NOVARTIS

Global Clinical Development - General Medicine

LJN452

Clinical Trial Protocol CLJN452A2202 / NCT02855164

A randomized, double-blind, placebo controlled, 3- part, adaptive design, multicenter study to assess safety, tolerability and efficacy of tropifexor (LJN452) in patients with non-alcoholic steatohepatitis (NASH)

FLIGHT-FXR

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[redacted]

List of abbreviations

A1AT	Alpha-1-antitrypsin
ACR	Albumin-Creatinine ratio
AE	Adverse Event
AHA	American Heart Association
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AMA	Anti-mitochondrial antibody
ANA	Anti-nuclear antibody
ANIT	Alpha-Naphtha Isothiocyanate
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
[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
BMI	Body Mass Index
BSEP	Bile Salt Export Pump
BSL	Baseline visit
BUN	Blood Urea Nitrogen
C4	7α-Hydroxy-4-cholesten-3-one
CDT	Carbohydrate Deficient Transferrin
CFR	US Code of Federal Regulations
CI	Confidence Interval
[redacted]	[redacted]
Cmax	Maximum drug concentration
COA	Clinical Outcome Assessment
CPO	Country Pharma Organization
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events version 4.03 (2010)
CYP3A4	Cytochrome P450 3A4
CYP7A1	Cytochrome P450 7A1
DAR	Dose Administration Record
DMC	Data Monitoring Committee
[redacted]	[redacted]
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EC50	Half Maximal Effect Concentration

[redacted]

EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
EMA	European Medicines Agency
[redacted]	[redacted]
EOS	End of Study
EOT	End of Treatment
FAS	Full analysis set
FGF19	Fibroblast Growth factor 19
[redacted]	[redacted]
FXR	Farsenoid X Nuclear Receptor
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLP	Good Laboratory Practice
HA	Hyaluronic Acid
HbA_{1c}	Glycosylated hemoglobin
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotropin
HCP	Health Care Professional
HCV	Hepatitis C virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
[redacted]	[redacted]
[redacted]	[redacted]
IA	Interim Analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFG	Impaired Fasting Glucose
INR	International Normalized Ratio
[redacted]	[redacted]
IN	Investigator Notification
IU	International Unit
IQR	Interquartile Range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
MAR	Missing at random
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease

[redacted]

MedDRA	Medical dictionary for regulatory activities
miRNA	Micro Ribonucleic acid
MMRM	Mixed-Effects Model Repeated Measures
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	Non-alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
NSAIDS	Nonsteroidal Anti-Inflammatory Drugs
OCA	Obeticholic Acid
OC/RDC	Oracle Clinical/Remote Data Capture
PBC	Primary Biliary Cirrhosis / Primary Biliary Cholangitis
PCR	Protein-Creatinine ratio
PD	Pharmacodynamics
[redacted]	[redacted]
PIIINP	Propeptide of Procollagen Type III
PK	Pharmacokinetic
PNPLA3	Patatin-like phospholipase domain-containing protein 3
PRO	Patient Reported Outcome
PSW	Premature Study Withdrawal
PT	Prothrombin Time
PUFA	Polyunsaturated Fatty Acids
QTcF	Corrected QT interval (Fridericia method)
RAN	Randomized set
RBC	Red Blood Cell
[redacted]	[redacted]
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety Set
SBP	Systolic Blood Pressure
sCr	Serum Creatinine
SCR	Screened set
SHP	Small Heterodimer Partner
SOC	System Organ Class
SPP	Safety Profiling Plan
SULT2A1	Sulfotransferase Family 2A Member 1
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBC	To Be Confirmed
TBL	Total Bilirubin
TD	Study Treatment Discontinuation
TIMP-1	Tissue Inhibitors of Metalloproteinases
Tmax	Time post-dose when Cmax occurs
TNF-α	Tumor Necrosis Factor α
TT	Thrombin Time
UGT1A1	UDP Glucuronosyltransferase 1 Family, Polypeptide A1
UGT1A3	UDP Glucuronosyltransferase 1 Family, Polypeptide A3
UGT2B4	UDP Glucuronosyltransferase 2 Family, Polypeptide B4

[redacted]

ULN	Upper Limit Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization
WHR	Waist-to-Hip ratio
WTH	Waist-to-Hip
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients fulfilling certain criteria
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 twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
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)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US 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 ID	A unique number assigned to each patient upon signing the informed consent
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 consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 3 (05-Oct-2017)

Amendment Rationale

The purpose of this amendment is to add Part C to the protocol to explore doses of tropifexor (LJN452) > 90 µg. Part C will enroll 150 patients to be treated for 48 weeks with 140 µg tropifexor, 200 µg tropifexor, or placebo once daily in a 1:1:1 randomization.

