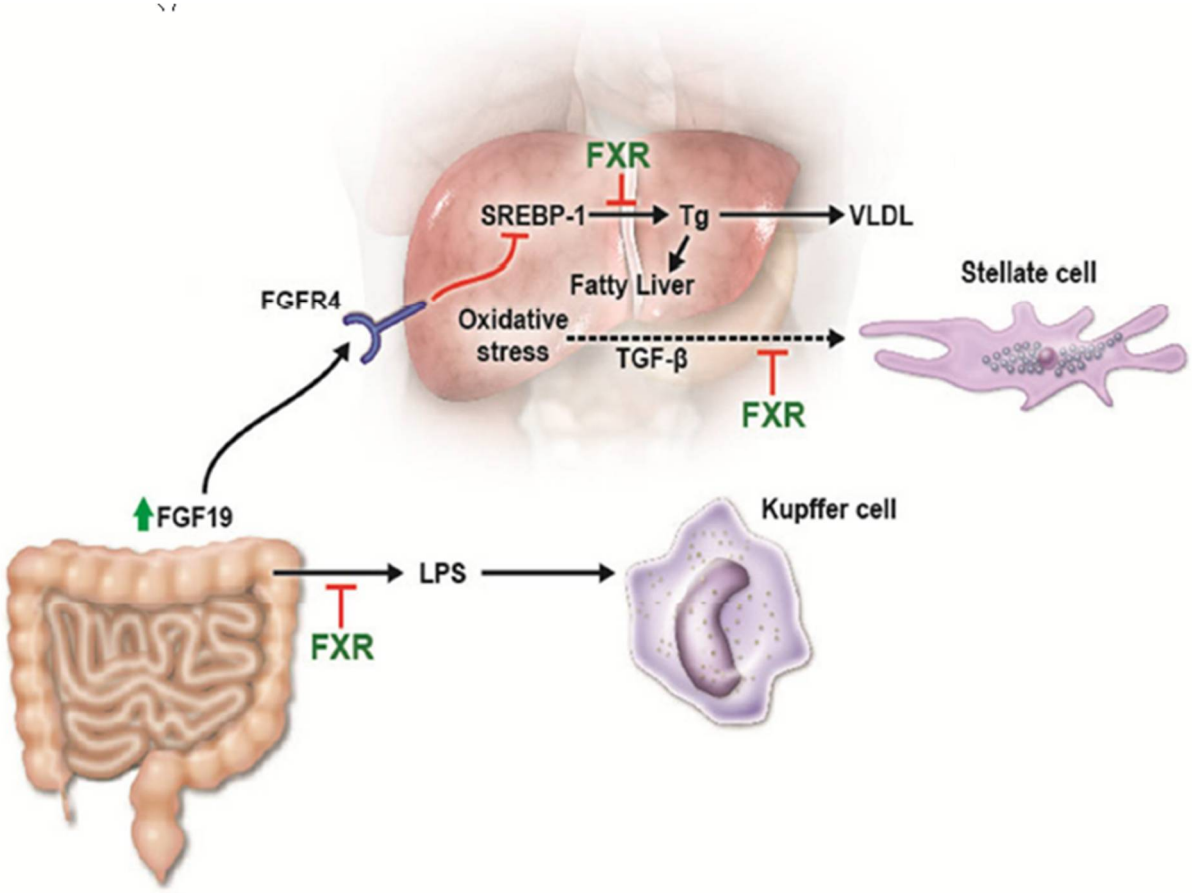
17.1.2.2.2 Tropifexor

Tropifexor, also known as LJN452, is a highly potent, specific and orally available non-bile acid agonist of the bile acid receptor FXR and is currently being evaluated in early phase healthy subject and patient studies.

17.1.2.2.3 Background on FXR receptor

The bile acid receptor, farnesoid X receptor (FXR), is a nuclear receptor expressed in liver, intestine and kidney. FXR acts as a sensor of elevated bile acids and initiates homeostatic responses to control bile acid levels and modulate other metabolic processes such as gluconeogenesis and lipogenesis (Pattni et al 2012, Walters et al 2015). FXR agonism modulates bile acid synthesis and detoxifying metabolism. In the setting of NASH, as shown in Figure 17-2 below, FXR agonism in both the liver and the gut has the potential to provide multimodal benefits which, in brief, include: reduction of fat accumulation in liver via decreased de novo lipogenesis, reduction of hepatic inflammation, anti-fibrotic effects mediated by stellate cells via decreased oxidative stress, and reduction of bacterial and lipopolysaccharide translocation from gut which induces inflammation (Schaap et al 2014).

Figure 17-2 Potential efficacy of FXR agonism in NASH



Adapted from Schaap et al 2014.

Clinical validation of a FXR agonist for the treatment of NASH has been shown in clinical trials with obeticholic acid (OCA), a semi-synthetic variant of the natural bile acid chenodeoxycholic acid. In a small study in 20 patients with NAFLD and type 2 diabetes mellitus in which OCA was given for 6 weeks, OCA 25 mg improved insulin sensitivity and reduced circulating alanine aminotransferase (ALT) concentrations (Mudaliar et al 2013). In a larger trial (n=219), it was shown that 45% of NASH patients receiving 25 mg OCA QD for 72 weeks had improved liver histology compared to 23% of NASH patients receiving placebo in the same period (Neuschwander-Tetri et al 2015). Commercially Confidential Information

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17.1.2.2.5 Tropifexor clinical data

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Tropifexor human safety and tolerability

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Currently participants are receiving monotherapy tropifexor in ongoing studies CLJN452X2201 (Primary Biliary Cholangitis [PBC]), CLJN452X2202 (primary Bile Acid Diarrhea [pBAD]) and CLJN452A2202 (non-alcoholic steatohepatitis [NASH]). Patients are also receiving tropifexor in combination with cenicriviroc in study CLJC242A2201J (NASH) at multiple sites across the world.

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In summary, in clinical studies tropifexor has been well tolerated to date, with doses currently being tested up to 200 µg orally in the ongoing phase 2 NASH program.

Please see the tropifexor Investigator's Brochure for more information on other potential or hypothetical safety risks.

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Tropifexor human efficacy in NASH

Preliminary data from the ongoing Novartis CLJN452A2202 study in patients with NASH provides evidence that tropifexor 90 µg daily for 12 weeks improved liver fat and ALT versus placebo. 140 µg and 200 µg daily doses of tropifexor are under evaluation in this study at the present time.

17.1.2.2.6 Tropifexor dose rationale

The current non-clinical safety profile of tropifexor (tropifexor IB), the DMC's recommendation based on first NASH clinical data and pharmacokinetic data, and clinical data in NASH patients to date from study CLJN452A2202, support evaluation of a tropifexor CCI in this study as outlined below.

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17.1.2.7 Specific restrictions for study participants

17.1.2.7.1 Prohibited medications

Use of the treatments displayed in Table 17-7 is NOT allowed for this treatment arm for the duration of the prohibited period defined below:

Table 17-7 Prohibited medications Commercially Confidential Information

Medication		Prohibited period start	Prohibited period end
OAT3 inhibitors	CCI	Within 5 half-lives or 7 days of randomization, whichever is longer	End-of-study visit

17.1.2.7.2 Dietary restrictions

There are no specific dietary restrictions.

17.1.2.7.3 Other restrictions

Not applicable.

17.1.2.8 Specific safety stopping rules

Not applicable.

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17.1.2.10 Specific study design considerations

As these treatments do not have extended half-lives, the EOS1 visit will serve as the end-of-study visit for participants randomized to this treatment arm.