NOVARTIS

Global Clinical Development - General Medicine

LJC242

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A randomized, double-blind, multicenter study to assess the safety, tolerability, and efficacy of a combination treatment of tropifexor (LJN452) and cenicriviroc (CVC) in adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis (TANDEM)

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List of abbreviations

A14	Inducible cytokine Alpha - 14
A1AT	Alpha-1-antitrypsin
A2	Inducible cytokine Alpha - 2
ACR	Albumin-creatinine ratio
AE	Adverse Event
AHA	American Heart Association
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMA	Anti-mitochondrial antibodies
ANA	Anti-nuclear antibodies
ANIT	Alpha-Naphtha Isothiocyanate
[redacted]	[redacted]
APTT	Activated Partial Thromboplastin Time
ASMA	Anti-smooth muscle antibody
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area Under Curve
AUDIT	Alcohol Use Disorders Identification Test
AV block	Atrioventricular Block
b.i.d.	twice a day
[redacted]	[redacted]
BSEP	Bile Salt Export Pump
BSL	Baseline visit
BUN	Blood Urea Nitrogen
[redacted]	[redacted]
C5M	Neo-epitope of MMP-2,9 mediated degradation of type V collagen
C6M	Neo-epitope of MMP-2 mediated degradation of type VI collagen
CAP	Controlled attenuation parameter
CCR2	C-C Motif Chemokine Receptor Type 2
CCR5	C-C Motif Chemokine Receptor Type 5
CD14	Cluster of differentiation 14
CDT	Carbohydrate deficient transferrin
CFR	US Code of Federal Regulations
[redacted]	[redacted]
Cmax	Maximum drug concentration
CPO	Country Pharma Organization
CRN	Clinical Research Network
CRO	Contract Research Organization
[redacted]	[redacted]
CSR	Clinical Study Report
CV	Central Vein

[redacted]

CVC	Cenicriviroc Mesylate
CYP3A4	Cytochrome P450 3A4
CYP7A1	Cytochrome P450 7A1
CYP2C8	Cytochrome P450 2C8
DBP	Diastolic Blood Pressure
DDI	Drug Drug Interaction
DMC	Data Monitoring Committee
[redacted]	[redacted]
EC50	Half Maximal Effect Concentration
eCRF	electronic Case Report Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
[redacted]	[redacted]
EMA	European Medicines Agency
EOT	End of treatment
EOS	End of study
eSource	Electronic Source
FAS	Full analysis set
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FXR	Farnesoid X Nuclear Receptor
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLP	Good Laboratory Practice
GLP-1	Glucagon-like Peptide-1
HA	Hyaluronic acid
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
hCG	Human Chorionic Gonadotropin
HCVAb	Hepatitis C virus antibody
[redacted]	[redacted]
HIV	Human Immunodeficiency Virus
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed Consent Form

[redacted]

ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
[redacted]	[redacted]
IN	Investigator Notification
INR	International Normalized Ratio
IQR	Interquartile range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine system
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
[redacted]	[redacted]
LLOQ	Lower limit of qualification
[redacted]	[redacted]
LT	Liver test
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial Infarction
[redacted]	[redacted]
NAFLD	Non-alcoholic Fatty Liver Disease
[redacted]	[redacted]
NASH	Nonalcoholic Steatohepatitis
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OCA	Obeticholic acid
[redacted]	[redacted]
PBC	Primary Biliary Cholangitis
PCR	Protein-creatinine ratio
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
PRO	Patient Reported Outcomes
[redacted]	[redacted]
PSC	Primary Sclerosing Cholangitis
PT	Prothrombin Time/Portal Triad
PUFA	Polyunsaturated Fatty Acids
QM	Quality Management
QTcF	Corrected QT interval (Fridericia method)
RAN	Randomized set
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAF	Safety set
SBP	Systolic Blood Pressure
sCD163	Soluble Cluster of differentiation 163
sCr	Serum Creatinine
SCR	Screened set
SHP	Small Heterodimer Partner
SAE	Serious Adverse Event
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
T2DM	Type-2 Diabetes Mellitus
TBL	Total Bilirubin
TEAE	Treatment-emergent Adverse Event
TD	Treatment Discontinuation
TG	Triglycerides
[redacted]	[redacted]
[redacted]	[redacted]
TT	Thrombin Time
UGT1A1	UDP Glucuronsyltransferase 1 Family, Polypeptide A1
UGT	UDP Glucuronsyltransferase
ULN	Upper Limit Normal
[redacted]	[redacted]
WBC	White Blood Cells
WHO	World Health Organization
[redacted]	[redacted]
WoC	Withdrawal of Study Consent
yGT	y-Glutamyltranspeptidase

[redacted]

Glossary of terms

Control drug	Drugs(s) 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
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg b.i.d).
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol).
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulations (CFR) 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject Identification (ID)	A unique number assigned to each patient upon signing the informed consent.
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.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment.
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy.
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data.

[redacted]

Amendment 3

Amendment rationale

The conduct of clinical trials has been impacted by the COVID-19 pandemic and related measures including national goverment mandates, closures of local hospitals and research facilities, reassigment of research personnel, patient travel restrictions and delays in the shipment of study treatment and trial supplies.

The purpose of this amendment is to implement a plan for treatment continuity, patient safety monitoring and maintaining the integrity of the trial. The implemented measures are only for the period of the COVID-19 pandemic, and standard visit schedule and assessments as outlined in Table 6-1 should resume as soon as patients are able to visit study sites and undergo all end of treatment assessments

At the time of amendment (V03) release, enrollment is completed with 193 patients randomized.

Changes to the protocol

This amendment provides the option to extend the study treatment for patients who are unable to come to site for the week 48 visit as scheduled due to COVID-19 pandemic restrictions.

The changes to specific sections of the protocol are as below:

- Section 3.6: Updated to clarify the possible benefits and risks of longer study treatment
- Section 5.5.2: updated to include the stepwise approach to extend study treatment for patients who are unable to come to the study site for their Week-48, End of treatment (EOT) visit as scheduled per study protocol due to COVID-19 pandemic related restrictions
- Section 6 and table 6.1: updated to include remote consultation for patients who are unable to come to the study site for their study visits (except week-48, End of treatment visit) as scheduled per study protocol due to COVID-19 pandemic related restrictions. The footnotes revised to clarify the instructions for urine pregnancy test and study treatment extension.
- Section 9.5.1: updated to clarify analysis plan for the delayed Week 48, End of Treatment (EOT) visits due to COVID-19 pandemic related restrictions

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. This amendment is required to ensure trial continuity due to COVID-19 pandemic and related measures, therefore it will be implemented prior to Health Authority and IRB/IEC approval.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 2

Amendment rationale

Based on feedback received from Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), the protocol has been amended to address the recommendations as indicated below;

- [redacted]
- Section 6, Table 6-1: The footnotes are revised to clarify the instructions for liver biopsy [redacted]
- Section 6.5.6 and Table 6-1: Monthly pregnancy test is required during the study and updates to specify the instructions for urine pregnancy test

In addition, further clarifications and corrections were made as specified below:

- Section 4.2, exclusion criteria 4: updated to clarify that patient may be considered if patient received only placebo in previous trial
- Section 4.2, exclusion criteria 14: corrected the unit for serum albumin to g/dL instead of mg/dL
- Section 5.5.9: Added instructions for emergency code break
- Section 6, Table 6-1: updates to assessment schedule to align with the protocol descriptions
    - Added exercise assessment in the schedule of assessment to be consistent with Section 5.5.4.1
    - [redacted]
- Section 6.1.1 added to include optional pre-screening assessments
- [redacted]
- Section 7.2 updated to include SAE reporting for pre-screening
- Section 16, Table 14-1: Editorial correction to the threshold for AST and ALT baseline value to read, "ALT and/or AST > 3 × ULN but ≤ 5 × baseline AND total bilirubin > 2 × ULN"
- Minor changes (typographical and corrections) throughout the document.

At the time of amendment (V02) release, enrollment is ongoing with 57 patients screened and 9 patients randomized. A copy of this amended protocol will be sent to the IRB/IEC and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent Form (ICF) and requires an additional optional pre-screening ICF. Sites are required to update and submit for approval a revised ICF and pre-screening ICF that takes into account the changes described in this protocol amendment.

[redacted]

Amendment 1

Amendment rationale

Amendment 1 implements recommendations from the US FDA. In addition, clarifications and corrections were made. At the time of this amendment (V01) release, the study has not started and no patients were enrolled.

The major modifications to the protocol are:

- Section 1: Updates were done to include information for tropifexor, cenicriviroc and the combination, including non-clinical data, clinical pharmacology data, toxicology data, combination safety considerations, drug-drug interaction data for the combination and the rationale for use of the combination in this study.
- Section 4.2 Exclusion criteria 14: Revised cut-off values for total bilirubin and alkaline phosphatase. The units are now consistently stated in mg/dL. Exclusion criteria 25: Revised platelets limit.
- Section 5.5.8.1: Revised dose limit for rosuvastatin and simvastatin to 10 mg daily, since CVC co-administration may increase their exposure and added the caution to monitor closely.
- [redacted]

Additional clarifications and corrections are:

- [redacted]
- Section 3.1: Updated the duration of screening period in figure 3-1 to be consistent with schedule of assessments
- [redacted]
- [redacted]
- Section 8.5: Added the provision of adjudication of possible drug related liver injury cases
- Section 12: References updated
- [redacted]
- Minor changes (typographical and corrections) throughout the document.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation. The changes herein do not affect the Informed Consent.

[redacted]

Protocol summary

Protocol number	CLJC242A2201J
Full Title	**A randomized, double-blind, multicenter study to assess the safety, tolerability, and efficacy of a combination treatment of tropifexor (LJN452) and cenicriviroc (CVC) in adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis (TANDEM)**
Brief title	Study of safety, tolerability, and efficacy of a combination treatment of tropifexor and cenicriviroc in adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis
Sponsor and Clinical Phase	Novartis Phase 2b
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the safety, tolerability, efficacy [redacted] of two regimens of tropifexor and cenicriviroc (CVC) (further described as tropifexor + CVC) compared to monotherapies tropifexor and CVC in patients with NASH and liver fibrosis.
Primary Objective(s)	The primary objective of this study is to evaluate the safety and tolerability of tropifexor + CVC in patients with NASH with fibrosis stage F2/F3 by monitoring adverse events, vital signs and laboratory values during 48 weeks of treatment as compared to monotherapy with each of tropifexor and CVC
Secondary Objectives	To characterize the efficacy of different doses of the combination drug tropifexor + CVC in patients with NASH with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) compared to baseline biopsy.
Study design	This study is a randomized, double-blind, multicenter study to evaluate the safety and tolerability of tropifexor + CVC as compared to monotherapy with each of tropifexor and CVC.
Population	Adult male and female patients with histologic evidence of NASH with stage 2 or 3 fibrosis based on centrally-read liver biopsy. The study will include a total of approximately 200 patients.
Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed. • Male and female patients 18 years or older (at the time of the screening visit). Patients must weigh at least 50 kg (110 lb) and no more than 200 kg (440 lb) to participate in the study. • Adequate liver biopsy sample for evaluation by a central reader. • Presence of NASH as demonstrated by histologic evidence based on liver biopsy - NASH with fibrosis stage F2/F3, demonstrated on liver biopsy during the screening period. Alternatively, a historical biopsy can be used if performed within 6 months prior to screening, if: ❖ the patient has been receiving any of the therapies listed in Table 5-4, the dose must have been stable (since 1 month before the biopsy up to and including screening), ❖ the patient's weight has been stable (maximum weight loss of 10% since biopsy up to and including screening).

[redacted]

Key Exclusion criteria	• Previous exposure to elafibranor, CVC, tropifexor, obeticholic acid (OCA), LMB763 or any other FXR agonist. • Participated in a clinical trial and treated with any investigational product being evaluated for the treatment of liver fibrosis or NASH in the 6 months before screening (subjects documented to be assigned to placebo in such trials may be eligible immediately following completion of their participation in the previous trial). • Patients taking medications prohibited by the protocol. An overview of prohibited medications is given in Table 5-2, and the summary of medications permitted only if on stable dose is in Table 5-4 • Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the modified AUDIT questionnaire ≥ 8 • Uncontrolled diabetes defined as glycated hemoglobin (HbA1c) ≥ 9% at screening • Patients who are not candidates for liver biopsy • Presence of cirrhosis on liver biopsy or medical history
Study treatment	Tropifexor 140 µg once daily, CVC 150 mg once daily, tropifexor 140 µg + CVC 150 mg once daily and tropifexor 90 µg + CVC 150 mg once daily
Efficacy assessments	• Liver histology (biopsy) [redacted] • Liver tests • Coagulation test [redacted]
Key safety assessments	• Adverse events monitoring • Monitoring of laboratory markers in blood and urine • ECG • Vital signs • Physical examinations
Other assessments	[redacted]
Data analysis	There are no pre-specified hypotheses and statistical models in this study. The analysis of primary variables will be based on descriptive statistics (summary table of absolute and relative adverse event frequencies, summary tables of laboratory parameters and vital signs).

[redacted]

	There is a single secondary objective in this study which is to characterize the efficacy of tropifexor + CVC as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) relative to baseline biopsy. There are two estimands that will be used to evaluate this objective. The first estimand is the difference on the proportion of patients on the different tropifexor + CVC regimens who achieve at least a one point improvement in fibrosis at Week 48 compared to tropifexor and CVC monotherapy patients. The second estimand is the difference in the proportion of patients on the different tropifexor + CVC regimens who achieve resolution of steatohepatitis at Week 48 relative to baseline compared to tropifexor and CVC monotherapy patients. Differences between tropifexor + CVC combination therapy and monotherapy with tropifexor or CVC with respect to these proportions (response rates) will be evaluated using a Cochran-Mantel-Haenszel test controlling for baseline fibrosis stage (F2/F3). The estimand will be evaluated in the FAS population.
Key words	Tropifexor, LJN452, cenicriviroc, CVC, non-alcoholic steatohepatitis, NASH, phase 2, liver biopsy, randomized

[redacted]

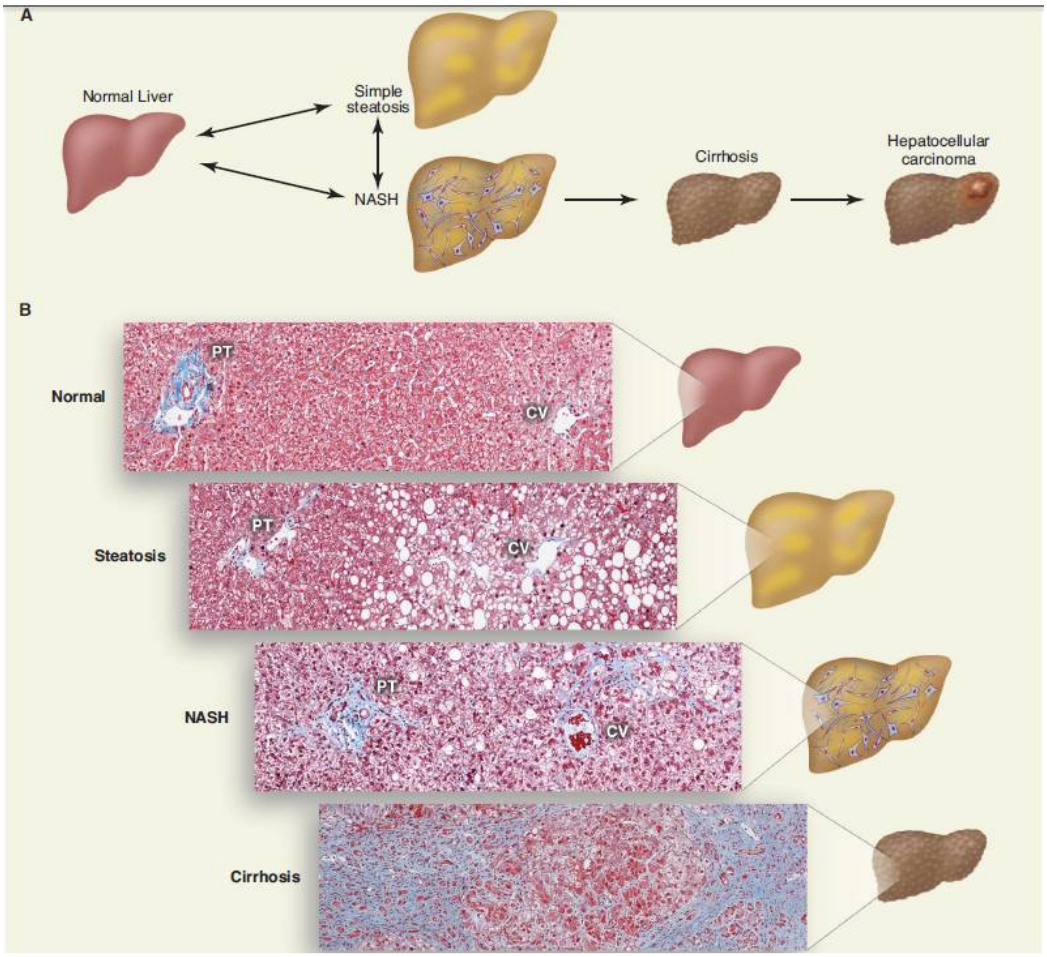
1 Introduction

1.1 Background

Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis

Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in developed countries with a global prevalence of 25% (Younossi ZM 2011, Cohen JC 2011, Younossi et al 2016). NAFLD is often a "silent" liver disease and usually associated with obesity, Type-2 diabetes mellitus (T2DM), dyslipidemia, hypertension and metabolic syndrome. Although most patients with NAFLD have a benign course, a subset of these patients may have the more severe and progressive form of NAFLD called nonalcoholic steatohepatitis (NASH), which is characterized by the presence of ballooning degeneration and lobular inflammation with or without perisinusoidal fibrosis in addition to steatosis.

Figure 1-1 Schematic progression of NAFLD/NASH



The disease spectrum of nonalcoholic fatty liver disease. (A) Schematic of progression of NAFLD. The accumulation of Triglycerides (TG) within lipid droplets in hepatocytes causes steatosis. Steatosis associated with inflammation, cell death, and fibrosis is referred to as NASH, which can progress to

cirrhosis. Individuals with cirrhosis have an increased risk of hepatocellular carcinoma (HCC). (B) Histological sections illustrating normal liver, steatosis, NASH, and cirrhosis. Collagen fibers are stained blue with Masson's trichrome stain. The portal triad (PT), which consists of the hepatic artery, portal vein, and bile duct, and the central vein (CV) are shown (Figure from Cohen JC 2011).

The projected estimate of NASH with advanced fibrosis is approximately 4.1 million adults in the US. (Kabbany MN 2017). Estimates vary due to the diagnostic modality used, study heterogeneity, but also the region of the world studied. Among NAFLD patients, NASH estimates are 29%-59% in North America. In the overall global population, NASH prevalence is 3.8% (3-6.45%) (Foster et al 2012, Younossi et al 2016). Patients with NASH can progress to cirrhosis, liver decompensation, hepatocellular carcinoma (HCC), need for a liver transplantation, and are at increased risk of death from liver disease. The incidence of advanced liver disease, liver failure and HCC related to NAFLD/NASH are increasing dramatically and NASH is projected to become the most common indication for liver transplantation (Beste LA 2015, Wong 2015, Neuschwander and Tetri B 2003). NASH is the cause of progressive fibrosis in the patients with NAFLD. Fibrosis is the most important histological feature associated with all-cause mortality (e.g. cardiovascular disease) and liver complications in NASH (Angulo 2015, Ekstedt 2006). Despite recent improvements in soluble biomarkers, liver biopsy is still the gold standard for diagnosing NASH and assessing the stage of fibrosis in patients with NAFLD. Of note, rapid progressors may proceed to develop cirrhosis in only a 10-year period (Singh S 2015). Reducing liver fibrosis is expected to improve the long-term clinical outcomes of patients with NASH (Ratziu V 2015).