Use of the 90 µg dose in Part B, and subsequent use of tropifexor doses > 90 µg, were recommendations from the Data Monitoring Committee (DMC) upon review of the Part A interim analysis data. The DMC review revealed no safety concerns at the doses up to 90 µg studied in Part A. PK/PD modeling and simulation of the Part A data at the time of the DMC interim analysis suggested that exposures of AUC > 40 ng*h/mL should be explored to better define the maximum response for the ALT, AST, FGF-19 and GGT biomarkers evaluated.

Modeling of the Part A PK data indicates that exposure at the doses explored in Parts A and B were approximately 40 ng*h/mL at the 90 µg dose, 25 ng*h/mL at the 60 µg dose, 15 ng*h/mL at the 30 µg dose and 5 ng*h/mL at the 10 µg dose. Extrapolation of the modeled PK Part A data shows that for doses of 140 µg and 200 µg approximately 80% and 95% of patients, respectively, will achieve an AUC > 40 ng*h/mL, and these doses will approximate AUC values of 60 and 80 ng*h/mL respectively. Therefore the 140 µg and 200 µg doses were selected for use in Part C to complete the broad dose finding approach in this study.

Initial non-clinical oral gavage toxicology studies conducted in rats and dogs for up to 13-weeks limited the upper systemic exposures to tropifexor in patients to 70 ng*h/mL and 12 weeks of treatment in previous versions of this protocol (v00 – v02). Non-clinical toxicity studies exploring higher doses for longer duration have been ongoing. Newly available results from 26-week rat and 39-week dog toxicity studies indicate that greater FXR activation is possible (both *in vitro* and *in vivo*) at higher exposure levels than those currently used in Parts A and B of this trial. These chronic toxicology studies support a higher NOAEL. The higher systemic exposure to tropifexor achieved at the NOAEL in these toxicity studies is AUC0-24h > 274 ng*h/mL in dogs which is more than 3 x greater than the predicted exposure at 200 µg (AUC = 80 ng*h/mL) in NASH patients.

Due to the longer term toxicity data now available, study duration will be increased to 48 weeks. Longer term treatment provides the opportunity for inclusion of biopsies in this trial. Paired liver biopsies at baseline and at Week 48 will be included for all patients in Part C of this study. Inclusion criteria for Part C 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, AND ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females). The phenotypic diagnosis of NASH will not confer eligibility in Part C.

Changes to the protocol

The main modifications to the protocol are:

1. Tropifexor, the newly assigned INN, replaces LJN452 throughout the protocol.

[redacted]

2. Sample Size - Overall sample size for the study is 345 patients.

   Part B: As a result of the DMC selection of one Part A dose (90 μg) for Part B, the sample size is 120 patients as specified in previous versions of the protocol and outlined in Section 3.1, Study Design. This is not a change to the original study design options. The Part B sample size has been updated in the following Sections:

   - Protocol summary
   - Figure 3-1
   - Section 4 - Population

   Part C will include 150 patients. Details were added throughout the protocol. These include

   - Requirement for liver biopsy for eligibility
   - 48 weeks duration
   - Doses of 140 and 200 μg

3. Use of doses 140 and 200 μg in Part C - Section 5.2 and throughout.
4. Study Design - Section 3.1 was updated to include Part C
5. Diagnosis of NASH was modified to include the requirement for liver biopsies in Part C in the following sections:

   - Protocol Summary
   - 4.1 Inclusion Criteria

     Diagnosis of NASH:

     - **Parts A & B**: Presence of NASH as demonstrated by ONE of the following:
       - Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, (i.e. fibrosis in the absence of established cirrhosis) no diagnosis of alternative chronic liver diseases
     - **Part C (All patients)**: Adequate liver biopsy sample for evaluation by Central Reader to confirm Histologic evidence of NASH based on liver biopsy obtained during the Screening period or within 6 months before randomization with a diagnosis consistent with NASH, fibrosis level F2 or F3, and no diagnosis of alternative chronic liver diseases. Permitted therapies must be stable as outlined in Table 5-5 (from 1 month prior to biopsy up to and including screening)

     AND (all Parts)

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

     OR (for Parts A and B only)

     - Phenotypic diagnosis of NASH based on presence of ALL THREE of the following:
       - ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) **AND**

[redacted]

- BMI ≥ 27 kg/m2 (in patients with a self-identified race other than Asian) or ≥23 kg/m2 (in patients with a self-identified Asian race) **AND**
- Diagnosis of Type 2 diabetes mellitus by having either:
  - $HbA_{1C} \geq 6.5\%$ or
  - Drug therapy for Type 2 diabetes mellitus

6. Liver biopsies required for eligibility and at End of Treatment at Week 48 in Part C. In sections 6.2.6, 6.4.9 and throughout.

[redacted]

8. Assessment Schedule for Part C added in Table 6-2 to include visits through week 48.
9. Secondary [redacted] endpoints added to assess histologic changes by biopsy for Part C patients in Sections 2, 9, and throughout. Primary endpoint remains unchanged at Week 12 for all study Parts.
10. Editorial Changes throughout.

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 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]

Summary of previous amendments

Amendment 2 (07-Mar-2017)

Amendment rationale

The purpose of Amendment 2 is to ensure that the protocol text clearly outlines that a second interim analysis of Part A, to include data collected up to Week 16, will be conducted. Additionally, the eligibility criteria are updated based on the accumulating experience from ongoing Part A, other NASH studies, input from study investigators, and review of recent literature. Additional clarifications and corrections of small errors are made at this time.

At the time of amendment 2, Part A enrollment is ongoing. More than 154 patients have been screened and 39 patients have been randomized to double-blind treatment.

Changes to the protocol

The main modifications to the protocol are:

- Section 4.1 Inclusion Criteria:

3: Update on the cut-off for ALT elevation to ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females). Although 'elevated' ALT is part of the robust formula for determining NASH in diabetic patients, the accumulating experience indicates that there is a wide overlap of ALT values between patients with biopsy proven NASH (81±60) and those with simple fatty liver (52±34) (Bazick et al., 2015). Although ALT values vary little between laboratories based on technical issues, the laboratory 'normal' ALT is often not associated with true normal values which vary between genders. This is highlighted by an extensive review of this subject (Liu et al., 2014) in which the upper limits of normal for ALT are 38 IU/L in males and 28 IU/L in females. Similar and somewhat more conservative of these values, 43 IU/L in males and 28 IU/L in females, have been now chosen to define ALT cutoff for eligibility in this amendment. The consensus around lower values of 'normal' ALT is further reflected by the recently issued ACG Clinical Guideline on the Evaluation of Abnormal Liver Chemistries (Kwo et al 2017) which declares that ALT levels greater than the true "healthy normal ALT" cutoff values 29 to 33 IU/L for males and 19 to 25 IU/L for females should be further evaluated. The updated cut-off values adapted in this protocol, 43 IU/L (males) and 28 IU/L (females) are 1.5 times the values of 29 and 19 in the ACG Guideline.

- Section 4.2 Exclusion Criteria:

18: Hepatitis C virus exclusion clarified to reflect the original intent to exclude patients with active HCV (positive HCV RNA by PCR) and not previous infection as reflected in HCV antibody.

20: Cholecystectomy was removed as an exclusion. LJN452 is a non-bile acid FXR agonist without significant enterohepatic recirculation. Therefore the absence of the gall-bladder should have little or no effect on the activity of LJN452.

26: GLP-1 agonist exclusion modified to exclude GLP-1 agonists if not on a stable dose for 3 months prior to screening. Phenotypic definition of NASH includes type 2 diabetes. GLP-1

[redacted]

agonists are frequently prescribed for this patient population. If patients are on a stable dose of GLP-1 agonists for 3 months prior to screening, meet eligibility criteria, and remain on the same dose throughout the study, the effect on change from baseline on protocol assessments is expected to be minimal. This is similar to how the protocol approaches other interventions with some suggestion of anti-NASH activity such as vitamin E.