There are no globally approved treatments for NASH. Several studies have been conducted with Vitamin E and thiazolidinediones, but no long-term benefits have been demonstrated. There are potential new therapies being evaluated, currently in phase II or III trials, but the reported efficacy from the available studies are still lacking substantial benefit. The significant global burden of NASH, the currently available study results especially when considered with multifactorial etiology of NAFLD/NASH suggests that combination therapy of different mechanisms of actions will be a more effective therapy for NASH patients.

Farnesoid X receptor: tropifexor

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 (Figure 1-1) (Pattni et al 2012, Walters et al 2015). In the liver, FXR agonism modulates bile acid synthesis and detoxifying metabolism. FXR agonist increases expression of genes involved in canalicular and basolateral bile acid efflux and bile acid detoxifying enzymes while inhibiting basolateral bile acid uptake by hepatocytes and inhibiting bile acid synthesis (Calkin and Tontonoz 2012). FXR activation represses bile acid synthesis in the liver through induction of Small Heterodimer Partner (SHP), which is a negative regulator of CYP7A1, the rate-limiting enzyme of the neutral bile acid biosynthetic pathway (Goodwin et al 2000). Furthermore, FXR agonists increase excretion of bile acids through the kidney, increase bile acid binding proteins in the ileum and stimulate FGF15 (in rodents) or FGF19 (in humans) expression (a key regulator of bile acid metabolism).

[redacted]

Pharmacological activation of the farnesoid X nuclear receptor (FXR) has been proposed as a target for the treatment of NASH (Cariou 2008, Porez et al 2012). Clinical validation of an 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 patients with NAFLD and Type 2 diabetes mellitus in which OCA was given for 6 weeks, it was shown that OCA improved insulin sensitivity and reduced circulating alanine aminotransferase (ALT) concentrations (Mudaliar et al 2013).

In a larger trial, it was shown that 45% of NASH patients receiving 25 mg OCA once daily for 72 weeks had improved liver histology compared to 23% of NASH patients receiving placebo in the same period (Neuschwander and Tetri et al 2015).

Tropifexor is a highly potent, specific and orally available non-bile acid agonist of the bile acid receptor FXR and is currently being evaluated in phase II patient studies. The Investigator's Brochure (tropifexor IB) provides a detailed review of the pre-clinical and clinical information on tropifexor available to date.

Assessment of tropifexor in non-clinical studies

Tropifexor is a potent and selective non-steroidal FXR agonist with an EC_{50} of 0.32 nM in a cell-based FXR reporter gene assay and in a biochemical co-activator interaction assay with >30,000 fold selectivity over other nuclear receptors (ERα, GR, LXRα, PPARγ, RXR, and PXR). Single and repeat oral dosing lead to dose-dependent increases in FXR target genes (e.g. liver BSEP and SHP, ileum SHP and FGF15). Moreover, tropifexor protects rats from ANIT-induced cholestasis in a chronic setting. The major glucuronide metabolite found in humans, (CKS577) is approximately 10-fold less potent compared to tropifexor and about 50% in maximal efficacy in cellular studies.

[redacted]

[redacted]

In conclusion, the no observed adverse effect level (NOAEL) was 0.03 mg/kg/day in both the 26-week rat and the 39-week dog toxicity studies. The highest anticipated systemic exposure of around AUC0-24h 60 ng.hr/mL in study CLJC242A2201J is expected at the maximal proposed clinical dose of 140 µg in the monotherapy arm. This exceeds the exposure measured at the rat NOAEL (mean AUC0-24h 27.1 ng.hr/mL) but is well below the exposure measured in dogs at the NOAEL (mean AUC0-24h 274 ng.hr/mL). Based on the nature of the non-clinical findings, their monitorability and reversibility and the fact that the dog appears to be the most relevant species for risk assessment, the intended clinical trial design, is not considered to pose an undue risk to subjects.

[redacted]

No meaningful off-target or central nervous system effects have been identified *in vitro* from the receptor binding profile.

In safety pharmacology studies, tropifexor did not cause meaningful effects on the main cardiac ion channels *in vitro* or alter vital functions (body temperature; respiratory, cardiovascular and central nervous systems) in rats and dogs.

Tropifexor showed no genotoxic potential *in vitro* and *in vivo*. Also tropifexor showed no phototoxicity potential *in vitro*.

Embryo-fetal toxicity studies have been completed in rats and rabbits. In rats, tropifexor showed no effect on embryo-fetal development or pregnancy parameters at up to 1.0 mg/kg/day. In rabbits, tropifexor was toxic to the embryo/fetus and teratogenic at maternally-toxic doses ≥ 1 mg/kg/day, the no observed effect level (NOEL) was 0.3 mg/kg/day.

Assessment of tropifexor in clinical studies

Pharmacokinetic, safety and tolerability data are available from the First-in-Human study CLJN452X2101 [redacted]

No safety concerns were identified in single dose studies up to 3000 µg tropifexor. [redacted]

Part A of the ongoing phase 2 study CLJN452A2202 in NASH patients has been analyzed. A robust dose-dependent effect on reducing GGT, ALT and AST was observed. No safety concerns were identified with doses ranging from 10 to 90 µg orally once daily for 12 weeks. The DMC for study CLJN452A2202, upon review of CLJN452A2202 Part A data, recommended to investigate doses higher than 90 µg. Thus, 90 µg and 60 µg were tested in Part B (ongoing), and 140 µg and 200 µg are currently used in Part C.

[redacted]

Part 1 of the CLJN452X2201 study in PBC patients is ongoing. No safety concerns were identified with doses ranging from 30 to 90 µg orally once daily for 4 weeks.

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.

C-C chemokine receptor type 2 and type 5 inhibitor: cenicriviroc

Cenicriviroc mesylate (CVC) is an oral, dual antagonist of C-C motif chemokine receptor types 2 and 5 currently in clinical development for the treatment of liver fibrosis in adult patients with NASH. The Investigator's Brochure (CVC IB) provides a detailed review of the pre-clinical and clinical information on CVC available to date.

Human pharmacokinetic and pharmacodynamic as well as safety and tolerability data are further described in the CVC IB. Briefly, CVC has demonstrated antifibrotic activity in animal models of liver and renal fibrosis (Lefebvre et al 2016). Preclinical (Lefebvre et al 2016, Puengel et al 2016, Tacke et al 2015, Mossanen et al 2016) and clinical evidence (Friedman et al 2017, Lefebvre et al 2016, Thompson et al 2016) support its anti-inflammatory and antifibrotic properties, which are mediated by C-C motif chemokine receptor types 2 and 5 blockade.

The mechanism of action of CVC, as an anti-inflammatory and anti-fibrotic agent, supports its use in liver diseases, such as liver fibrosis associated with NASH. CVC treatment decreases the recruitment and migration of CCR2-expressing monocytes to the site of liver injury, mainly via CCR2 antagonism, thereby reducing the infiltration of pro-inflammatory, monocyte-derived macrophages into the liver (Krenkel O 2017). In addition, CCR5 antagonism by CVC is expected to impair the migration, activation, and proliferation of collagen-producing activated hepatic stellate cells and myofibroblasts, therefore reducing fibrogenesis.

Assessment of cenicriviroc in non-clinical studies

In vitro data with CVC have demonstrated that it blocks the binding of C-C motif chemokine ligand 2 (CCL2; also known as monocyte chemotactic protein 1 [MCP-1]) to CCR2, and also blocks the binding of CCR5 ligands, CCL3 (also known as macrophage inflammatory protein [MIP]-1α, CCL4 (also known as MIP-1β and CCL5 (also known as regulated on activation normal T-cell expressed and secreted [RANTES]), to CCR5. Ex vivo experiments showed that nanomolar concentrations of CVC achieved 98% receptor occupancy of CCR2 on human monocytes and ~90% receptor occupancy for CCR5 on human CD4+ and CD8+ T-cells. Additionally, CVC was an efficient inhibitor of monocyte and human lymphocyte (primarily T-cells) migration in vitro. CVC's anti-inflammatory and antifibrotic effects have been evaluated in a range of nonclinical models of inflammation and fibrosis, and has demonstrated activity in multiple animal fibrosis models.

The effects of CVC on the central nervous, cardiovascular, and respiratory systems were examined in a core battery of safety pharmacology studies. CVC at oral doses up to 1600 mg/kg had no effects on the general physical condition or behavior of rats. CVC had no significant effects on blood pressure, heart rate, body temperature, or electrocardiogram (ECG) parameters (including PR interval, QRS duration, QT interval, and corrected QT interval) at

[redacted]

oral doses up to 2000 mg/kg in cynomolgus and no effects on the respiratory rate, tidal volume, minute volume, or enhanced pause (Penh) up to 24 hours post-dose.

Toxicology studies showed no target organ toxicity, thus no adverse liver findings, in mice or monkeys. In rats, the liver was the primary target organ identified in repeat dose studies, with biliary hyperplasia being the primary finding. Overall, the risk for hepatobiliary effects due to CVC appears to be low. The nonclinical data suggest that CVC will not adversely affect the liver at or near clinical exposures. Liver findings were present in only 1 of 3 species and when present, a high safety margin was apparent (>27-fold). CVC was not genotoxic, and did not adversely affect fertility or embryofetal development (refer to CVC IB for further details).

Assessment of cenicriviroc in clinical studies

Overall, as of January 2018, approximately 1154 participants have been exposed to CVC in completed and ongoing clinical studies (January 2018 Development Safety Update Report cutoff). CVC doses ranged from 25 mg to 900 mg across all CVC studies. There was no apparent dose- or exposure-relationship for safety.

- Overall, CVC was generally well tolerated in the Phase 1 studies evaluating single doses of CVC up to 900 mg and at multiple daily doses of up to 900 mg for ≥7 days.
- In participants with mild to moderate hepatic impairment, CVC 150 mg QD for 14 days was generally well tolerated regardless of level of hepatic impairment, and no safety concerns were identified in this population.
- In the Phase 1 studies, most adverse events (AEs) were mild or moderate in severity. The most commonly observed AEs (≥ 2%) with CVC in single-dose studies were headache, nasopharyngitis, all abdominal pain, nausea, vomiting, diarrhea, contact dermatitis, and somnolence. The most commonly observed AEs (≥ 2%) with CVC in multiple-dose studies were headache, and constipation.
- In the CENTAUR Phase 2b study in adult participants with NASH with liver fibrosis, CVC appears to be safe with no notable differences observed compared to previous clinical studies in incidence of treatment-emergent AEs and laboratory abnormalities, including liver transaminase elevations, which were generally similar between treatment groups. Safety findings in CENTAUR were consistent with that of the extensive clinical experience with CVC, including the Phase 2 HIV studies.

Study 652-2-203 (CENTAUR) is a 2-year placebo-controlled Phase 2b study in 289 adult participants with liver fibrosis and NASH. Enrollment completed in June 2015 and Year 2 database lock was performed on 22 August 2017. In CENATUR, the Year 1 primary endpoint of NAFLD Activity Score (NAS) improvement by at least 2 points (and no worsening of fibrosis) in the intent-to-treat (ITT) population and the key secondary endpoint of resolution of steatohepatitis (and no worsening of fibrosis) was achieved in a similar proportion of subjects on CVC (N = 145) and placebo (N = 144) (16% vs 19%, p = 0.52 and 8% vs 6%, p =0.49, respectively). However, the fibrosis endpoint (i.e., improvement in fibrosis by at least 1 stage and no worsening of steatohepatitis) was met in twice as many subjects on CVC than placebo in the ITT population (20% vs 10%; p = 0.02). At Year 1, a higher proportion of participants in the CVC group (29%) compared with the combined placebo group (19%) had an improvement of at least 1 stage at Year 1 per the NASH CRN staging system. Similarly, a higher proportion of participants in the CVC group (35%) compared with the combined

placebo group (22%) had an improvement of at least 1 stage at Year 1 per the Ishak fibrosis staging system. Treatment benefits were greater in those with higher disease activity and fibrosis stage at baseline. Biomarkers of systemic inflammation were reduced with CVC. In summary, CVC showed a clinically meaningful antifibrotic benefit and anti-inflammatory activity in NASH patients with liver fibrosis.

To determine the durability of histological improvement achieved after 1 year of treatment, improvement in fibrosis by ≥ 1 stage was assessed in subjects with available biopsy results at all 3 timepoints (baseline, Year 1, and Year 2). Results from this analysis showed that the proportion of subjects in the CVC group who achieved improvement in fibrosis by ≥ 1 stage at the end of Year 1 and maintained this benefit at Year 2 was twice the proportion of subjects in the placebo group (60% versus 30%, respectively). The durable antifibrotic effect of CVC was also more apparent in the subgroup of subjects with Stage 3 fibrosis at baseline, for which the antifibrotic benefit at Year 2 was maintained in 86% of subjects in the CVC group versus 60% in the placebo group. Furthermore, in the subgroup of subjects with fibrosis Stage 2 or 3 at baseline, a higher proportion of subjects receiving CVC achieved a ≥ 2-stage improvement in fibrosis (and no worsening of steatohepatitis) at Year 2 relative to subjects receiving placebo (9.3% in the CVC group versus 2.7% in the placebo group, from baseline to Year 2). When only subjects with Stage 3 fibrosis at baseline were included in the analysis, 14.0% of subjects receiving CVC versus 4.2% of subjects receiving placebo for 2 years achieved a ≥ 2-stage improvement in fibrosis (and no worsening of steatohepatitis) at Year 2. CVC had a generally comparable safety and tolerability profile to placebo over 2 years. Overall, the results from the final Year 2 analysis confirmed the clinically meaningful antifibrotic effect of CVC treatment observed in the Year 1 primary analysis (Ratziu et al 2018).

Given that severity of fibrosis stage has been shown to be the only histological feature independently associated with clinical outcomes over the long term, these results provide additional evidence of the potential of CVC as a safe and efficacious pharmacologic treatment for liver fibrosis in adults with NASH.

In CENTAUR, the safety profile of CVC (150 mg QD) was comparable to that in participants treated with placebo and was well tolerated over 2 years. The types, severity, and frequency of TEAEs reported after 2 years of CVC treatment was consistent with those reported after 1 year of treatment. The overall incidence of TEAEs during the study was similar across the treatment groups (≥ 95.0% of participants in each group). No deaths occurred during the study. The frequency and types of TEAEs reported were comparable between treatment groups during Year 1 and Year 2.

- The frequency of treatment-related events reported after 2 years of CVC treatment was comparable to that reported after 1 year of treatment (41.7% vs 42.1%).
  - The most frequently reported drug-related TEAEs of at least Grade 2 severity through 1 year of treatment were fatigue (2.8%) and diarrhea (2.1%) in the CVC arm and headache (3.5%) in the placebo arms.
  - The most frequently reported study drug-related TEAEs of at least Grade 2 severity through 2 years of treatment were fatigue (5.0%) in the CVC/CVC group, headache

[redacted]

in the placebo/CVC group (6.6%), and ALT increased (3.3%) in the placebo/placebo group.

- For participants who crossed-over from placebo and received CVC for 1 year, the frequency of TEAEs reported (44.3%) was similar to that reported in participants who received 1 year CVC during Treatment Period 1 of the study (41.7%). A smaller number of participants experienced TEAEs that resulted in discontinuation of study drug.
- After 2 years of CVC treatment, the number of participants who discontinued the study due to a TEAE was greater than that reported for participants treated with 2 years of placebo (4.1% vs 0), but was comparable to that reported after 1 year of treatment (6.3%).
  - The only AE leading to discontinuation, regardless of causality, reported in at least 2 participants in the CVC/CVC group was ALT increased (3 participants, 2.5%); all were Grade 3 severity.
- Although the number of participants who experienced serious adverse events (SAEs) increased after 2 years of CVC treatment compared to placebo (18.2% vs 11.8%), almost all were considered not-related to study drug and did not lead to study discontinuation.
- Only 1 participant experienced a study drug-related event (Grade 3 heart arrhythmia), and only 1 event led to discontinuation (Grade 3 congestive heart failure considered not related to study medication).
- With the exception of treatment-emergent Grade 3 and 4 amylase elevations and Grade 4 lipase elevations observed more frequently in the CVC arms versus the placebo arm (3.3% versus 1.7%, 2.2% versus 0.0%, and 21.1% versus 16.7%, respectively), the incidence of treatment-emergent Grade 3 or 4 laboratory results were generally similar between the CVC arms and the placebo arm
- No meaningful changes in vital signs or anthropometric parameters were observed.
- Overall, the proportion of participants with confirmed liver transaminase elevations that met protocol-defined biochemical criteria for suspected drug-induced liver injury was 9.7% in the CVC group and 7.6% in the placebo group during the first year of treatment. The frequency did not increase in CVC-treated participants in Arm A after an additional year of treatment with CVC. No cases of Hy's law were observed in the study. Among the participants who met the criterion for suspected drug induced liver injury, 2 hepatobiliary adverse events of autoimmune hepatitis were reported during Year 1 (1 participant in the CVC Arm A and 1 participant in the placebo Arm C). These participants did not continue onto treatment during Year 2. In addition, a case of possible autoimmune hepatitis was observed upon liver biopsy (1 subject in CVC Arm A, event not reported as an AE or SAE by the investigator). No cases of autoimmunehepatitis were observed during Year 2 of the study.
- There have been no deaths related to CVC treatment.

Based on the results of CENTAUR, the Phase 3 AURORA study was initiated in April 2017 to study the antifibrotic benefit of CVC as compared with placebo in adults with NASH and Stage 2 or 3 fibrosis. CVC is currently also in Phase 2 development in subjects with primary sclerosing cholangitis (PSC).

[redacted]

In over 1000 subjects treated, including those with NASH and liver fibrosis, HIV-1 infection, and cirrhotics with hepatic impairment, CVC demonstrated good safety and tolerability (Abdelmalek M et al 2017, CVC IB), supporting evaluation in combination therapy with tropifexor for the treatment of liver fibrosis associated with NASH.

This study is the first study with a combination of tropifexor and CVC in patients with biopsy confirmed NASH and it aims to assess safety and tolerability as well as efficacy after daily dosing for 48 weeks.

Tropifexor and cenicriviroc (combination) pre-clinical data

A preclinical animal study investigating the potential additive effects of CVC and tropifexor in STAM mouse models of diet induced NASH, shows that combination therapy of tropifexor and CVC further improved steatosis, ballooning, and inflammation as measured by NAS vs. vehicle when compared to either agent as monotherapy (Laffitte B, AASLD 2017 abstract # P-2052). The combination of tropifexor and CVC was associated with more pronounced reductions in lobular inflammation and hepatocellular ballooning. Tropifexor, CVC, and the combination all reduced fibrosis to a similar extent vs. vehicle. These preclinical combination data supports further evaluation in humans.

Tropifexor and cenicriviroc (combination) toxicology data

In accordance to the International Conference on Harmonization (ICH) guidance on non-clinical safety studies (ICH) M3 (R2) section XVII (combination drug toxicity testing), 4 and 13 week GLP combination studies were performed in rats to support the long term clinical development of the 2 investigational drugs CVC and tropifexor as combination therapies for NASH.

CVC and/or LJN452 were administered separately or in combination, daily via oral gavage to rats for 28 days (Study 652-9-1059). The groups and doses were as indicated in the Table 1-1 below:

Table 1-1 Study design 28 day oral gavage combination study

Group	No. of Animals		CVC Dose Level (mg/kg/day)	CVC Dose Concentration (mg/mL)	LJN452 Dose Level (mg/kg/day)	LJN452 Dose Concentration (mg/mL)
	M	F				
1 (Control)	10	10	0	0	0	0
2 (CVC low)	10	10	30	6.0	0	0
3 (CVC high)	10	10	100	20.0	0	0
4 (LJN452 low)	10	10	0	0	0.03	0.006
5 (LJN452 High)	10	10	0	0	1.0	0.2
6 (CVC+LJN452) (low)	10	10	30	6.0	0.03	0.006
7 (CVC+LJN452) (high)	10	10	30	6.0	1.0	0.2

Source: Study 652-9-1059

CVC = Cenicriviroc; F = Female; M = Male

[redacted]

Administration of CVC alone or in combination with LJN452 was generally well-tolerated when administered via oral gavage for 28 days. The only effects noted during in-life phase were slightly decreased mean body weight and body weight change for males administered 1.0 mg/kg/day LJN452, alone or with 30 mg/kg/day CVC and slightly decreased food consumption for males administered 1.0 mg/kg/day LJN452 with 30 mg/kg/day CVC.

Clinical pathology changes were seen primarily in animals administered LJN452 and consistent with the changes reported in previous studies with LJN452 and with the expected pharmacology of the drug. Most of the test-article related clinical chemistry effects may be associated with expected pharmacology of the test article(s).

Clinical pathology changes in animals administered CVC included minimally to mildly lower absolute monocyte counts which was attributed to the pharmacology of CVC (CCR2 antagonism) and was not noted in animals administered LJN452 alone.

Based on the microscopic findings, primary target tissues for LJN452 were the liver, kidney, and intestines as previously reported in other studies with LJN452 alone. These findings may be attributable to the pharmacologic activity of LJN452, as FXR is highly expressed in the liver, kidney, and intestines. Secondary findings, consistent with stress, were observed in the thymus and prostate in animals administered LJN452, which correlated with decreased individual and/or group thymus and prostate weights, respectively, as well as decreased individual terminal body weights.

In conclusion, administration of CVC alone caused no microscopic findings indicative of toxicity and administration of CVC in combination with of LJN452 had no impact on toxicity of LJN452.

CVC and LJN452 were administered in combination daily via oral gavage to rats for at least 13 weeks to assess the reversibility, persistence, or delayed occurrence of any effects after an 8-week recovery phase (Study 1984-T01-052).

The groups and doses are presented in the Table 1-2 below:

Table 1-2 Study design 13 weeks oral gavage combination study

Group	Sub-group	No. of Animals		CVC Dose Level (mg/kg/day)	CVC Dose Concentration (mg/mL)	LJN452 Dose Level (mg/kg/day)	LJN452 Dose Concentration (mg/mL)
		M	F				
1 (Control)	1 (Tox)	15	15	0	0	0	0
	2 (TK)	3	3				
2 (Low)	1 (Tox)	15	15	3	0.6	0.03	0.006
	2 (TK)	6	6				
3 (High)	1 (Tox)	15	15	30	6	0.5	0.1
	2 (TK)	6	6				

Source: Study 1984-T01-052

CVC = Cenicriviroc; F = Female; M = Male; Tox = Toxicity; TK = Toxicokinetic.

[redacted]

No LJN452 or CVC related effects on mortality, clinical observations, ophthalmic observations, functional observational battery (neurobehavioral observations, elicited behaviors, or open field observations) occurred.

During the dosing phase, males administered ≥ 3/0.03 mg/kg/day (CVC/LJN452) gained slightly less weight compared to controls, while females gained more. Both effects reversed during the recovery phase.

Several relatively minor, CVC- and LJN452-related clinical pathology findings were observed at the terminal sacrifice in animals administered ≥ 3/0.03 mg/kg/day CVC/LJN452. These findings were attributed to the pharmacologic activity of CVC (CCR2 antagonism/decreased monocytes) or LJN452 (FXR agonism); those changes were similar to the one observed with the single agents (see above).

At the terminal sacrifice, CVC- and LJN452-related microscopic findings occurred in the liver, kidney, intestine (cecum, duodenum, and ileum) and the spleen. In the liver, minimal to moderate hepatocyte hypertrophy and periportal vacuolation was observed microscopically in animals administered 30/0.5 mg/kg/day. Higher liver weights correlated with hepatocellular hypertrophy and hepatocyte vacuolation in animals administered 30/0.5 mg/kg/day, hepatocellular hypertrophy in females administered ≥3/0.03 mg/kg/day. In the intestine, an increased incidence of crypt/gland ectasia was noted in the cecum, duodenum, and ileum of animals administered 30/0.5 mg/kg/day. In the kidney, a CVC and LJN452-related increased incidence of basophilic tubules was noted in the cortex of males administered 30/0.5 mg/kg/day. Higher spleen weights correlated with the microscopic finding of increased marginal zone size in animals administered 30/0.5 mg/kg/day; this change is consistent with the effect of a pharmacological inhibition of CCR2 by CVC in the spleen (Flaishon 2004 et al). At the recovery sacrifice, no CVC and LJN452-related microscopic findings were observed, indicating reversibility of the changes observed during the dosing phase. The NOAEL is 30/0.5 mg/kg/day CVC/ LJN452).

Overall, the toxicity findings observed during the single agent studies and the combination studies were similar. The changes in clinical pathology were either due to the CCR2 pharmacology (decreased monocytes) or FXR agonism and were similar in the combination studies compared to the single agent studies. The primary target organs observed microscopically were the liver, kidney and gastrointestinal tract and were similar in the combination studies compared to the single agent studies. The nature and the severity of the findings in these organs were also similar. In addition, minimal to mild increased marginal zone in the spleen was observed after 13 weeks of treatment at 30/0.5 mg/kg/day CVC/LJN452. Although the mechanism of action has not been determined, this change is consistent with a pharmacological inhibition of CCR2 in the spleen (Flaishon 2004 et al). The NOAEL in the 13 week study was the high dose of 30/0.5 mg/kg/day CVC/LJN452.

In conclusion, the findings in the 4- and 13- week combination therapies were aligned with the findings observed in similar studies with the single agents and/or with their expected pharmacology.

Clinical tropifexor and cenicriviroc – drug-drug interaction results

A single site, randomized, parallel 3-arm, double-blind, double-dummy drug-drug interaction

[redacted]

(DDI) study was conducted in healthy subjects (LJC242A2101). [redacted]

In summary, single drug treatment of tropifexor or CVC at 60 µg or 150 mg respectively, and the combination therapy of the two drugs at the same doses, all administered once daily for 14 days, were safe and well tolerated in healthy volunteer subjects. The safety and tolerability of the combination treatment of CVC + tropifexor were comparable to those of each of the mono therapy treatment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

Day 14 AUC0-24h and Cmax values correspond to values at steady state.

In summary, the co-administration of tropifexor has no marked impact on the pharmacokinetic profile for CVC, but co-administration of CVC reduces the tropifexor exposure (both Cmax and daily AUC) by about 35% at steady-state. In conclusion, available results from the DDI study support the investigation of the combination treatment of tropifexor

[redacted]

with CVC in clinical trials.

Tropifexor and cenicriviroc – clinical DDI and food

The tropifexor + CVC drug-drug interaction study CLJC242A2101 in healthy subjects suggested that co-administration of CVC reduces tropifexor exposure (both Cmax and AUC 0-24h) by about 35%. No safety concerns were identified at the doses of 60 µg tropifexor alone, 150 mg CVC alone or their combination, administered once daily with a standard breakfast for 14 days. In addition, an across-study exploratory comparison indicated that tropifexor plasma exposure (both Cmax and AUC) at 60 µg administered fasted (study CLJN452X2101) is similar to that at the same dose administered following a standard breakfast (study CLJC242A2101).

In summary, as compared to the fasted status, a high-fat meal increases tropifexor exposure but a standard meal appears not to. It is recommended that NASH patients, in this study, will be dosed following a standard meal without high fat (i.e. per AHA diet see appendix 17).

Tropifexor and cenicriviroc (combination) - safety considerations

In the DDI study (CLJC242A2101) the safety and tolerability of the combination treatment of tropifexor + CVC were found to be comparable to those of each of the mono therapy treatment. No additional particular safety considerations are expected for the combination of tropifexor and cenicriviroc, beyond those previously observed for each of the individual monotherapies (see section 1.1 and section 3.6 for risks). As both drugs may increase liver transaminases, there is a potential for an additive effect, thus close liver monitoring is included. Diarrhea has been identified as a non-serious adverse effect for cenicriviroc and is a possible (but unconfirmed) adverse effect of tropifexor from animal studies.

Tropifexor and cenicriviroc (combination) - rationale

Due to the multifactorial etiology of NAFLD/NASH and limited monotherapy results so far, the combination therapy of compounds with different mechanisms of actions may provide more effective therapy for NASH patients.

This study will combine the potent FXR agonist (anti-steatotic, anti-inflammatory and anti-fibrotic) tropifexor and the CCR2/5 inhibitor (anti-inflammatory and anti-fibrotic) cenicriviroc. The preclinical animal study STAM mouse models of diet induced NASH, shows that combination therapy of tropifexor and cenicriviroc have additive effects on steatosis, ballooning, and inflammation.

Both tropifexor and cenicriviroc as monotherapy are currently being evaluated in phase 2 and phase 3 clinical trials, respectively CLJN452A2202 (clinicalTrials.gov Identifier: NCT02855164) and AURORA (clinicalTrials.gov Identifier: NCT03028740), and to date have shown improvements on biomarkers and in case of cenicriviroc improvements in liver fibrosis in NASH patients.

In summary, these two drugs have different mechanisms of action (FXR and CCR2/5 inhibitor), and this multi target approach may lead to greater efficacy than monotherapy alone.

[redacted]

1.2 Purpose

The purpose of this study is to assess the safety, tolerability, efficacy [redacted] of two regimens of tropifexor and cenicriviroc (CVC) (further described as tropifexor + CVC) compared to monotherapies tropifexor and CVC in patients with NASH and liver fibrosis. Data from this study will be used to evaluate whether further development of combination therapy with tropifexor + CVC in the treatment of patients with non-alcoholic steatohepatitis (NASH) and liver fibrosis is beneficial.

2 Study objectives and endpoints

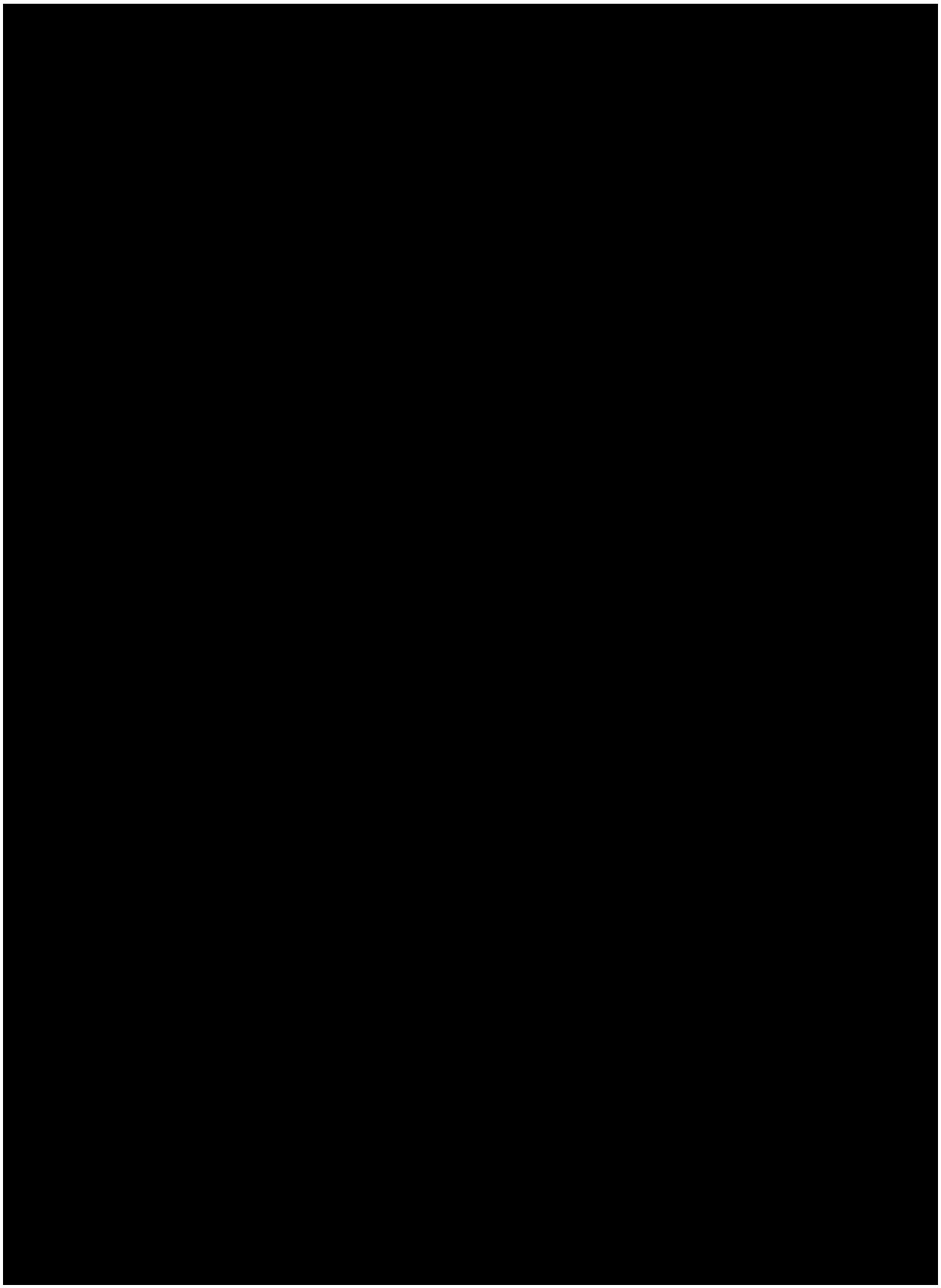
2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
To evaluate the safety and tolerability of tropifexor + CVC in patients with NASH and fibrosis (stage 2 or 3 as per NASH CRN histological score, F2/F3) by monitoring adverse events, vital signs and laboratory values during 48 weeks of treatment as compared to monotherapy with each of tropifexor and CVC	Occurrence of adverse events, serious adverse events, adverse events resulting in discontinuation of study treatment, adverse events of special interest and changes in vital signs and laboratory values over 48 weeks of treatment
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
To characterize the efficacy of tropifexor + CVC in patients with NASH with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) compared to baseline biopsy	Proportion of patients who have at least a one point improvement in fibrosis Proportion of patients with resolution of steatohepatitis

[redacted]

[redacted]



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3 Investigational plan

3.1 Study design

This study is a 48-weeks, randomized, double-blind, multicenter study that will consist of a screening period, a treatment period starting from randomization on Day 1 and running to Week 48, and a follow up period of 4 weeks after the last dose of study treatment. The total study duration is up to 62 weeks.

The screening period starts from the time of the signing of informed consent and continues for up to 10 weeks when all inclusion/exclusion criteria have been evaluated and all baseline assessments have been performed.

Patients are eligible to participate in the study if they have histological evidence of NASH and liver fibrosis stage 2 or 3 (NASH clinical research network (CRN) staging criteria)

[redacted]

demonstrated on liver biopsy during the screening period. Alternatively, a historical biopsy can be used if performed within 6 months prior to screening, if:

- the patient has been receiving any of the therapies listed in Table 5-4, the dose must have been stable (since 1 month before the biopsy up to and including screening),
- the patient weight has been stable (maximum weight change/loss of 10% since biopsy up to and including screening).

For the patients who do not have an historical liver biopsy, it is recommended to review any historical available ultrasound based elastography (e.g. [redacted] ARFI, 2D-Shear Wave Elastography, where available) prior to performing the liver biopsy.

[redacted]

At baseline, approximately 200 patients whose eligibility is confirmed will be randomized in a 1:1:1:1 ratio, resulting in approximately 50 patients randomized in each of the four arms:

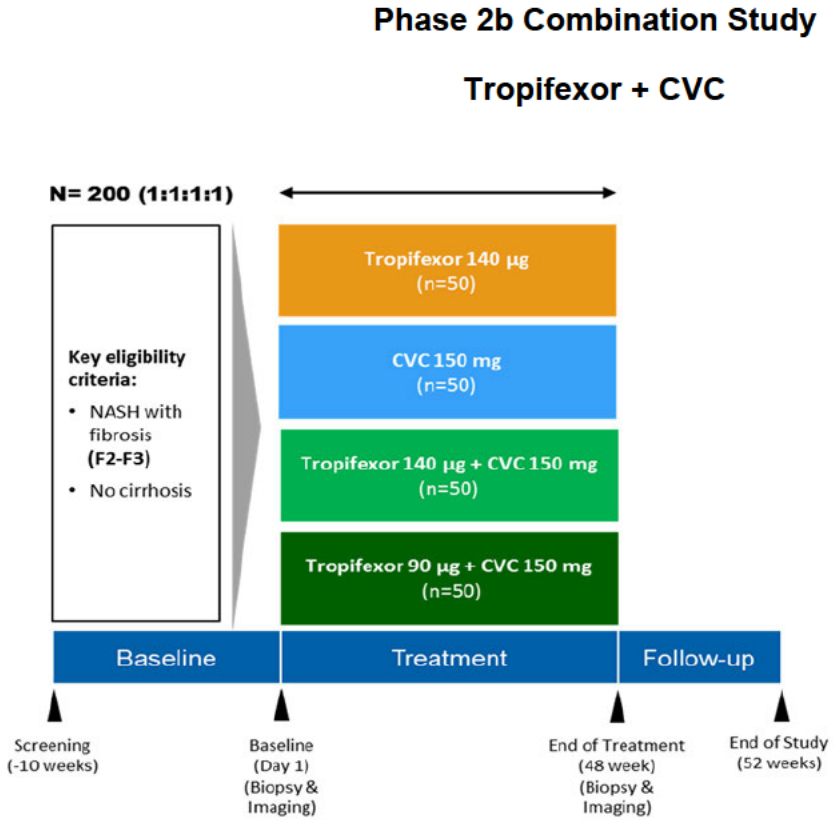
Arm A: tropifexor 140 µg, once-daily

Arm B: CVC 150 mg, once-daily

Arm C: tropifexor 140 µg + CVC 150 mg, once-daily

Arm D: tropifexor 90 µg + CVC 150 mg, once-daily.

Figure 3-1 Study design



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3.2 Rationale for study design

A Novartis sponsored Phase 2 trial (CLJN452A2202) is ongoing, with the purpose to identify the appropriate doses of tropifexor in patients with NASH, the tropifexor doses selected for this study are based on the currently planned doses being utilized in that study (CLJN452A2202).

The availability of long term non-clinical toxicity data supports the treatment duration with tropifexor up to 48 weeks and the inclusion of a histological endpoint (GLP–toxicology studies of 13 weeks duration, and longer term GLP-toxicology of 26 weeks duration in rat and 39 weeks in dog studies (tropifexor IB). For tropifexor monotherapy a long term efficacy study (CLJN452A2202) is ongoing, with 48 week treatment period and safety follow-up to Week 52 which will provide the opportunity for evaluation of histological improvement by paired biopsies at Baseline and Week 48.