- Various Sections: Primary objective(s)

The Key secondary endpoint 'To determine the dose-response relationship of LJN452 on liver fat content by changes in quantitative MRI determined fat' has been included in the primary objective.

- To determine safety and tolerability of different doses of LJN452
- To determine the dose-response relationship of LJN452 on markers of hepatic inflammation in NASH (ALT and AST)
- To determine the dose-response relationship of LJN452 on liver fat content by changes in quantitative MRI determined fat

Hepatic fat is a key component of NASH. MRI determination of hepatic fat fraction is considered by many to be the best measure of hepatic fat due to its precision and ability to average fat content over several areas of the liver. Elevation of hepatic fat reduction to an additional, independent primary end-point is due to recognition that reduction of hepatic fat content has been demonstrated in studies of similar length (12 weeks) and that the sensitivity of the ALT response signal is somewhat diminished by modification of the ALT entry criteria. LJN452 has been demonstrated to have multi-modal actions in animal models including the reduction of hepatic fat in the fa/fa rat.

- Various Sections: Second interim analysis of Part A Week 16 data clarified.
- Section 5.5.8: Prohibited medication section was simplified and requirements for stable doses of concomitant medications were clarified.
- Tables 6-2, 16-1 and 16-2: Week 6, 4 hour post-dose PK sample was added to complement the PD sample collected at this timepoint.
- [redacted]
- Section 10.5: New Novartis template language for 'Quality' section was added.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes herein do not affect the Informed Consent.

Amendment 1

Amendment rationale

Amendment 1 is being issued to implement recommendations from the US FDA to modify certain details of study CLJN452A2202. Additional clarifications and corrections of small errors are made at this time.

At the time of the amendment, the study has not started and no patients were enrolled.

[redacted]

Changes to the protocol

The major modifications to the protocol are:

- Title page and protocol summary: added the new acronym for the study
- Section 4 and Section 6: Revision of Exclusion criterion 19 into "eGFR less than 60 mL/min" and increase in the frequency of monitoring serum creatinine, as well as increase in blood urea nitrogen (BUN).
- Several sections: Updates to define baseline levels of AST, ALT, GGT and bilirubin as mean of screening and baseline values.
- Section 5: Inclusion of additional discontinuation criteria for patients who develop an AE of Common Terminology Criteria for Adverse Events (CTCAE) of grade 3 related to the study drug, or for patients who develop an AE of CTCAE of grade 4 or higher regardless of attribution to study drug.
- Section 5.5.4.1: Removal of grapefruit juice restriction in the dietary restriction section
- Section 5.5.8: Updated list of prohibited UGT inhibitors.
- [redacted]
- Table 6-1 (Section 6.1) and Section 6.2.7: Added condition for hepatitis serology testing
- [redacted]
- Section 7: Updates to include the use of the CTCAE grading system for adverse events (AEs).
- Several sections: Updates to outline that the DMC will be alerted if more than 3 patients develop an AE of CTCAE of grade 3 or higher in the same system organ class.
- Several sections: Updates to reflect that patients with an elevation of ALT or AST > 2x baseline will have liver function retest re-assessed within 48-72 hours, and repeated in similar time frames until levels stabilize or decrease.
- Several sections: Updates to include that patients who develop medically important laboratory abnormalities or medically important AEs that are related to study drug will be followed until these events have resolved or stabilized (change in follow up period 2). The following will be considered as medically important:
  i) severe AEs (CTCAE grade ≥3),
  ii) serious AEs,
  iii) hepatic and renal AEs,
  iv) elevated liver enzymes (ALT, AST or alkaline phosphatase >2x ULN and >1.5x baseline)
- Several sections: Updates to include that there will be reporting of PK data for interim analysis evaluation by DMC at Week 8.
- Editorial changes 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.