Paired liver biopsies at baseline and at Week 48 will be included for all patients in this study. Inclusion criteria will require histologic evidence consistent with NASH and fibrosis level, F2 or F3 at baseline, based on liver biopsy (as determined by a central reader) obtained during the screening period or within 6 months before randomization.

CVC at a dose of 150 mg once daily is currently in Phase 3 (AURORA) clinical development for the treatment of liver fibrosis in adults with NASH and in Phase 2 development in subjects with primary sclerosing cholangitis (PSC). Overall, over 1000 subjects have been exposed to CVC in both ongoing and completed studies (CVC IB).

In a 2-year placebo-controlled Phase 2b study (652-2-203-CENTAUR, Friedman et al 2017), 289 adult patients with liver fibrosis and NASH were randomized. The recent data on CVC reported significant antifibrotic benefit in subjects with NASH, in addition to decreasing markers of systemic inflammation.

All the available data for both compounds support the use of the tropifexor and CVC monotherapies and combination regimens for a total duration of 48 weeks.

The current available reports of NASH monotherapy studies have been lacking significant efficacy. The expectation of a combined therapy is to improve efficacy based on the combination of different mechanisms of action. In this study we are combining a potent FXR (anti-steatotic, anti-inflammatory and anti-fibrotic) and a CCR2/5 inhibitor (anti-inflammatory and anti-fibrotic).

The patient population will be described in more detail in Section 4 below.

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

Tropifexor is currently being studied in NASH as monotherapy in study CLJN452A2202. The initial range of doses of 10 µg to 90 µg tropifexor studied in CLJN452A2202 Part A were chosen on the basis of safety and likely pharmacological activity, indicated by elevation of FGF19 up to 6 h after dosing in the First-in-Human study CLJN452X2101, and preclinical experience (tropifexor IB).

The DMC for study CLJN452A2202, upon review of CLJN452A2202 Part A data, recommended to investigate doses higher than 90 µg. The current non-clinical safety profile of

[redacted]

tropifexor (tropifexor IB), the DMC's recommendation based on first NASH clinical data and pharmacokinetic data, all support the investigation of tropifexor doses of > 90 µg.

[redacted]

The CVC dose of 150 mg has been used in over 1,000 patients with a good safety profile (Abdelmalek M et al 2017) and as per the recent DDI study CLJC242A2201 results co-administration of LJN452 was not found to significantly change CVC exposure. Thus 150 mg CVC is to be used for combination and reference arm in this study.

In summary, the doses for this study were selected based on the expected increased efficacy of the combination therapy, compared to individual monotherapies, while maintaining the safety of the patients.

3.4 Rationale for choice of comparator

Currently there is no treatment approved for patients with NASH but there are several investigational drugs under clinical development for this disease. The most promising drug candidates tested to date have shown only moderate effect size in histologic improvement in hepatic fibrosis and inflammation when tested as monotherapy treatment. Both tropifexor and CVC are currently being evaluated in phase 2 and phase 3 clinical trials, respectively CLJN452A2202 (clinicalTrials.gov Identifier: NCT02855164) and AURORA (clinicalTrials.gov Identifier: NCT03028740). Both these double-blind monotherapy trials in patients with NASH and liver fibrosis include a placebo arm as a comparator. On this smaller phase 2b study, two regimens of combination of tropifexor and CVC will be compared to monotherapies arms of tropifexor and CVC.

These two drugs have different mechanisms of action (FXR and CCR2/5 inhibitor) and with this study we will learn if the combination of tropifexor and CVC will lead to a greater efficacy than achieved with tropifexor or CVC monotherapies. Also this study will provide potentially useful information for future combination therapy development plans, [redacted]

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

3.6 Risks and benefits

As well as the risks and potential risks described in the tropifexor and CVC (TBR-652) Investigators' Brochures, there may be unknown risks to tropifexor and CVC which may be unforeseen.

Tropifexor

Based on the mechanism of action of tropifexor as a highly potent and specific agonist of the Farnesoid X Receptor (FXR) and data acquired in the First-in-Human study CLJN452X2101 and in nonclinical toxicology studies the risk-benefit assessment of tropifexor is as follows:

Transient and asymptomatic increases in ALT have been identified as an adverse reaction to tropifexor in healthy volunteers. Potential toxicities to be considered for tropifexor include more severe liver effects, gastrointestinal effects, coagulation effects, renal function abnormalities, and embryo-fetal toxicity. In addition it is anticipated that tropifexor may have pharmacodynamic effects on drug metabolism and elimination. Guidelines for the evaluation and detection of these potential toxicities and for their management and for minimization of risk if they do arise are discussed in the tropifexor Investigator's Brochure.

Tropifexor treatment may have the anticipated benefits on biliary metabolism (reduced synthesis and increased detoxification), lipid profile (lowering triglycerides) and anti-fibrotic activities (reduced hepatic fibrosis) may improve pathophysiology and patient outcomes over longer term treatment in longer-term development studies.

In addition to usual study monitoring, patients' liver tests will be followed closely, especially early in therapy, in conjunction with the Data Monitoring Committee (DMC), including frequent checks of a liver safety panel and drug dosage dose reduced or discontinued if necessary.

Cenicriviroc

CVC is currently in Phase 3 clinical development for the treatment of liver fibrosis in adults with NASH and in Phase 2 development in subjects with primary sclerosing cholangitis (PSC). Overall, over 1000 subjects have been exposed to CVC in both ongoing and completed studies, with a maximum exposure available of ≥ 48 weeks of treatment in approximately 260 subjects. CVC doses ranged from 25 mg to 900 mg across all CVC studies.

Study 652-2-203 (CENTAUR) is an ongoing 2-year placebo-controlled Phase 2b study in 289 adult patients with liver fibrosis and NASH. CVC demonstrated significant antifibrotic benefits in adult subjects with NASH, in addition to decreasing markers of systemic inflammation after only one year of treatment (CVC IB).

Toxicology studies showed no target organ toxicity, thus no adverse liver findings, in mice or monkeys. In rats, the liver was the primary target organ identified in repeat dose studies, with biliary hyperplasia being the primary finding. Overall, the risk for hepatobiliary effects due to CVC appears to be low. The nonclinical data suggest that CVC will not adversely affect the liver at or near clinical exposures. Liver findings were present in only 1 of 3 species and when

present, a high safety margin was apparent (> 27-fold). CVC was not genotoxic, and did not adversely affect fertility or embryofetal development (CVC IB).

In humans, the overall safety experience showed no apparent dose- or exposure-relationship for safety.

Overall, CVC was generally well tolerated in the Phase 1 studies evaluating single doses of CVC up to 900 mg and at multiple daily doses of up to 200 mg for ≥ 10 days.

In patients with mild to moderate hepatic impairment, CVC 150 mg once daily for 14 days was generally well tolerated regardless of level of hepatic impairment, and no safety concerns were identified in this population.

In the CENTAUR study in adult patients with NASH with liver fibrosis, CVC appears to be safe with no notable differences observed in previous clinical studies in incidence of treatment-emergent adverse events (TEAE) and laboratory abnormalities, including liver transaminase elevations, which were generally similar between treatment groups. Safety findings in CENTAUR were consistent with that of the extensive clinical experience with CVC, including the Phase 2 HIV studies (CVC IB).

Study conduct

[redacted]

Paired liver biopsies (baseline and Week 48) are required for all patients. Baseline biopsies will confirm the diagnosis of NASH (steatosis, [redacted]) and presence of fibrosis. The primary risk of liver biopsy is pain, bleeding from the site of needle entry into the liver, although this occurs in less than one per cent of patients. Other possible major complications include the puncture of organs, such as the kidney, lung, colon, or the gallbladder. In order to reduce the risk of bleeding, the coagulation status must be assessed in all patients prior to a biopsy.

Patients participating in this study might have reductions in hepatic fat and liver fibrosis; it is possible that this is a clinical benefit. For this reason, paired liver biopsies have been included in this study providing evaluation of long-term efficacy, with the potential benefit of histologic improvement of NASH and fibrosis. There may be patient benefit in the ancillary dietary and exercise counseling accompanying the pharmacologic intervention.

The patients who are unable to visit site due to the COVID-19 pandemic, either due to related measures or perceived risk of infection, may extend study treatment beyond week 48 for up to approximately 10 weeks (see section 5.5.2). The study treatment extension must be discussed with the impacted patients thoroughly and documented, including the possible benefits and risks of longer treatment duration. A longer treatment duration might provide greater benefits. A treatment duration up to 72 weeks has been shown exhibit an appropriate safety profile for another FXR-agonist obeticholic acid (Younossi ZM et al 2019) and treatment up to 2 years for CVC. No additional or different risks are expected with longer treatment duration.

[redacted]

4 Population

The study population will consist of approximately 200 adult male and female patients with histologic evidence of NASH and fibrosis (stage 2 or 3 as per NASH CRN histological score, F2/F3); see Inclusion and Exclusion criteria for details.

The study will be conducted in approximately 90 centers worldwide. Since a screening failure rate is expected to be around 66%, approximately 600 patients may be screened.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients 18 years or older (at the time of the screening visit). Patients must weigh at least 50 kg (110 lb) and no more than 200 kg (440 lb) to participate in the study.
3. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
4. Adequate liver biopsy sample for evaluation by a central reader.
5. Presence of NASH as demonstrated by histologic evidence based on liver biopsy - NASH with fibrosis stage F2/F3, demonstrated on liver biopsy with evaluation by central reading during the screening period. Alternatively, a historical biopsy can be used if performed within 6 months prior to screening and evaluated by central reader, if:
   - the patient has been receiving any of the therapies listed in Table 5-4, the dose must have been stable (since 1 month before the biopsy up to and including screening),
   - the patient's weight has been stable (maximum weight loss of 10% since biopsy up to and including screening).

4.2 Exclusion criteria

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

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

1. Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer.
2. History of hypersensitivity to any of the study drugs or its excipients or to drugs of similar chemical classes.
3. Previous exposure to elafibranor, CVC, tropifexor, obeticholic acid (OCA), LMB763 or other FXR agonist.
4. Participated in a clinical trial and treated with any investigational product being evaluated for the treatment of liver fibrosis or NASH in the 6 months before screening (subjects documented to be assigned to placebo in such trials may be eligible immediately following completion of their participation in the previous trial).

[redacted]

5. Patients taking medications prohibited by the protocol. An overview of prohibited medications is given in Table 5-2, and the summary of medications permitted only if on stable dose is in Table 5-4.
6. History of treated or untreated malignancy of any organ system, other than localized basal cell carcinoma of the skin or treated cervical intraepithelial neoplasia, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
7. Pregnant or nursing (lactating) women.
8. 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 30 days after stopping of tropifexor and/or CVC medication. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). 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 investigational drug. 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 subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- 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 investigational drug.

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

Sexually active males must use a condom during intercourse while taking drug and for 30 days after stopping tropifexor and/or CVC 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.

9. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the modified AUDIT questionnaire ≥ 8

[redacted]

10. Inability to reliably quantify alcohol consumption based upon local study physician judgment
11. History or evidence of ongoing drug abuse, within the last 6 months prior to randomization. Marijuana use is not allowed if it is determined to be medically inappropriate by the investigator
12. Prior or planned (during the study period) bariatric surgery (e.g. gastroplasty, roux-en-Y gastric bypass)
13. Uncontrolled diabetes defined as HbA1c ≥ 9% at screening
14. Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities (confirmed at screening visit 2):
    - Serum albumin < 3.2 g/dL
    - International Normalized Ratio (INR) > 1.3
    - Total bilirubin > 1.3 mg/dL (including Gilbert's syndrome)
    - ALT or AST > 5× ULN
    - Alkaline phosphatase > 300 IU/L
    - History of esophageal varices, ascites or hepatic encephalopathy
    - Splenomegaly
15. Previous diagnosis of other forms of chronic liver disease:
    - Hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) positive
    - Hepatitis C antibody (HCVAb) positive with the following 2 exceptions:
        - Subjects previously treated for viral hepatitis C with at least a 3-year period since documented sustained virologic response at Week 12 (post-treatment) may be eligible if all other eligibility criteria are met
        - Subjects with presence of hepatitis C antibody but negative hepatitis C virus (HCV) ribonucleic acid (RNA) without treatment (i.e., spontaneous clearance) may be eligible if all other eligibility criteria are met
    - History of autoimmune liver disease:
        - Primary biliary cholangitis as defined by the presence of at least 2 of these criteria:
        - Biochemical evidence of cholestasis based mainly on alkaline phosphatase elevation
        - Presence of anti-mitochondrial antibodies (AMA)
        - Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
    - Primary sclerosing cholangitis

[redacted]

- History of Wilson's disease
- History of Alpha-1-antitrypsin (A1AT) deficiency
- History of hemochromatosis or iron overload.
- Drug-induced liver disease as defined on the basis of typical exposure and history
- Known bile duct obstruction
- Suspected or proven liver cancer
- Any other type of liver disease other than NASH

16. Calculated eGFR less than 60 mL/min/1.73m^2 (using the MDRD formula)
17. History of biliary diversion
18. History of liver transplantation or planned liver transplant
19. Known positivity for Human Immunodeficiency Virus (HIV) infection
20. Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study
21. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - QTcF interval of greater than 450 ms at screening
    - History of familial long QT syndrome or known family history of Torsades de Pointes
22. History of inflammatory bowel disease
23. Patients who are not candidates for liver biopsy
24. Presence of cirrhosis on liver biopsy (F4 by NASH CRN System) or medical history
25. Patients with an abnormal platelet count (see reference ranges in central laboratory manual)

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Tropifexor:

Dosage form: 10 µg, 30 µg, 90 µg and 100 µg hard gelatin capsules.

Presentation: Bottles

[redacted]

Tropifexor Placebo:

Dosage form: hard gelatin capsules

Presentation: Bottles

CVC:

Dosage form: 150 mg coated tablet

Presentation: Bottles

CVC Placebo:

Dosage form: coated tablet

Presentation: Bottles

Novartis will provide sufficient supplies of tropifexor and CVC to last each patient between visits (or more).

5.1.2 Additional treatment

No additional treatment beyond investigational drug and placebo is provided in this trial.

5.2 Treatment arms

Patients (n = 200) will be assigned at baseline visit to one of the following 4 treatment arms in a ratio of 1:1:1:1 in a blinded manner. Placebo capsules/tablets will be given in each treatment arm where necessary to maintain blinding.

Arm A: tropifexor 140 µg, once-daily

Arm B: CVC 150 mg, once-daily

Arm C: tropifexor 140 µg + CVC 150 mg, once-daily

Arm D: tropifexor 90 µg + CVC 150 mg, once-daily

In order to maintain the blind, placebo capsules matching tropifexor 10, 30, 90 and 100 µg capsules and placebo tablets matching CVC 150 mg will be given to patients as indicated in Table 5-1, so that all patients will receive 3 capsules and 1 tablet per day. One capsule/tablet from each of the 4 bottles dispensed should be taken with food (e.g. immediately following a meal) and at about the same time each day.

5.3 Treatment assignment and randomization

At baseline visit, all eligible patients/subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the patient. The randomization number will not be communicated to the caller.

[redacted]

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients/subjects and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

[redacted]

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

5.4 Treatment blinding

This is a double-blind study: patients, investigator staff, persons performing the assessments, and Novartis clinical trial team (or delegates) will remain blinded to the identity of study treatments from the time of randomization (until final database lock), using the following methods: 1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exception: bioanalyst. 2) The identity of the treatments will be concealed by the use of placebos that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. Additional placebo capsules/tablet will be given in active treatment groups when needed to maintain blinding.

[redacted]

Unblinding will only occur in the case of patient emergencies (see Section 5.6) and at the conclusion of the study.

5.5 Treating the patient

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

5.5.1 Patient numbering

Each subject is uniquely identified by a Subject Number assigned by Novartis. The Subject Number is composed of a site number and a sequential number. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number available in electronic data capture (EDC) system. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site must select the electronic case report form (eCRF) book with a matching Subject Number in the EDC system to enter data.

[redacted]

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the appropriate eCRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a certain treatment. Investigator staff will identify the study drug package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique subject number.

For patients who are unable to come to the study site for their end-of-treatment visit (week-48) and the liver biopsy visit as scheduled per study protocol due to the COVID-19 pandemic:- the investigator may consider to extend the study treatment to allow the visit (including liver biopsy) to be performed later. This can be done using the following stepwise approach:

- The study medication dispensed at week 40 should have about 2 weeks' excess medication. The liver biopsy visit can be delayed until the medication runs out.
- If this is not sufficient, an unscheduled visit can be performed (by phone if necessary) and an additional 4-week supply of study medication requested via IRT and send the medication to patient's home address (if considered safe and appropriate). If feasible, central or local lab assessments (Liver tests, Serum BUN & Creatinine) should be performed every 8 weeks to monitor the patient's safety.
- If that is still not sufficient, a second 4-week supply of study medication can be requested via IRT.

The Investigator should ensure that this study treatment extension is discussed with the impacted patients thoroughly, including the possible risks and benefits of longer treatment duration. The discussion and the patient's willingness to extend the study treatment duration should be recorded in the source documents.

5.5.3 Handling of study and additional treatment

5.5.3.1 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. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the patient except for the medication number.

[redacted]

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the trial. Patients/subjects will be asked to return all unused study treatment and packaging at each visit or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Patients should be instructed to take the dose of study medication daily, in the morning, with food (e.g. immediately after a meal) at approximately the same time each day except the days with a morning visit. On the days where there are study visits, if the visit is in the morning time, the patients should take their doses at the clinic following a meal. From the baseline day onwards, patients will be instructed to take 1 tablet and 3 capsules each day during the duration of the study.

The patient will be dispensed 4 bottles for each 4 weeks period and should take one tablet from one bottle and 3 capsules (one from each of the other 3 bottles).

Table 5-1 Overview of treatment - type and number of capsules and tablets taken per day

Treatment arm	CVC 150 mg tablet	CVC placebo	Tropifexor 10µg capsule	Tropifexor 30µg capsule	Tropifexor 90µg capsule	Tropifexor 100µg capsule	Tropifexor placebo
A	0	1	1	1	0	1	0
B	1	0	0	0	0	0	3
C	1	0	1	1	0	1	0
D	1	0	0	0	1	0	2

Dosing recommendations:

- Patients should take the medications in the morning with food (e.g. immediately after a meal) and at about the same time each day.
- Patients should be instructed to swallow the capsules whole and not to chew them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Missed doses should not be made up.

All kits of study treatment assigned by the IRT will be recorded/databased in the IRT.

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

validity of the study. It should be emphasized to the patient that the study medication bottles are not identical; the patient must take one tablet or capsule from each bottle each day. The patient must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

5.5.4.1 Dietary restrictions

No alcohol consumption is allowed for 8 hours before each dose of study medication. Alcohol should also not be consumed for 8 hours before each study visit.

To keep the fat intake as constant as possible, patients participating in this study will be instructed to carefully adhere to American Heart Association (AHA) diet or local equivalent if there is a country specific recommended diet (Appendix 5). Patients will be asked about dietary compliance to the AHA diet (or local equivalent) as outlined in Table 6-1. Patients should also be counseled regarding appropriate exercise as per local standards, and will be asked about their exercise as outlined in Table 6-1.

5.5.5 Permitted dose adjustments and interruptions of study treatment

For potential drug-related adverse events, temporary interruptions are permitted up to 28 consecutive days. Study drugs can be reintroduced under careful monitoring if the investigator feels it is in the best interest of the patient. Interruption of study drug for more than 28 consecutive days should lead to permanent discontinuation of the patient from study drug with the respective follow-up visits.

Investigational treatment dose adjustments are not permitted.

These changes must be recorded on the appropriate eCRF.

5.5.6 Rescue medication

Use of rescue medication is not allowed in this study.

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the appropriate eCRF.

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 patient or allowing a new medication to be started.

5.5.8 Prohibited medication

Use of the treatments displayed in the below table (Table 5-2) is NOT allowed after the start of investigational drug.

[redacted]

Table 5-2 Prohibited medications

Medication	Guidance
Inhibitors, inducers and sensitive substrates of drug metabolizing enzymes	
Specific UGT1A1 inhibitors: atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine, and zafirlukast	Prohibited from first drug intake to end-of-study visit
Herbal remedies inhibiting UGT1A1: Silybum marianum (sylamarin, milk thistle) and *Valeriana officinalis* (valerian)	Prohibited from first drug intake to end-of-study visit
Non-selective UGT inhibitors: diclofenac, probenecid, valproic acid	Prohibited from first drug intake to end-of-study visit
Strong CYP3A4 inhibitors: VIEKIRA PAK2, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat (GS-9350), indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole,mibefradil, LCL161, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, saquinavir, idelalisib, boceprevir, darunavir/ritonavir.	Prohibited use from first drug intake to end-of-study visit
Strong CYP3A4 inducers: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort (*Hypericum perforatum*), rifabutin, phenobarbital, mitotane, enzalutamide.	Prohibited from first drug intake to end-of-study visit
Strong CYP2C8 inhibitors: gemfibrozil, clopidrogrel.	Prohibited from first drug intake to end-of-study visit
Sensitive CYP3A4 substrates with narrow therapeutic index (i.e. drugs that should not be co-administered with weak CYP3A4 inhibitors): astemizole, cisapride, cyclosporine, dihydroergotamine, ergonovine, ergotamine, ergotamine, methylergonovine, pimozide, quinidine, sirolimus, tacrolimus, terfanadine, thioridazine.	Prohibited from first drug intake to end-of-study visit
Sensitive CYP3A4 substrates exceptions: midazolam, triazolam	Use only allowed for sedation on the day of the liver biopsy or for surgical outpatient procedures. If given after intake of study drug, the first dose should be reduced by 50% of the recommended dose and titrated according to the desired clinical response.
Sensitive CYP3A4 substrates exceptions: intravenous alfentanil or fentanyl	Use is allowed for sedation on the day of screening biopsy but is not allowed for any procedure after intake of study drug.
Sulfasalazine and methotrexate	Prohibited from first drug intake to end-of-study visit

[redacted]

Medication	Guidance
Vitamin E	Prohibited at doses > 400 IU/day

5.5.8.1 Drugs to be used with restrictions

If required, the medications specified on Table 5-3 should be used with caution, at the lowest dose possible and for the shortest duration possible considering individual subject risk-benefit considerations. Clinical monitoring and dose titration are recommended to achieve the desired clinical response. Other medications of a similar class should be considered if possible. Consult the individual medication prescribing information for additional guidance.

Table 5-3 Drugs that are allowed but must be taken with caution

Medication	Guidance
Acid-reducing agents (H_2 receptor antagonists, proton-pump inhibitors)	Acid reducing agents should be administered at least 2 hours after study drug administration. When possible, use of an H_2 receptor antagonists (except cimetidine) or antiacids is preferred over a proton-pump inhibitor. It is recommended to start with the lowest dose of these agents and titrate according to clinical response. H_2 receptor antagonists (e.g. famotidine or ranitidine) should preferably be given from 2 to 12 hours after administration of study drug at a dose that does not exceed doses comparable to famotidine 40 mg daily. Antiacids (e.g. aluminium hydroxide, calcium carbonate, magnesium carbonate, magnesium hydroxide or bismuth subsalicylate) should preferably be given at least 4 hours after administration of study PPIs (e.g., omeprazole, lansoprazole, esomeprazole, pantoprazole, rabeprazole, or delansoprazole) should preferably be given approximately 3 hours after administration of study drug at a dose that does not exceed doses comparable to omeprazole 20 mg daily.
Lipid lowering agents	The maximum recommended daily doses of atorvastatin, simvastatin, lovastatin (CYP3A4 substrates), pravastatin (CYP3A4 substrate and weak CYP2C8 inhibitor) and rosuvastatin (BCRP substrate) are restricted as follows: atorvastatin 40 mg, simvastatin 10 mg, lovastatin 40 mg, pravastatin 40 mg, and rosuvastatin 10 mg; pitavastatin use is allowed without dose restriction. CVC may increase the exposure of rosuvastatin and simvastatin and patients taking these drugs concomitantly could be at increased risk for adverse effects. Monitor patients closely for symptoms of myopathy or liver injury.
PDE5 inhibitors	The recommended starting doses for these CYP3A4 substrates are as follows: sildenafil 25 mg, tadalafil 2.5 mg and vardeafil 2.5 mg.

Patients on medications specified in Table 5-4 can be included if the dose has been stable for at least 1 month before the baseline biopsy (historical or performed during screening).

A stable dose is defined as a dose within 25% of the baseline dose.

No new use of the medications in Table 5-4 is allowed between 1 month before the baseline biopsy and until Study Completion.

[redacted]

Table 5-4 Medications permitted only if dose is stable within 25 percent of baseline dose

Medication
Oral anti-diabetic medications such as pioglitazone, metformin and/or sulfonylureas
GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide
Fibrates, niacin
Vitamin E
Pentoxifylline

5.5.9 Emergency breaking of assigned treatment code

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will provide:

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

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

Study treatment must be discontinued after emergency unblinding. The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A patient will be considered to have completed the study when the patient has completed the last visit planned in the protocol.

Continuing care should be provided by investigator and/or referring physician based on patient availability for follow-up.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

This continuing care for patients who complete 48 weeks of treatment may include enrollment in an extension study, if any, to allow for therapy beyond 48 weeks.

For all patients who discontinue treatment early or who complete treatment and do not rollover to an extension study (if available), a safety follow-up visit (visit EOS) should be conducted 4 weeks after last treatment (EOT, Week 48). The information to be collected at this follow up visit includes concomitant medications, adverse events, and laboratory samples, as detailed on Table 6-1.

[redacted]

5.6.2 Discontinuation of study treatment

Discontinuation of study treatment for a patient occurs when study drug is stopped earlier than the protocol planned duration, and can be initiated by either the patient or the investigator. The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

Study treatment must be discontinued under the following circumstances:

- Patient wish
- Pregnancy (Ref. protocol Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations (Section 5.5.8)
- Any situation in which study participation might result in a safety risk to the patient
- Emergence of the following adverse events:
  - Hypersensitivity reaction to tropifexor or CVC
  - For ALT, AST, total bilirubin and/or alkaline phosphatase elevations mandating study treatment discontinuations (Section 7.3 and Table 14-1 for further instructions and monitoring).
  - Specified renal events (Section 7.4 and Table 15-1 for further instructions and monitoring).
  - Other SAE that are related to study drug.
  - Other life-threatening SAE regardless of attribution to study drug.
  - Any other adverse events, abnormal laboratory values or abnormal test result that indicate a safety risk to the patient.
  - Decompensated cirrhosis as defined by ascites, bleeding esophageal varices, hepatic encephalopathy, jaundice or any other liver decompensation related symptom.

The appropriate personnel from the study site and Novartis will assess whether study treatment should be discontinued for any patient whose treatment code has been broken inadvertently for any reason. Study treatment must be discontinued after emergency unblinding. If discontinuation of study treatment occurs, the patient should NOT be considered withdrawn from the study. The patient should return to the clinic as soon as possible, after discontinuation of study drug, for a study treatment discontinuation visit. Treatment discontinuation visit assessments detailed in the treatment discontinuation visit (TD) in Table 6-1 should be completed and recorded in the appropriate eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the appropriate eCRF. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

During the Treatment discontinuation visit (TD), at least the following data should be collected:

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

For patients who discontinue study treatment prematurely before the end of the treatment period for any reason other than withdrawal of informed consent, the TD visit (EOT) and Week 52 (EOS) visits must be performed.

[redacted]

If study drug discontinuation occurs because treatment code has been broken, refer to protocol Section 5.5.9.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

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

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

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in Table 6-1.

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

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

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

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her planned end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the patient must be seen as soon as possible and treated as a prematurely discontinued patient. The investigator may be informed of additional procedures to be followed in order to ensure that

[redacted]

adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "X" when the visits are performed. An 'S' indicates the data for that assessment are in the source documents at the site.

Patients who have been screened and have a screening visit recorded in the IRT system at the time that the planned enrollment number is met will be allowed to enter the trial and to be randomized if they are eligible.

Patients must be seen for all visits on the designated day, or as close to it as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit 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 reconciled on the appropriate eCRF.

For patients who are unable to come to the study site for their scheduled visit due to COVID-19 pandemic and related measures, consider to conduct patient study visits on schedule as a remote consultation (except the Week 48, End Of Treatment visit) and send the medication to patient's home adress (if considered safe and appropriate). At these visits, the occurence of AEs or SAEs, change in co-medications, study drug compliance, alcohol and AHA diet compliance should be determined. Patients with child bearing potential must be reminded to perform urine pregnacy test at home every 4 weeks.

Any unplanned assessments for: Vital signs, ECG, Hepatitis serology, Liver tests, Serum BUN and Creatinine, Coagulation panel, [redacted] Clinical chemistry panel, HbA1c, Urinalysis and Serum pregnancy test must be recorded in the unplanned eCRF.

For patients who discontinue study treatment prematurely before the end of the treatment period for any reason other than withdrawal of informed consent, the Week 48, planned End of Treatment (EOT) and Week 52 End of Study (EOS) visits must be performed.

If a patient refuses to return for these assessments or is unable to do so, every effort should be made to contact them, or a knowledgeable informant, by telephone or by sending appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g. potential occurrence of AEs or SAEs) and the primary reason for the patient's premature withdrawal should be determined. Documentation of attempts to contact the patient should be recorded in the patient source documents.

Refer to Section 5.6 for additional details regarding procedures for patients who discontinue study treatment or prematurely withdraw.

Patients will be contacted for safety evaluations during the 30 days following the last administration of study treatment.

[redacted]

Patients who develop medically important laboratory abnormalities or medically important adverse events (AE) that are considered related to study drug will be followed beyond the End of Study visit until these events have resolved or stabilized.

The following will be considered as medically important:

i. severe AEs,
ii. serious AEs,
iii. hepatic and renal AEs,
iv. elevated liver enzymes (ALT, AST or alkaline phosphatase >2x ULN and >1.5x baseline).

[redacted]

Table 6-1 Assessment schedule

Periods	Screening		Treatment Period										Post Treatment Follow Up	Notes
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
Screening														
Informed consent	X													
Pharmacogenetic informed consent	X													
Inclusion / Exclusion criteria	X	X	X											
Demography	X													
Medical history/ current medical conditions	X													
Protocol solicited medical history	X													
Assessments														
Physical examination[3]	S	S	S		S	S	S	S	S	S	S	S	S	
Prior and concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Surgical and medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	
Alcohol history / compliance with protocol	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smoking history	X													

[redacted]

Periods	Screening		Treatment Period										Post Treatment Follow Up	Notes
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
[redacted]														
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[4]	X								X			X		
[redacted]														
Liver Biopsy[14]		X										X		Biopsy to be performed no later than 2 weeks prior randomization
Adverse Events / Serious AE	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]														

[redacted]

Periods	**Screening**		**Treatment Period**										**Post Treatment Follow Up**	**Notes**
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
[redacted]														
Modified AUDIT questionnaire[15]		X	X	X	X	X	X	X	X	X	X	X	X	
Randomization via IRT			S											
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X		
Drug dispensing			S		S	S	S	S	S	S	S			
Drug administration record			X		X	X	X	X	X	X	X	X		
Drug compliance					S	S	S	S	S	S	S	S		
AHA Diet Review			S		S		S	S	S	S	S	S	S	
Diet Compliance			X				X		X			X	X	
Exercise assessment			S				S		S			S	S	
Blood collection														
Hepatitis serology[5]	X													
Liver tests	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum BUN and Creatinine	X		X		X	X	X	X	X	X	X	X	X	
Coagulation panel	X	X	X				X		X			X		Only INR at screening visit 2
[redacted]														

Periods	Screening		Treatment Period										Post Treatment Follow Up	Notes
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
[redacted]														
Hematology	X		X				X		X		X	X	X	
Clinical chemistry panel[7]	X		X				X		X		X	X	X	
HbA1c	X													
[redacted]														

Periods	**Screening**		**Treatment Period**										**Post Treatment Follow Up**	**Notes**
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
Urine														
Dipstick / routine Urinalysis with Reflex Micro	X		X		X	X	X	X	X	X	X	X	X	
Serum pregnancy test[12]	X													
Urine pregnancy test[12]		S	S	S	S	S	S	S	S	S	S	S	S	The urine pregnancy test should be performed every 4 weeks up to the follow up visit, including at week 20, 28, 36 and 44, and during any treatment extension period.
Drug screen	X		X											
Study Completion Form	X													

[redacted]

Periods	Screening		Treatment Period										Post Treatment Follow Up	Notes
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	

TD: treatment discontinuation; X: assessment to be recorded on clinical database; S: assessment to be recorded on source documentation

1: Screening visit 2 should only be conducted if eligibility is confirmed at screening visit 1;

2: Screening visit 2 should be done at least two weeks prior baseline visit to allow sufficient time for liver biopsy central reading

3: Full physical examination at screening visit 1, baseline, Week 12, 24 and 48

4: For any ECGs with safety concerns, one additional ECG must be performed to confirm the safety finding

5: Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) positive, Hepatitis C antibody (HCVAb)

[redacted]

7: See assessments in Section 6.5.4.2. At screening visit 1 this also includes ferritin, transferrin saturation, iron, and if not historically available also ANA, ASMA and AMA

[redacted]

[redacted]

Periods	Screening		Treatment Period										Post Treatment Follow Up	Notes
Week	**-10 to -2**	**-2[1] (no later than)[2]**	**BSL**	**2**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48[16] TD/EOT**	**52 EOS**	
[redacted]														

12: Only for pre-menopausal women who are not surgically sterile. The urine pregnancy test should be performed every 4 weeks up to the follow up visit including at week 20, 28, 36 and 44 (including during treatment extension due to COVID-19 pandemic and related measures)

13: Assessment at EOT not to be done in case of premature treatment discontinuation unless the patient has received at least 8 weeks of study treatment

14. Paired liver biopsies (≤ 6 months or at least 2 weeks prior to baseline and at week 48) are required to confirm the diagnosis of NASH (Steatosis, [redacted]) and presence of fibrosis. Baseline biopsy slides, prepared from biopsies performed during the screening period or =< 6 months prior to the screening visit, will be sent to a Central Reader to determine eligibility.

Assessment at EOT not to be done in case of premature treatment discontinuation unless the patient has received at least 24 weeks of study treatment

15. Full questionnaire AUDIT at screening, short questionnaire at other visits

16. For patients who are unable to come to the study site for week 48, End of Treatment (EOT) visit including liver biopsy as scheduled due to COVID-19 pandemic, you may consider to extend the study treatment as indicated in section 5.5.2.

[redacted]

6.1 Information to be collected on screening failures

All patients who have signed informed consent and discontinue before randomization into the study at Baseline Visit are considered screening failures. If a patient discontinues before entering the treatment epoch, IRT must be notified within 2 days and the reason for not entering the study will be recorded on the appropriate eCRF. In addition, the following eCRFs should be completed: Visit Date, Informed Consent, Demography, Inclusion/Exclusion Criteria, Subject Re-Screening (if applicable), Disposition, Withdrawal of Consent (if applicable) and AE should be completed for any SAEs that occurred during the screening epoch. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

If a patient is a screening failure, but is rescreened and subsequently enrolled, the reason for the original screening failure must be documented in the source documents. A new subject ID will be assigned to the patient.

If for any reason the patient is a screen failure, the patient may be rescreened. There is no restriction on the number of times a potential patient may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening.

If a patient rescreens for the study, THEN the patient must sign a new ICF and be issued a new patient number prior to any screening assessment being conducted for the patient under the new screening patient number. For all patients, the investigator/qualified site staff will record if the patient was rescreened on the rescreening eCRF and any applicable screening numbers the patient was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the Informed Consent eCRF to correspond to the new screening patient number. Informed Consent for a rescreened patient must be obtained prior to performing any study-related assessment or collecting any data for the new Screening Visit. For rescreening, all screening assessments must be performed as per protocol.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.1.1 Pre-screening

Prior to screening visit 1 optional pre-screening assessments may be carried out, including [redacted] assessments and/or local laboratory tests (HbA1c, platelets, INR, total bilirubin, ALT, AST, Alkaline phosphatase and serum albumin as applicable) to assess patient eligibility for inclusion. Prior to any assessments being carried out the pre-screening informed consent form must be signed by the patient.

Only data related to SAE's 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.

[redacted]

6.2 Patient demographics/other baseline characteristics

All baseline assessments should be performed prior to first study treatment administration. These may be in the screening period (e.g. demographics) or at the Randomization Visit (e.g. PROs), depending on the assessment.

6.2.1 Demographic Information

Patient demographic data to be collected at screening on all patients include: age, gender, race, ethnicity and child-bearing potential (for females only).

6.2.2 Medical history

Any relevant medical history including surgical/medical procedures, protocol solicited medical history, and/or current medical conditions before obtaining informed consent will be recorded in the Medical History eCRF. Significant findings that are observed after the patient has signed the informed consent form and that meet the definition of an AE must also be recorded in the AE eCRF (see Section 7.1 for the timeframe to record AEs during the screening period). Whenever possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2.3 Alcohol history and assessments

Any history of alcohol use will be recorded in the eCRF. Further, the Alcohol Use Disorders Identification Test (AUDIT) will be administered to the patients at the screening visit 2 and as indicated in Table 6-1. At screening visit 2 the 10-item questionnaire will be used, whereas at the following visits, the shortened version (AUDIT-C), a 3-item questionnaire will be used.

6.2.4 Smoking history

The current and/or previous use of tobacco products will be recorded, as well as the estimated number of pack-years based on the approximate consumption per year. Non-smokers will be advised not to start smoking during the study.

6.2.5 Prior and concomitant medications

Concomitant medications and prior medications taken over the 6 months preceding study enrollment will be captured at the screening visit, and updated at the baseline visit.

6.2.6 Liver evaluation

6.2.6.1 Liver biopsy

Patients must have histologic evidence of NASH and liver fibrosis stage 2 or 3 (NASH clinical research network (CRN) staging criteria) demonstrated on liver biopsy during the Screening period. Alternatively, a historical biopsy can be used if performed within 6 months prior to screening, if:

[redacted]

- the patient has been receiving any of the therapies listed in Table 5-4, the dose must have been stable (since 1 month before the biopsy up to and including screening),
- the patient weight has been stable (maximum weight loss of 10% since biopsy up to and including screening).