[redacted]

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]

Protocol summary

Protocol number	LJN452A2202
Full Title	A randomized, double-blind, placebo controlled, 3- part, adaptive design, multicenter 12-week study to assess safety, tolerability and efficacy of tropifexor (LJN452) in patients with non-alcoholic steatohepatitis (NASH): FLIGHT-FXR
Brief title	Study of safety and efficacy of tropifexor in patients with non-alcoholic steatohepatitis (NASH)
Sponsor and Clinical Phase	Novartis Phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To assess the safety and tolerability profile of tropifexor and to determine the early hepatic response to different doses of tropifexor in patients with phenotypic or histologic (in Part C) non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further development of tropifexor in the treatment of patients with NASH
Primary Objective(s)	The primary objective of the study is to determine safety and tolerability of different doses of tropifexor by monitoring adverse events Moreover, the study will determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH by changes in ALT and AST from baseline to Week 12. The study will also determine the dose-response relationship of tropifexor on liver fat content by changes from baseline to Week 12 in quantitative MRI determined fat
Secondary Objectives	To determine the effect of different doses of tropifexor on anthropometric assessments (weight, BMI, waist-to-hip (WTH) ratio) over time To determine the dose-response relationship of tropifexor on FGF19 over time, a marker of FXR target engagement in the gut, and C4, a marker of hepatic target engagement To determine the dose-response relationship of tropifexor on markers of liver fibrosis commonly available such as Fibroscan® (in a subset of patients), enhanced liver fibrosis panel (ELF), and fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®) To determine the dose-response relationship of tropifexor on GGT, a marker of cholestasis To determine the effect of tropifexor on fasting lipid profile To determine the pharmacokinetics (PK) of tropifexor To determine the effect of tropifexor compared to placebo with respect to occurrence of potential itch based on a visual analog scale (VAS) rating scale To determine effects of tropifexor on primary endpoints in the subset of patients who have historical biopsy data, both overall and by subsets defined by fibrosis score and/or NAS score as feasible (based on the extent of available data) Additional Secondary Endpoints for Part C Only:

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	To determine safety and tolerability of different doses of tropifexor by monitoring adverse events up to the end of the study. To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH by changes in ALT and AST from baseline to Week 48. To determine the dose-response relationship of tropifexor on liver fat content by changes from baseline to Week 48 in quantitative MRI determined fat To characterize the efficacy of tropifexor in patients with NASH and F2/F3 fibrosis as assessed by histological (biopsy based) improvement after 48 weeks of treatment relative to baseline compared to placebo
Study design	This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose finding, 3-part, adaptive, study to assess the safety, tolerability and efficacy of six doses of tropifexor as compared to placebo in patients with non-alcoholic steatohepatitis (NASH).
Population	Adult male and female patients with EITHER histologic evidence of NASH on liver biopsy within 2 years prior to randomization and elevated ALT, OR phenotypic diagnosis of NASH based on elevated ALT, Type 2 diabetes mellitus or elevated HbA_{1c} and increased BMI, in both cases accompanied by liver fat >10% on centrally-read MRI. The study will include a total of approximately 345 patients of which approximately 75 patients will enroll in Part A, approximately 120 patients in Part B and 150 in Part C.

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)
	• Diagnosis of NASH:
	• **Parts A & B**: Presence of NASH as demonstrated by ONE of the following:
	  • Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, (i.e. fibrosis in the absence of established cirrhosis) no diagnosis of alternative chronic liver diseases
	• **Part C (All patients):** Adequate liver biopsy sample for evaluation by Central Reader to confirm Histologic evidence of NASH based on liver biopsy obtained during the Screening period or within 6 months before randomization with a diagnosis consistent with NASH, fibrosis level F2 or F3, and no diagnosis of alternative chronic liver diseases. Permitted therapy must be stable as outlined in Table 5-5 (from 1 month prior to biopsy up to and including screening)
	  • **AND (all Parts)**
	  ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females)
	OR (for Parts A and B only)
	• Phenotypic diagnosis of NASH based on presence of ALL THREE of the following:
	  ○ ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) **AND**
	  ○ BMI ≥ 27 kg/m2 (in patients with a self-identified race other than Asian) or ≥23 kg/m2 (in patients with a self-identified Asian race) **AND**

[redacted]