Five to eight Baseline Biopsy slides, unstained and prepared from biopsies performed during the screening period or =< 6 months prior to the screening visit, will be sent to a Central Reader to determine eligibility. Patients will be treated for 48 weeks and an end of treatment biopsy will be performed and slides submitted to the Central Reader. A manual detailing all the requirements will be supplied to each study site.

For the patients who do not have an historical liver biopsy, [redacted] may be a useful pre-screening tool prior to liver biopsy for cases of indeterminate clinical NASH (F2/F3) diagnosis.

In case of premature treatment discontinuation, the end of treatment biopsy should only be performed if the patient has received at least 24 weeks of study treatment.

[redacted]

6.2.7 Other baseline characteristics

Baseline characteristic data to be collected on all patients include (all labs are central) (see also Table 6-1):

12-lead ECG, vital signs, drug testing, hematology, clinical chemistry, urinalysis, physical examination, [redacted], past medical history record of HIV, Hepatitis B or C serology, anti-nuclear antibodies (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), iron, ferritin, transferrin saturation, Hemoglobin A_{1c} (HbA_{1c}), [redacted] A serum pregnancy test will be performed for women of child-bearing potential, [redacted]

[redacted]

6.2.8 Screening visit 2 – additional assessments

The second screening visit should only be conducted if eligibility is confirmed at screening visit 1. Assessments for this visit include: Liver biopsy, [redacted] and other non-lab assessments as indicated in Table 6-1.

The period between screening visit 1 and the anticipated randomization / baseline visit is a maximum of 10 weeks. Screening visit 2 should be done at least two weeks prior baseline visit to allow sufficient time for liver biopsy central reading.

A repeat of the liver test, INR as well as the serum pregnancy test (if applicable). Both repeat tests should be in compliance with protocol requirements before randomization of the patient.

6.3 Treatment exposure and compliance

All doses of study treatment administration will be recorded on the appropriate CRF page. Compliance will be assessed by means of site and subject-specific drug accountability by Novartis study personnel during the site monitoring visits using medication pack numbers, Drug Label Form information and information collected by IRT.

6.4 Efficacy

All efficacy assessments should be performed prior to the administration of study treatment. The recommended order for the efficacy assessments is described below.

[redacted]

All remaining study visits procedures (e.g. laboratory samples collection, vital signs measurement, [redacted] etc.) must be completed prior to administration of study treatment.

[redacted]

[redacted]

[redacted]

6.4.2 Liver tests

ALT, AST, GGT, total alkaline phosphatase (and isoenzymes if total alkaline phosphatase is > ULN, and 5'nucleotidase if either GGT or total alkaline phosphatase is > ULN during study participation), total bilirubin, direct bilirubin and albumin will be assessed as indicated in Table 6-1.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reactive bilirubin will be quantified. The methods for assessment and recording are specified in the laboratory manual. Some of the liver tests may be completed as part of the blood chemistry panel.

6.4.3 Coagulation tests

Coagulation parameters including APTT, PT, INR and TT will be assessed as indicated in Table 6-1.

The methods for assessment and recording are specified in the laboratory manual.

[redacted]

[redacted]

[redacted]

6.4.9 Liver biopsy

Patients will have paired liver biopsies (Baseline and EOT, after 48 weeks of treatment). Fibrosis staging and scores of steatohepatitis markers (steatosis, [redacted]) [redacted] will be determined by a Central Reader. Five (5) to eight (8) unstained liver biopsy sections, must be prepared and submitted to the central histopathologist who will confirm eligibility prior to randomization. If a suitable historical biopsy sample from which slides can be prepared is not available, the liver biopsy can be performed any time during the 10 week screening period, and should only be performed in subjects who fulfill Screening visit 1 inclusion criteria. [redacted] Additional details regarding liver biopsy requirements can be found in the accompanying central biopsy manual.

[redacted]

[redacted]

[redacted]

6.4.10 Appropriateness of efficacy assessments

The secondary [redacted] for this protocol include direct markers of NASH as measured by liver histology. The secondary efficacy variables selected for this protocol are to detect clinically meaningful changes in liver fat, liver enzymes and indirect markers of NASH. Improvement in steatosis and fibrosis as determined by liver histology is recommended as a valid endpoint by regulators (Sanyal et al 2016).

[redacted].

6.5 Safety

Standard safety parameters and measures will be collected including adverse events and serious adverse events according to definitions and process detailed in the protocol.

6.5.1 Physical examination

A physical examination of the patient will be performed on patients according to the schedule defined in Table 6-1.

A complete physical examination will include the examination of general appearance, hydration status, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing the Informed Consent Form must be included in the Medical History screen on the patient's CRF. Significant findings that occur after signing the Informed Consent Form which meet the definition of an AE must be recorded in the Adverse Event screen of the patient's CRF (Section 7).

[redacted]

6.5.2 Vital signs

Clinically notable vital signs are defined in Appendix 1.

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 6-1. After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic (SBP) and diastolic (DBP) blood pressure will be measured with an appropriately sized cuff. Note that large cuffs are required in overweight and obese patients. If blood pressure is high (i.e., SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg, or $\geq$ 130/80 for patients with diabetes or chronic renal insufficiency), blood pressure measurement will be repeated after a 5 minutes rest and confirmed by other arm. All measurements should be recorded in source documents and the lowest reading entered in the CRF.

If possible, assessments should be performed using the same equipment and by the same qualified study site staff member throughout the study.

[redacted]

6.5.4 Laboratory evaluations

Laboratory evaluations will be assessed as indicated in Table 6-1.

A central laboratory will be used for analysis of all specimens collected. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Section 13 (Appendix 1).

[redacted]

One sample of serum will be frozen and stored. This sample will be used to repeat study lab tests when needed. It may also be used for additional testing.

6.5.4.1 Hematology

Red blood cell (RBC) count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count, absolute differential WBC count, and platelet count will be measured as indicated in Table 6-1.

6.5.4.2 Clinical chemistry

The following will be measured as indicated in Table 6-1:

Clinical chemistry: sodium, potassium, chloride, bicarbonate, calcium, phosphate, blood urea nitrogen (BUN)/urea, serum creatinine, uric acid, creatine kinase, total protein, [redacted] haptoglobin and HbA1c. The estimated glomerular filtration rate (eGFR) will be calculated using the MDRD formula based on the patient's age at the time of measurement, gender and race.

At screening visit 1, the following assessments will be included: HbA1c, ferritin, transferrin saturation, iron, and if not historically available also ANA, ASMA, and AMA.

Optional: If the investigator requires additional data to evaluate the current alcohol use of the patient at the screening visit, the carbohydrate deficient transferrin (CDT) test can be assessed using the central lab.

Liver tests: see Section 6.4.2

Coagulation: see Section 6.4.3

[redacted]

6.5.4.3 Urinalysis

A clean-catch midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments, as indicated in Table 6-1.

Parameters to be evaluated by urine dipstick test will include specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood. Standard microscopic evaluation of urinary sediments will be performed if the urine dipstick test shows abnormalities.

Spot urine for calculation of protein to creatinine ratio can be aliquoted from the clean-catch urine specimen.

6.5.5 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

[redacted]

Single 12 lead ECGs are collected. The original ECGs on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site. The original trace will be sent electronically for central review directly from the ECG machine.

A standard 12-lead ECG will be recorded at the visits indicated in Table 6-1.

All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

12-lead ECG parameters (RR [Heart Rate], PR, QRS, and QT) are to be assessed.

Each ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), the ECG is repeated to confirm the diagnosis and both ECGs sent to the core laboratory for expedited review if applicable.

Clinically significant abnormalities must be recorded on the relevant section of the appropriate CRFs capturing medical history/Current medical conditions/AE as appropriate.

6.5.6 Pregnancy and assessments of fertility

A positive test at Screening Visit and/or Baseline Visit is an exclusion criterion for participating in the study. The urine pregnancy test will be repeated every four weeks up to the follow up visit (see Table 6-1) including at weeks 20, 28, 36,44 and during any treatment extension period . The tests will be performed at the clinical center or at patient's home. In case of home pregnancy test, the patients will be provided with urine pregnancy test kits. The result must be provided to the investigator at next scheduled visit, in case of positive test the patient must contact investigator immediately. A positive urine pregnancy test after start of study drug requires immediate interruption of study drug until serum hCG is performed and found to be negative. If positive, the patient will enter the post-treatment follow up period. See also Section 5.6.2.

Additional pregnancy testing might be performed if requested by local requirements.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population and have been used in previous trials in this indication or deemed appropriate based on non-clinical and early clinical experience. Patients are seen frequently during treatment and will be assessed for safety parameters

6.6 Other assessments

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

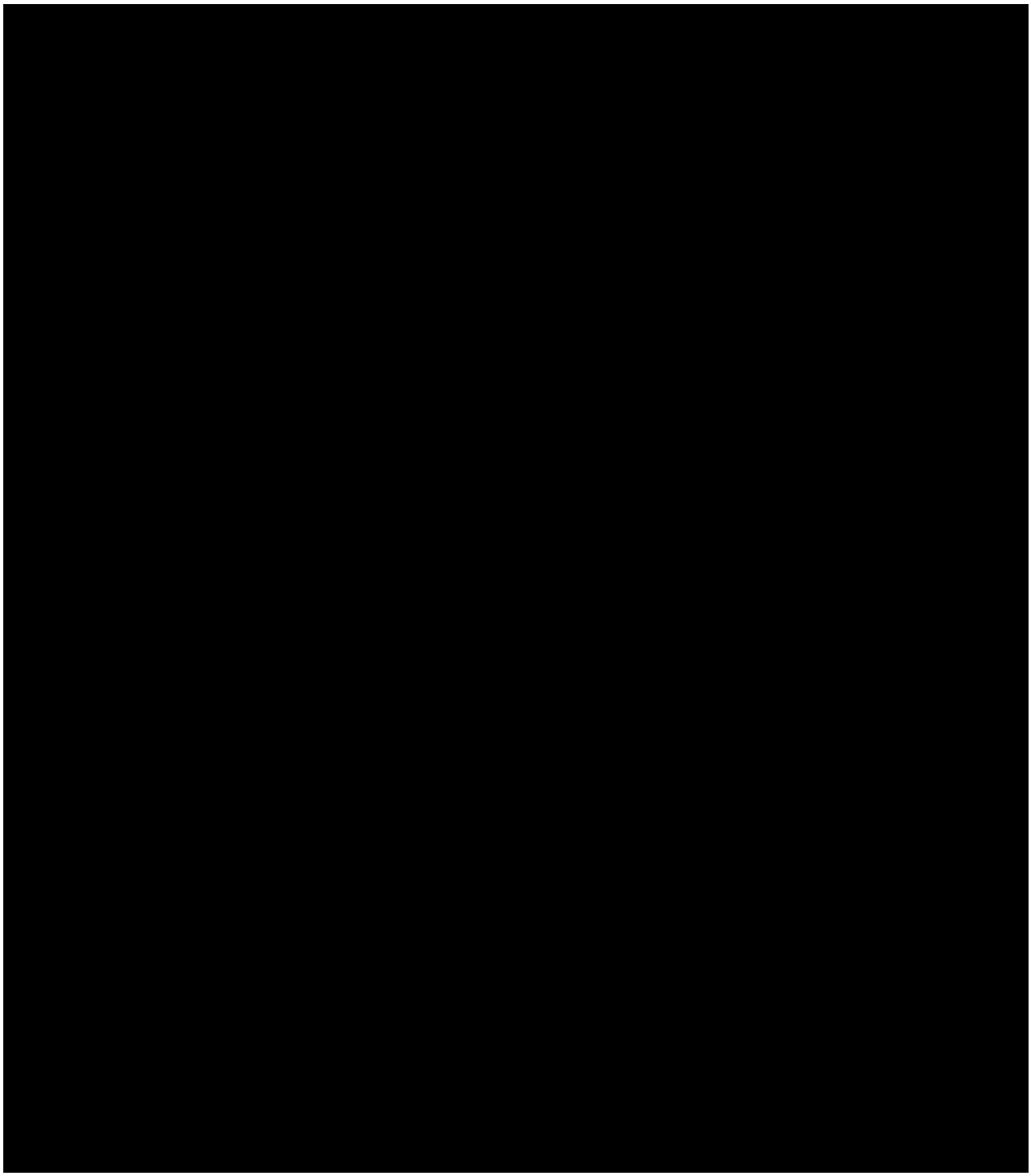
[redacted]

6.6.1 Clinical Outcome Assessments

6.6.1.1 Patient Reported Outcomes (PRO)

[redacted]

[redacted]



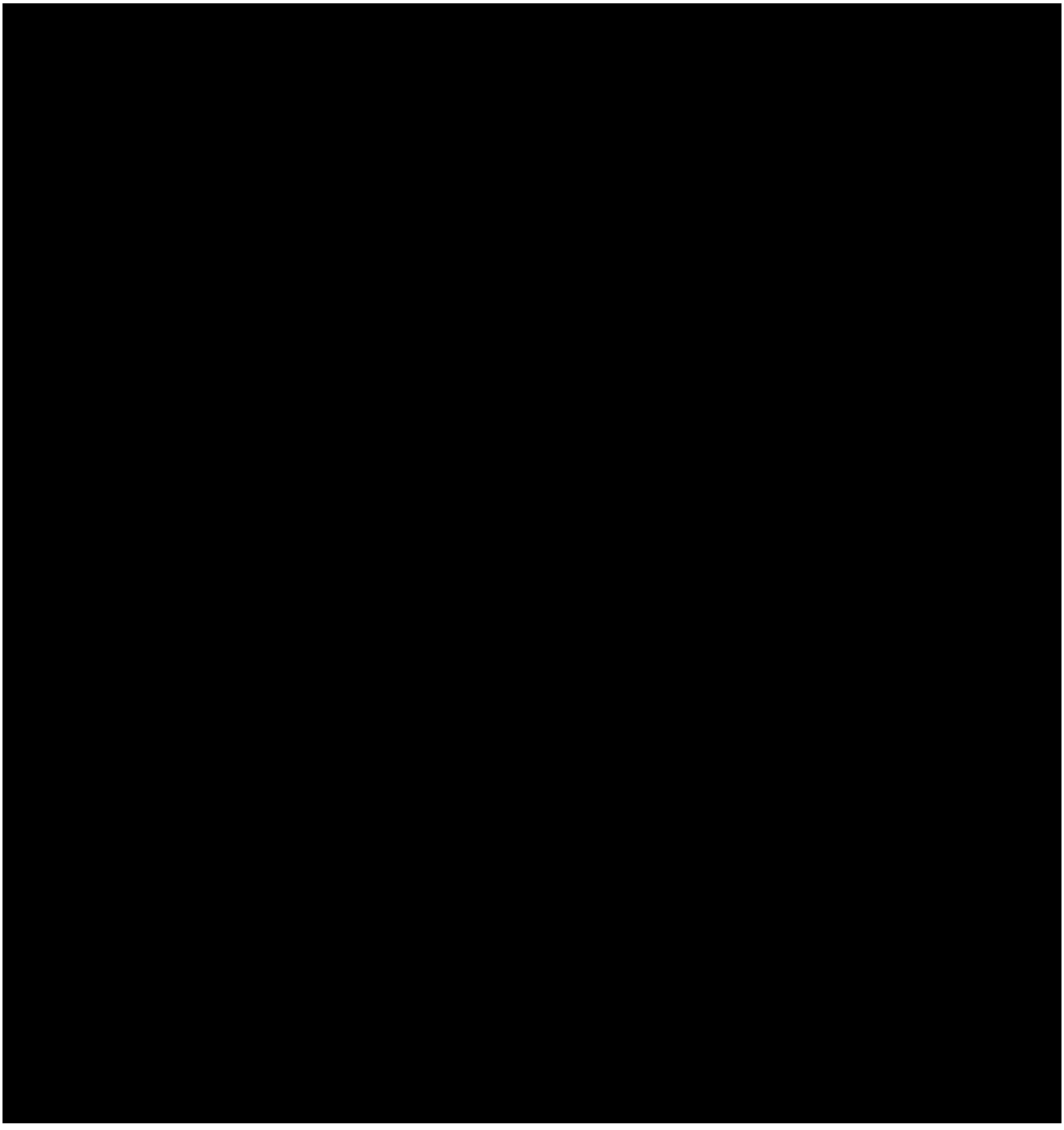
Trial feedback questionnaire

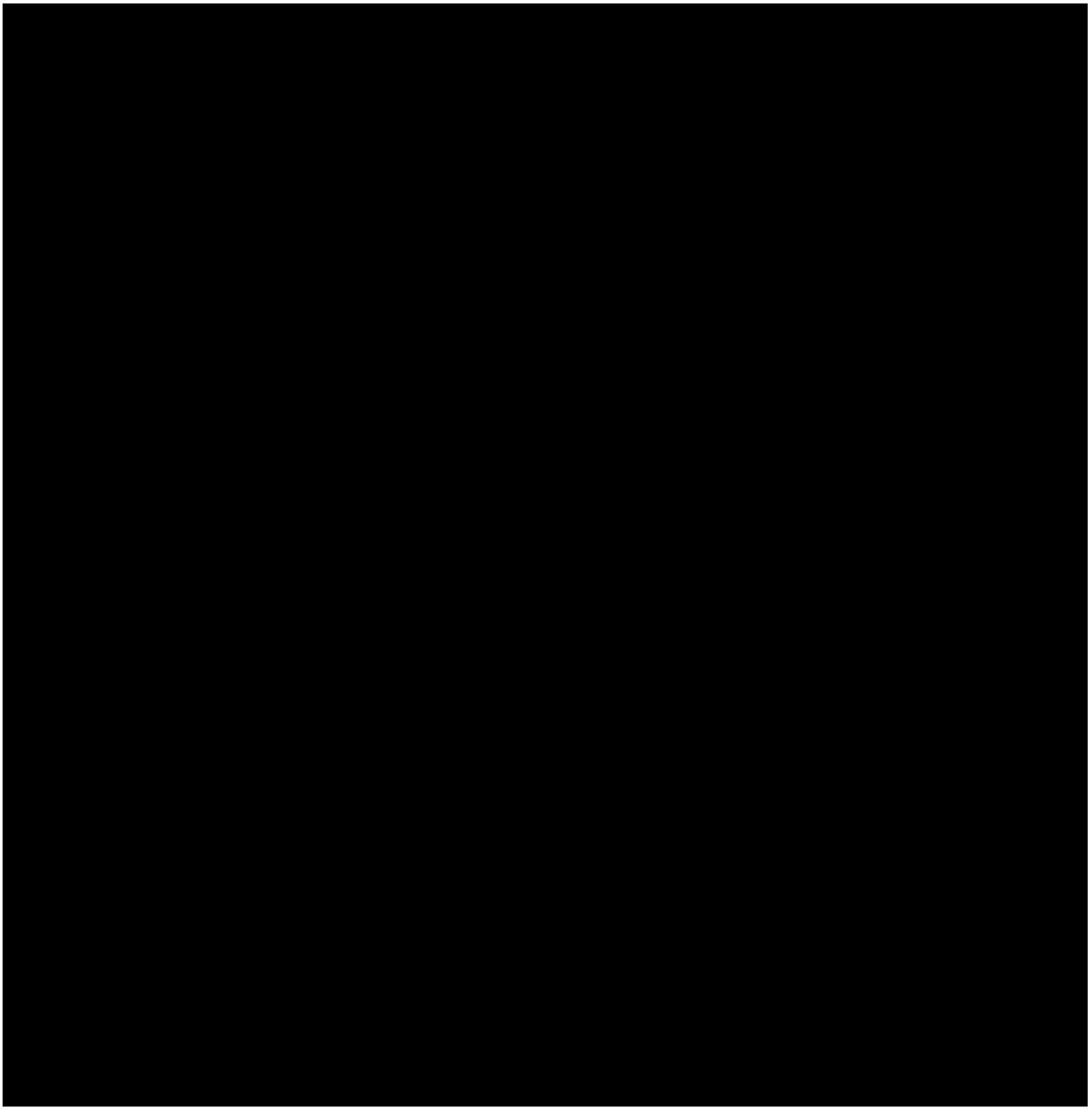
This trial will include an anonymized questionnaire, 'Trial Feedback Questionnaire' for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or adverse events

and therefore would not be trial data. Should any spontaneous information be collected about AEs, this would be transferred to the safety database.

6.6.2 Resource utilization

Not applicable.





7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [possibly including abnormal laboratory findings - see below], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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 patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the appropriate CRF capturing AEs under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

- the severity grade:
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding [investigational] treatment
- its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

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

- no action taken (e.g. further observation only)
- [investigational] treatment interrupted/withdrawn
- concomitant medication given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of

[redacted]

any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the patient informed consent and should be discussed with the patient during the study as needed. Any new information regarding the safety profile of the medicinal product 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 has then to be discussed with the patient.

The investigator must also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (Annex IV, ICH-E12D Guideline).

[redacted]

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (Annex IV, ICH-E12D Guideline).

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

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. 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. 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 with study procedures (i.e. blood sampling).

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.

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. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert and is thought to be related to the study treatment a Patient Safety 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

[redacted]

ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

7.3 Liver safety monitoring

To ensure patient 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 patients likely to have altered liver function at baseline, an adapted monitoring process will be followed.

Subjects who develop elevations in liver-related laboratory parameters and/or clinical symptoms suggestive of liver disease should be managed according to Table 14-1. If ALP, ALT, AST, or bilirubin elevations reach the specified thresholds outlined in Table 14-1, the subject must return to the study site for re-evaluation within 48 to 72 hours after the laboratory results becoming available, at which time central confirmatory laboratory testing will be performed. This includes ALP, ALT, AST, total and direct bilirubin and INR. Central laboratory values for INR that are greater than 1.5 should also be repeated in the local laboratory in addition to the central laboratory. At the same time repeat clinical laboratory samples are drawn, [redacted] If prompt evaluation is not possible within 48 to 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 subject must return to the study site as soon as possible for re-evaluation. 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.

If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption or discontinuation (as described in Table 14-1) if deemed appropriate and close monitoring, causality and clinical evaluation should be performed as below;

- Repeating the liver tests to confirm elevation as described in Table 14-1
- 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 patient if appropriate
- An investigation of the liver event which needs to be followed until resolution
- Obtain a more detailed history of symptoms and prior or concomitant diseases
- Obtain 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

[redacted]

- Rule out acute viral hepatitis Types A, B, C, D, and alcoholic hepatitis; hypoxic/ischemic hepatopathy; autoimmune hepatitis and biliary tract disease

- Obtain a history of exposure to environmental chemical agents

These investigations can include serology tests, liver biopsy, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion.

Any cases of possible drug-related liver injury will be blindly adjudicated by a hepatologist with expertise in drug-related liver injury and as necessary reviewed by the DMC which includes additional hepatologists.

Subjects 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 subject is asymptomatic. All follow-up information, and the procedures performed must be recorded on the appropriate CRFs.

7.4 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum event:
  - confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- Urine event
  - new onset (≥ 1+) proteinuria;
  - new onset (≥ 1+), hematuria or glycosuria

Every renal laboratory trigger or renal event as defined in Table 15-1 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Appendix 3.

7.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (European Medicines Agency definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the 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.

[redacted]

Table 7-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in CRF (Yes/No)	Document in eCRF capturing AE	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

7.6 Pregnancy reporting

To ensure patient safety, any pregnancy occurring in a study subject or their partner after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Patient Safety department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (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 patient records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis 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 patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or

assessments. All information on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients/subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRFs) using fully validated secure web-enabled software that conforms to US CFR 21 Part 11 requirements. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

Concomitant 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. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

[redacted]

[redacted]

[redacted]

Biopsy results will be read centrally and the results will be sent electronically to Novartis (or a designated CRO).

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

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis. The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

8.4 Data Monitoring Committee

This study will use the tropifexor program level external DMC. The committee will consist of at least two physicians and a statistician who are not otherwise associated with the study, and who are experienced in multicenter trials in hepatology and general medicine. The main tasks of the Committee for this study will be to review emerging safety data and primary efficacy data and provide recommendations to the Sponsor concerning safety.

The program Data Monitoring Committee Charter provides detail on the committee composition and processes.

The DMC will review safety, including AEs and laboratory parameters, on a regular basis. In addition, in the event that more than 3 patients develop similar SAEs, the DMC chairman will be alerted. Further details regarding relevant data and actions will be specified in the separate DMC charter.

8.5 Adjudication Committee

Any cases of possible drug-related liver injury will be blindly adjudicated by a hepatologist with expertise in drug-related liver injury and as necessary reviewed by the DMC which includes additional hepatologists.

[redacted]

9 Data analysis

The final (end-of study) analysis will be conducted on all patient data collected up to the Week 52 visit.

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

- Screened set (SCR) – All patients who signed the informed consent.
- Randomized set (RAN) – All patients who received a randomization number, regardless of receiving trial medication.
- Full analysis set (FAS) – All patients to whom study treatment has been assigned*. Following the intent-to-treat (ITT) principle, patients are analyzed according to the treatment they have been assigned to at randomization.
- Safety set (SAF) - All patients who received at least one dose of study drug and have at least one post-baseline safety assessment. Of note, the statement that a patient had no adverse events also constitutes a safety assessment. Patients will be analyzed according to the treatment received.

*excluding patients who were mis-randomized and did not take investigational drug. Mis-randomized patients are those who were not qualified for randomization, but were inadvertently randomized into the study.

The number of patients in each analysis set will be presented by treatment group and overall for the screened set.

9.2 Patient demographics and other baseline characteristics

Demographic variables and other baseline characteristics will be summarized for the FAS. Descriptive statistics (mean, median, standard deviation, minimum and maximum) will be presented for continuous variables for each treatment group and for all patients (total). The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients (total). In addition, all relevant medical history, and protocol solicited medical history will be summarized by treatment group.

9.3 Treatments

The duration of investigational treatment exposure (days) will be summarized by treatment group for the SAF, both descriptively (i.e. mean, standard deviation, median, quartiles, minimum and maximum) and by duration category (e.g. weeks).

The proportion of patients with dose reduction will be presented by treatment group.

Medications will be identified using the WHO dictionary including ATC code and presented for the SAF. Prior medications are defined as any medications taken prior to the randomization visit (regardless of whether they are stopped or continued after randomization). Concomitant medications and significant non-drug therapies are defined as those used during the double-

blind period. Prior and concomitant medications will be summarized by treatment group in separate tables. Medications will be presented in alphabetical order, by ATC codes and grouped by anatomical main group (the first level of the ATC code). Tables will also show the overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular anatomical main group.

Concomitant medications that were prohibited as per protocol and given during the conduct of the study as well as significant non-drug therapies will be provided in separate tables.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

Safety (to be assessed in SAF):

- Occurrence of adverse events
- Occurrence of serious adverse events
- Occurrence of adverse events resulting in permanent discontinuation
- Occurrence of adverse events of special interest
- Changes in Vital signs
- Changes in Laboratory data

9.4.2 Statistical model, hypothesis, and method of analysis

There are no pre-specified hypotheses and statistical models in this study. The methods to analyze the primary safety variables are outlined in Table 9-1.

Table 9-1 Primary variables and methods of analysis

Variable	Method of analysis
Occurrence of adverse events	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of serious adverse events	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of adverse events resulting in discontinuation or dose reduction of study treatment	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of adverse events of special interest	Summary table of absolute and relative frequency, overall and by type of AE as the risks are described for both tropifexor and CVC (risk definition for tropifexor are those that appear in in tropifexor and CVC IB)
Changes in vital signs	Descriptive statistics by visit
Changes in Laboratory data	Descriptive statistics by visit

9.4.3 Handling of missing values/censoring/discontinuations

Imputation of incomplete adverse events start and end dates will follow standard conventions and will be described in detail in the statistical analysis plan.

[redacted]

9.4.4 Sensitivity analyses

No sensitivity analyses are planned for the assessment of the primary variables.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

An overview of the secondary efficacy variables and planned analysis is given in Table 9-2.

Table 9-2 Secondary efficacy variables and analyses

Variable	Analysis
At least a one point improvement of fibrosis	Cochran-Mantel-Haenszel test controlling for baseline fibrosis stage for each tropifexor + CVC combination vs. each monotherapy treatment, with supporting information from risk differences, odds ratios with 95% confidence intervals
Resolution of steatohepatitis (as determined by central pathologist)	Cochran-Mantel-Haenszel controlling for baseline fibrosis stage for each tropifexor + CVC combination vs. each monotherapy treatment, with supporting information from risk differences, odds ratios with 95% confidence intervals

There is a single secondary objective in this study which is to characterize the efficacy of tropifexor + CVC in patients with NASH with fibrosis stage F2/F3 as assessed by histological improvement after 48 weeks of treatment compared to monotherapies (tropifexor and CVC) relative to baseline biopsy. There are two estimands that will be used to evaluate this objective.

The first estimand is the difference on the proportion of patients on the different tropifexor + CVC regimens who achieve at least a one point improvement in fibrosis at Week 48 compared to tropifexor and CVC monotherapy patients. It is assumed that anyone who does not have a Week 48 liver biopsy or does not remain on their randomized study treatment for at least 24 weeks (even if a Week 48 biopsy was obtained) will have their outcome imputed by multiple imputation (MI). For subjects who remain on their randomized study treatment for at least 24 weeks, but discontinue study treatment prior to Week 48, available Week 48 biopsy results will be used as observed. This is a hypothetical strategy addressing the question "what would be the outcome if subjects had stayed at least 24 weeks on treatment and a Week 48 biopsy had been obtained". Treatment differences between tropifexor + CVC combination therapy and monotherapy with tropifexor or CVC will be evaluated using a Cochran-Mantel-Haenszel test controlling for baseline fibrosis stage (F2/F3). The estimand will be evaluated in the FAS population.

The second estimand is the difference in the proportion of patients on the different tropifexor + CVC regimens who achieve resolution of steatohepatitis at Week 48 relative to baseline compared to tropifexor and CVC monotherapy patients. It is assumed that anyone who does not have a Week 48 liver biopsy result or does not remain on their randomized study treatment for at least 24 weeks will have their outcome imputed by multiple imputation (MI). The handling of intercurrent events (discontinuation of assigned treatment) is equivalent to the first estimand as described above Treatment differences between tropifexor + CVC combination therapy and monotherapy with tropifexor or CVC will be evaluated using a Cochran-Mantel-

[redacted]

Haenszel test controlling for baseline fibrosis stage (F2/F3). The estimand will be evaluated in the FAS population.

Due to COVID-19 pandemic, it may not be possible for patients to return on time for Week 48 visit to perform liver biopsy and according to drug dispensing plan in Section 5.5.2, the Week 48 liver biopsy can be delayed by approximately 10 weeks. Since the purpose of the secondary efficacy analysis is to evaluate the potential histological benefit of study treatment, all biopsies obtained, including those from eligible patients after week 48, will be included in the analysis.

Sensitivity analyses:

Sensitivity analyses will be conducted to account for delayed Week 48 biopsies due to extended treatment under COVID-19 pandemic. Further details are to be described in the statistcal analysis plan (SAP).

9.5.2 Safety variables

All safety variables (i.e. adverse events, laboratory data, vital signs, and ECG) will be summarized by treatment for all patients of the safety set. Safety variables which are part of the primary variables are listed in Table 9-1 as well. Analyses of the safety variables will be performed in the Safety Set.

9.5.2.1 Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized. AEs will be summarized by presenting, for each treatment group, the number and percentage of patients having experienced

- Any adverse event (AE),
- Any serious adverse event (SAE),
- Any adverse event by primary system organ class (SOC),
- Any adverse event by preferred term,
- Any adverse by severity,
- Any adverse event possibly related to study treatment (investigator assessment),
- Any adverse event resulting in discontinuation of study treatment,
- Any adverse events of special interest for tropifexor or CVC treatment.

Exposure adjusted tabulations of adverse events and tabulations of appropriate adverse events according to defined intervals will be provided as well. If a patient reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a patient reported more than one adverse event within the same primary system organ class, the patient will be counted only once with the greatest severity at the system organ class level, where applicable. A separate summary will be provided for deaths, if they occur during the course of the study.

[redacted]

9.5.2.2 Laboratory data

The summary of safety laboratory evaluations will be presented for the groups of laboratory tests (e.g. hematology, clinical chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for patients with both baseline and post baseline values. Relative and absolute frequencies of patients with liver events as defined in Appendix 2 will also be provided, as well as shift tables based on the normal laboratory ranges. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test category and treatment group.

The number and percentage of patients with clinically notable laboratory results after baseline will be presented. Clinically notable laboratory results, for those parameters where ranges are available. Only patients with laboratory results within the normal reference range from the central laboratory at baseline will be included in the tabulations.

Safety laboratory parameters which are also part of the efficacy analyses will be included in the safety tables as well (e.g. liver enzymes, lipids).

9.5.2.3 Baseline definition

Generally, baseline is defined as the last assessment before date and time of first administration of study drug; if only the date is available, the last assessment before or at the date of first administration of study drug will be used. For transaminases (ALT, AST, GGT) and bilirubin, the baseline value will be calculated as the mean of the last two assessments before first administration of the study drug, which are usually those taken at the Screening 2 and Baseline visit (if a test was performed).

9.5.2.4 Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for patients with both baseline and post-baseline values. Patients with notable vital signs as defined in Appendix 1 will be listed.

9.5.2.5 ECG

ECG data will be summarized by treatment and visit (post-baseline ECGs are performed at Week 24 and Week 48).

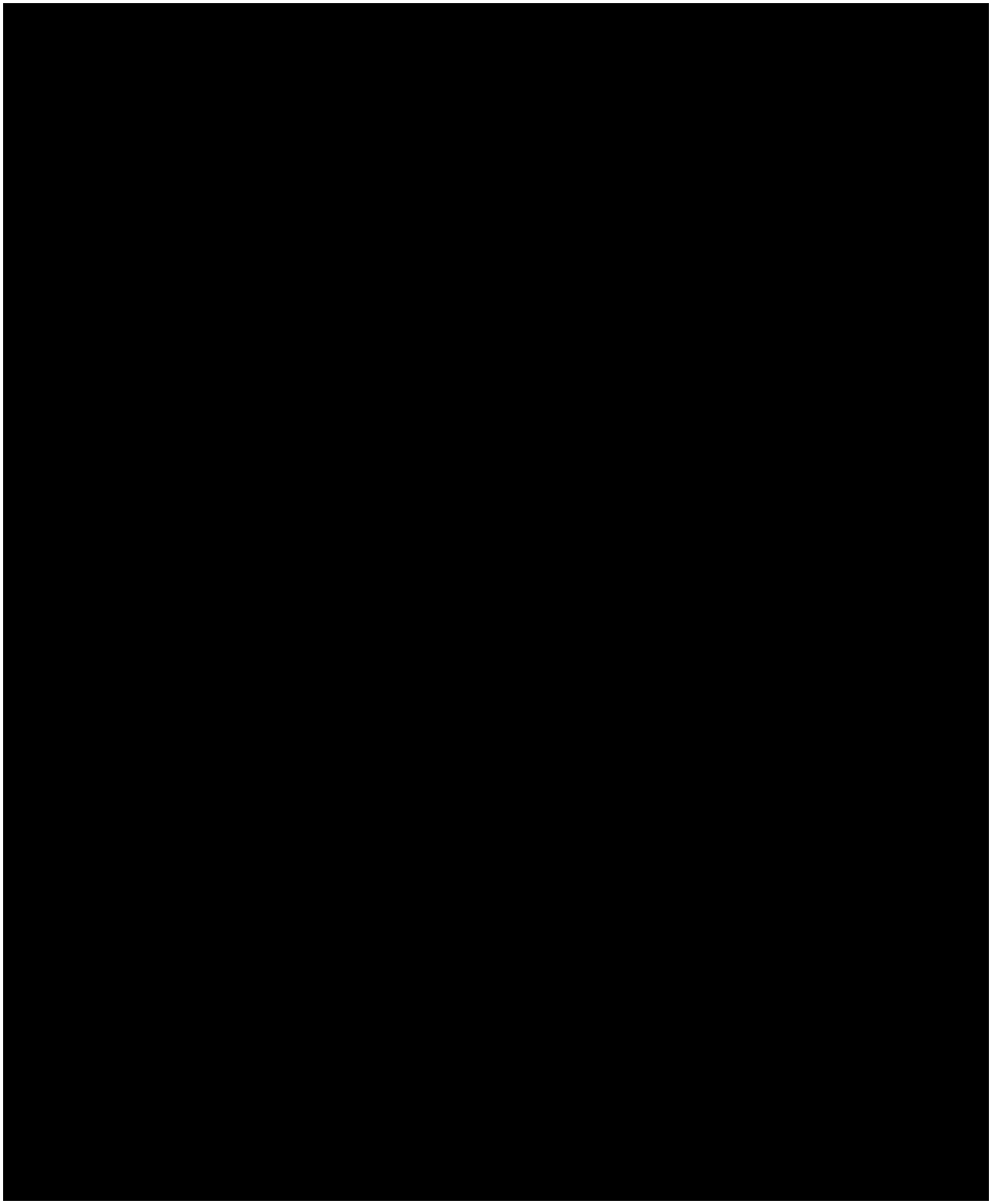
The Fridericia QT correction formula (QTcF) will be used for clinical decisions and for analyses.

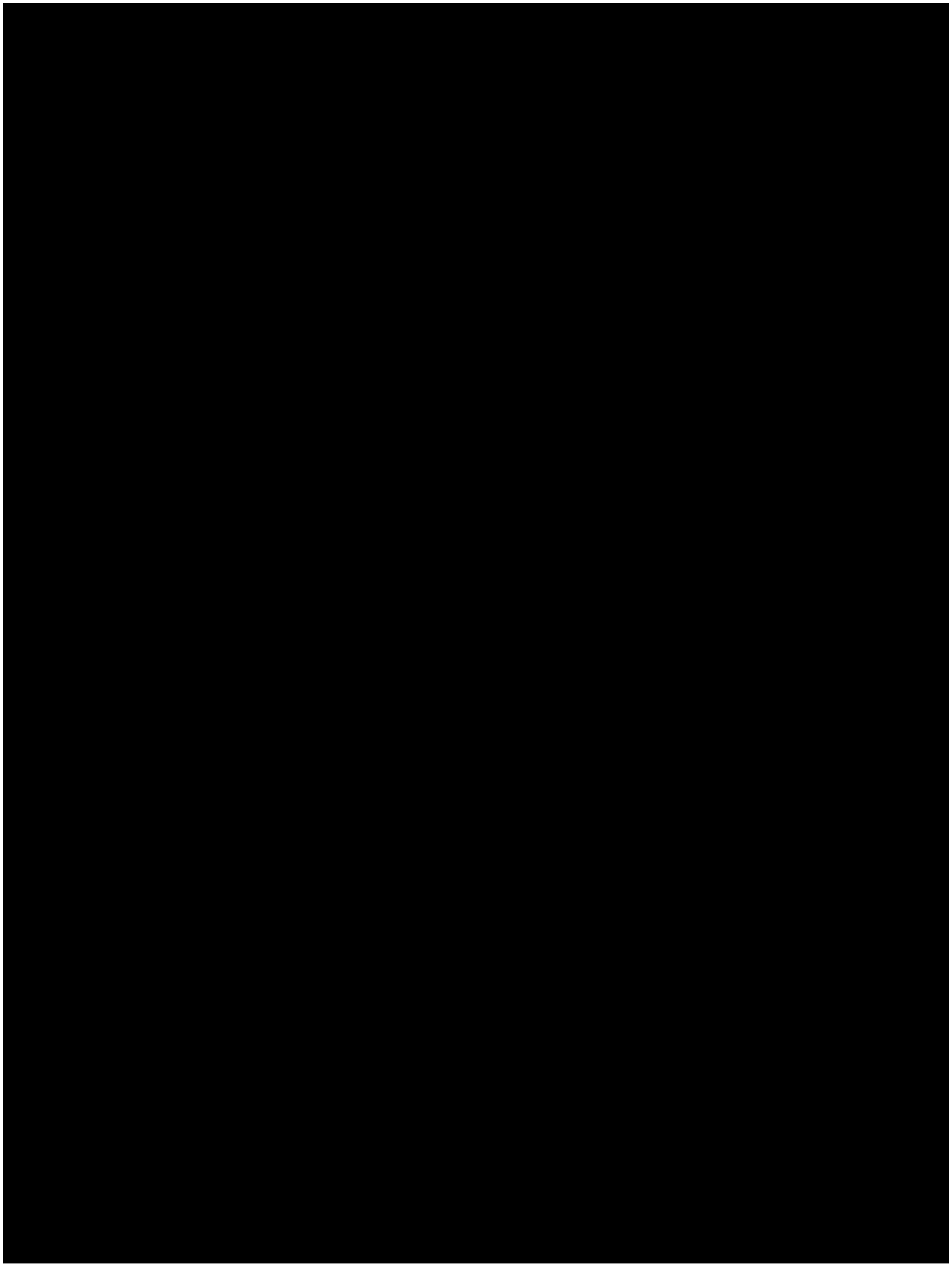
Notable QTcF values and changes from baseline will be summarized at Week 24 and Week 48. A notable value is defined as a QTcF interval of greater than 450 ms. The categories used for the change (increase) in QTcF are: $\leq$ 30 ms, > 30 to $\leq$ 60 ms and > 60 ms.

[redacted]

9.5.3 Resource utilization

Data relating to resource utilization will be used for the purpose of economic evaluation which will be carried out and reported as a separate activity.





9.7 Interim analyses

No interim analysis is planned for the study.

9.8 Sample size calculation

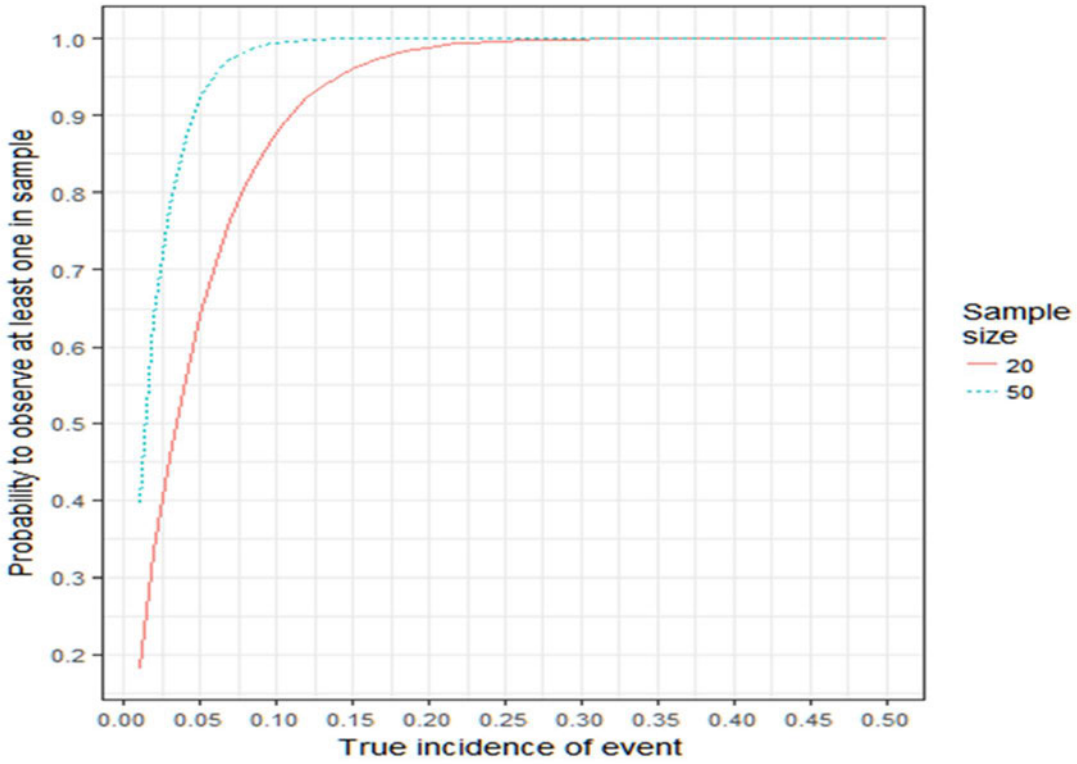
The primary objective of the study is to determine if there is a safe combination between one of the chosen doses of tropifexor and 150 mg of cenicriviroc. However, the assessment will be made based on the whole safety profile and not on quantitatively formulated hypotheses for distinct parameters. Therefore the sample size is based on the feasibility with respect to expected speed of enrollment and duration of the study, not on formal statistical criteria.

9.8.1 Power considerations with given sample size for safety assessment

Events with a true incidence of 30% and above are likely to be observed (almost 100% probability) in a group of 50 patients (size of each treatment group). Events with true incidences below 10% down to 3% are still very likely to be observed, while events are observed with less

than 50% probability only if the true incidence is less than about 2.5% (Figure 9-1). It is noteworthy, however, that a single patient constitutes 2% in a sample of 50.

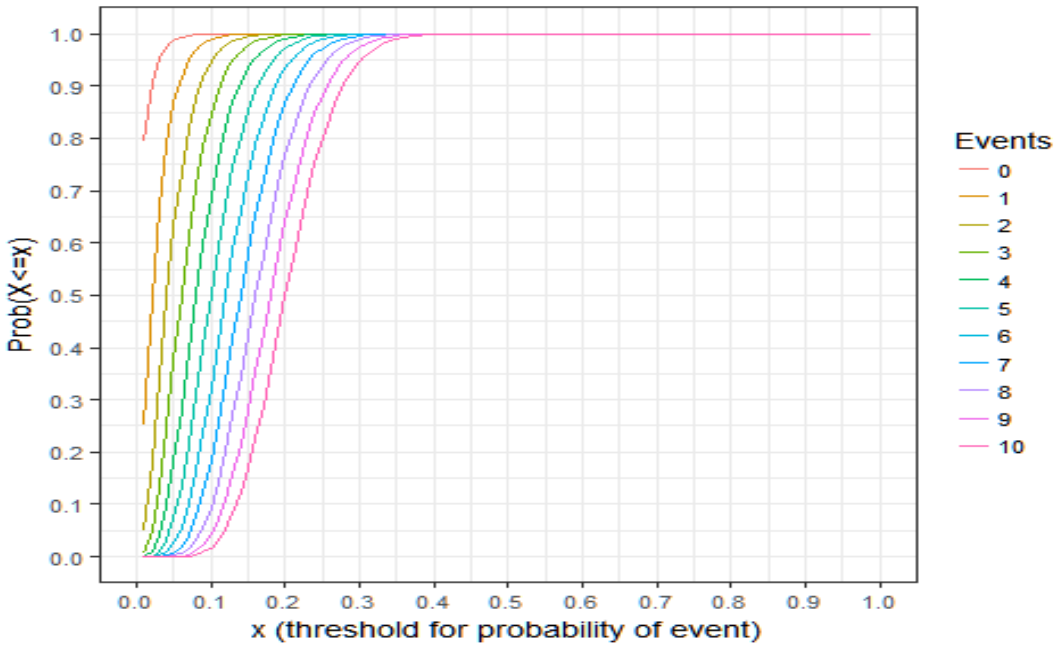
Figure 9-1 Binomial probability to observe an event with given sample size



Probabilities of the incidence being below a certain threshold are plotted in Figure 9-2 for a sample size of 50 patients when the event is observed in 0, 1, 2, ...,10 patients (assuming a beta distribution with prior shape parameters 0.33, 0.33).

[redacted]

Figure 9-2 Predictions for probability of event based on observed number



For example, if 0 events are observed, the probability (Prob) that the incidence is ≤ 5% would be 98.7%. If an event is observed in one patient, the probability that the incidence is ≤ 5% would be 86.6%. Similarly, if an event is observed in 10 patients (one fifth), the probability that the incidence is ≤ 20% would be approximately 50% (calculated using R function pbeta).

9.8.2 Power considerations with given sample size for efficacy assessment

To evaluate the effectiveness of tropifexor + CVC with respect to the proportion of patients who have at least a one point improvement in fibrosis at Week 48 compared to baseline (i.e, the response rate), one needs to consider the effect size that one is able to detect with respect to both tropifexor and CVC as monotherapy.

- For CVC, based on information from the CENTAUR Phase 2b study, Friedman 2017), it can be assumed that the monotherapy response rate at Week 48 in F2/F3 patients would be approximately 35%
- For tropifexor, a response rate of 42% is assumed (best-case scenario) based on the interpolation of expected Week 72 response rate and assuming linear improvement over time
- For the combined effect of tropifexor + CVC it will be assumed that 75% of the efficacy for CVC will be added to the effect of tropifexor (i.e. a response rate of 69%)

For comparisons between tropifexor + CVC and CVC monotherapy a 2-group continuity corrected χ^2 test of proportions with type error 0.10 (2-sided, no adjustment for multiple comparisons), a sample size of 50 per group results in a power of 95% (nQuery Advisor 7.0).

[redacted]

For comparisons between tropifexor + CVC and tropifexor monotherapy a 2-group continuity corrected χ^2 test of proportions with type error 0.10 (2-sided, no adjustment for multiple comparisons), a sample size of 50 per group results in a power of 81% (nQuery Advisor 7.0).

Further scenarios assuming different response rates for tropifexor and the magnitude of effect added to tropifexor by CVC are described in Table 9-4.

Table 9-4 Power for detecting a treatment difference between tropifexor + CVC and tropifexor and CVC monotherapy

Assumed tropifexor response rate	Assumed response rate of tropifexor + CVC	Power N = 50/arm vs. tropifexor monotherapy	Power N = 50/arm vs. CVC monotherapy
Current target 42% response rate at Week 48 (50% improvement over OCA)	½ effect of CVC added to tropifexor ((60%)	48%	75%
	¾ effect of CVC added to tropifexor (69%)	81%	95%
	Full effect of CVC added to tropifexor (77%)	96%	99%
Response rate between target and OCA at Week 48 (35%)	½ effect of CVC added to tropifexor (53%)	48%	48%
	¾ effect of CVC added to tropifexor (62%)	81%	81%
	Full effect of CVC added to tropifexor (70%)	96%	96%
Worst case: tropifexor same effect as OCA 28% at Week 48	½ effect of CVC added to tropifexor (46%)	50%	23%
	¾ effect of CVC added to tropifexor (55%)	82%	56%
	Full effect of CVC added to tropifexor (63%)	96%	81%

*Power calculated assuming a two-sided Type I error rate of 0.10

10 Ethical considerations

10.1 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 Japanese

Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients/subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if applicable after such consent has been provided by a legally acceptable representative(s) of the patient. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline 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, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

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 requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

[redacted]

10.3 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, informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to patients/subjects. 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.

[redacted]

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group 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 Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of patients/subjects 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, 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.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to patients/subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this

study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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[redacted]

13 Appendix 1: Clinically notable laboratory values and vital signs

The central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory reports. Investigators are responsible for reviewing these abnormal values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF. Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

SEE APPENDIX 2 FOR SPECIFIC LIVER EVENT AND LABORATORY TEST TRIGGER DEFINITIONS AND FOLLOW-UP REQUIREMENTS.

For ECGs, a notable QTc value is defined as a QTcF (Fridericia) interval of > 450 msec for males or > 460 msec for females, all such ECGs will be flagged by the Central CRO and require assessment for clinical relevance and continuance of the patient by the Investigator.

For vital signs, please see Table 13-1 for notable abnormalities.

Table 13-1 Notable abnormalities in vital signs

Vital signs		**Notable abnormalities**	
		Absolute	Relative to baseline
Pulse rate (beats/min)		> 130	> 120 and increase from baseline ≥ 15
		< 40	≤ 50 and decrease from baseline ≥ 15
Blood pressure (mmHg)	Systolic	> 200	≥ 180 and increase from baseline ≥ 20
		< 75	≤ 90 and decrease from baseline ≥ 20
	Diastolic	> 115	≥ 105 and increase from baseline ≥ 15
		< 40	≤ 50 and decrease from baseline ≥ 15

Note: these notable ranges should not be used as reference ranges to establish a clinical diagnosis

[redacted]

14 Appendix 2: Liver Monitoring and Follow-up Requirements

For transaminases (ALT, AST, GGT) and bilirubin, the baseline value will be calculated as the mean of the last two assessments before first administration of the study drug, which are usually those taken at the Screening 2 and Baseline visit.

Table 14-1 Management of Subjects 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], [redacted]	Interrupt dosing[e]
	ALT and/or AST > 3 × ULN but ≤ 5 × baseline 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], [redacted]	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], [redacted]	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], [redacted]	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] [redacted]	Interrupt dosing[e]

[redacted]

Baseline	Treatment-Emergent (Confirmed[a])	Liver-Related Clinical Symptoms[b]	Action taken	
			Monitoring[c]	Study Drug
	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], [redacted]	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], [redacted]	Interrupt dosing[e]
ALP				
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], [redacted]	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], [redacted]	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], [redacted]	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], [redacted]	Interrupt dosing[e]

[redacted]

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], [redacted]	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], [redacted]	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] [redacted]	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]

[redacted]

Baseline	Treatment-Emergent (Confirmed[a])	Liver-Related Clinical Symptoms[b]	Action taken	
			Monitoring[c]	Study Drug

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

[a] The required confirmatory measurement should be obtained within 48 to 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 symptoms of abdominal pain, 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 subjects 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 subjects should be closely monitored until resolution of clinical symptoms/stabilization of liver biochemistries to baseline levels or baseline grade of abnormality. In subjects 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, which are usually those taken at the screening 2 and baseline visit) 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 28 days (see Section 5.5.5). If significant liver abnormalities recur at any time after restarting study drug, then study drug must be permanently discontinued.

[f] In subjects with Gilbert's syndrome, in place of the total bilirubin criterion, use direct bilirubin > 2 × baseline.

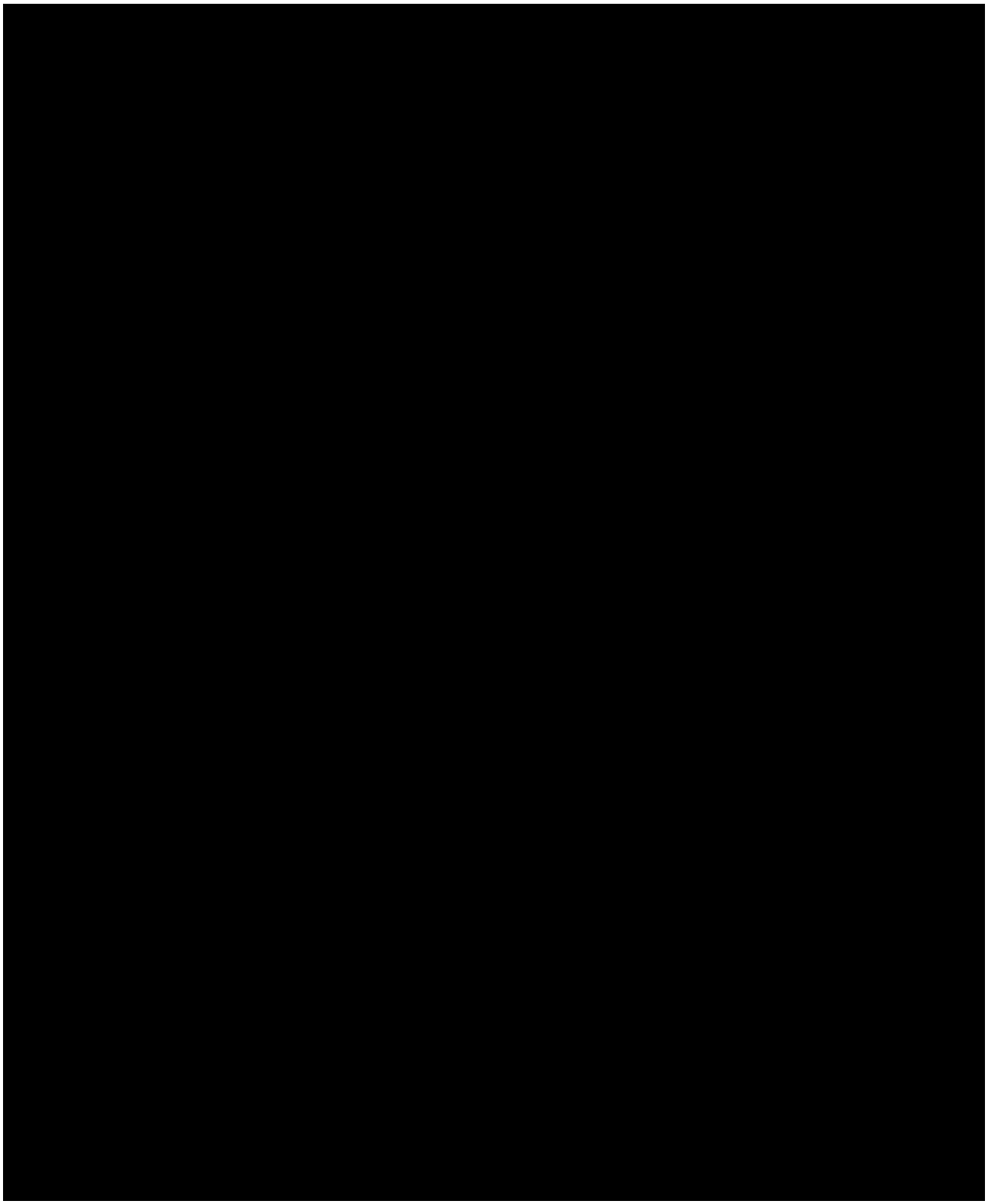
[g] Development of liver-related clinical symptoms in absence of biochemical abnormalities is an indication for prompt biochemical and physical evaluation to decide whether continued dosing is appropriate. If prompt evaluation is not poss ble, study drug should be interrupted and subject followed for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

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥ 1+ Albumin- or Protein-creatinine ratio increase ≥ 2-fold Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; Protein-creatinine ratio (PCR)≥ 150 mg/g or > 15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥ 1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥ 1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the eCRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	



17 Appendix 5: The American Heart Association (AHA) Recommended Diet

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

AHA recommends the following:

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

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

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

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

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

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

Limit drinks and foods with added sugar.

[redacted]