	○ Diagnosis of Type 2 diabetes mellitus by having either: - HbA_{1C} ≥ 6.5% or - Drug therapy for Type 2 diabetes mellitus • Liver fat ≥ 10% at screening as determined by the central MRI laboratory • Patients must weigh at least 40 kg (88 lb) and no more than 150 kg (330 lb) to participate in the study
Key Exclusion criteria	• Previous exposure to an FXR agonist including tropifexor • Patients taking medications prohibited by the protocol • Pregnant or nursing (lactating) women • Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the AUDIT questionnaire ≥8 • Uncontrolled diabetes defined as HbA_{1c} ≥ 9.5% within 60 days prior to enrollment • Presence of cirrhosis on liver biopsy or clinical diagnosis • Clinical evidence of hepatic decompensation or severe liver impairment • Previous diagnosis of other forms of chronic liver disease • Patients with contraindications to MRI imaging
Study treatment	Tropifexor 10 µg, 30 µg, 60 µg, 90 µg, 140 µg or 200 µg Matching placebo
Efficacy assessments	• MRI for hepatic fat fraction • Liver Function Test • Liver histology • Coagulation test • Markers of liver fibrosis • NAFLD Fibrosis score • Fasting lipids [redacted]
Key safety assessments	• Adverse events monitoring • Monitoring of laboratory markers in blood and urine • ECG • Vital signs • Physical examinations
Other assessments	Pharmacokinetics Biomarkers [redacted] VAS scale on itching [redacted]

[redacted]

	[redacted]
Data analysis	No formal hypothesis tests will be performed. The analysis of efficacy variables will be based on descriptive statistics and repeated measures ANCOVA and supported by graphical displays. A general dose-response relationship (trend versus placebo) will be examined using a multiple contrast test with optimal contrasts for different dose-response models on ALT and AST. Safety variables will be analyzed using summary statistics, including exposure adjusted incidence rates to account for different lengths of exposure across study parts. Specific safety and efficacy criteria for selection of the doses for Part B will be defined in the DMC charter. In Part C, biopsy based endpoints will be analyzed using descriptive statistics and logistic regression.
Key words	Tropifexor, LJN452, non-alcoholic steatohepatitis, NASH, phase 2, adaptive design, randomized

[redacted]

1 Introduction

1.1 Background

NASH

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the Western world (Ratziu et al 2010, Szczepniak et al 2005, Browning et al 2004). The clinical-histologic phenotype of the disease extends from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH). NASH includes not only fat in the liver but also inflammation which over time can lead to increasing fibrosis, cirrhosis and end stage liver disease. Estimates of the worldwide prevalence of NAFLD range from 6.3% to 33% with a median of 20% in the general population, based on a variety of assessment methods. The estimated prevalence of NASH is lower, ranging from 3 to 5% (Vernon et al 2011, Chalasani et al 2012). NASH is a worldwide problem with growing prevalence over the last few decades. One salient observation which relates to the increasing morbidity associated with NASH is that over the last decade it has risen from uncommon to the #2 indication for liver transplantation in the US (Wong et al 2015).

NASH is a condition characterized by increased fat accumulation in the liver and attendant inflammation. In addition to the histologic diagnosis of NASH, there is now a NAS (non-alcoholic steatohepatitis) activity score which assigns points for 3 key elements: steatosis, ballooning degeneration and lobular inflammation. NASH is highly associated with the metabolic syndrome and Type 2 diabetes mellitus and a NASH phenotype can be described using combinations of several features of metabolic syndrome (obesity, Type 2 diabetes mellitus) along with elevated ALT/AST and fatty infiltration of the liver. Some would broadly consider NASH to be the liver component of metabolic syndrome. NASH is a cause of progressive fibrosis, and is a leading cause of cirrhosis (Ekstedt et al 2006). Cirrhosis due to NASH increases the risk of hepatocellular carcinoma and NASH contributes substantially to the population burden of hepatocellular cancer (Starley et al 2010). NASH is also associated with an increased risk of cardiovascular mortality and type 2 diabetes mellitus (Targher et al 2010, Targher et al 2005). The role of the "NASH liver" in contributing to non-liver morbidity and mortality is not well understood.

There are no globally approved effective treatments for NASH. Several studies have been conducted with Vitamin E and thiazolidinediones, but no long term benefits have been demonstrated. There are a number of agents currently in various stages of testing for the treatment of NASH but no approved therapies to date.

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).

FXR

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

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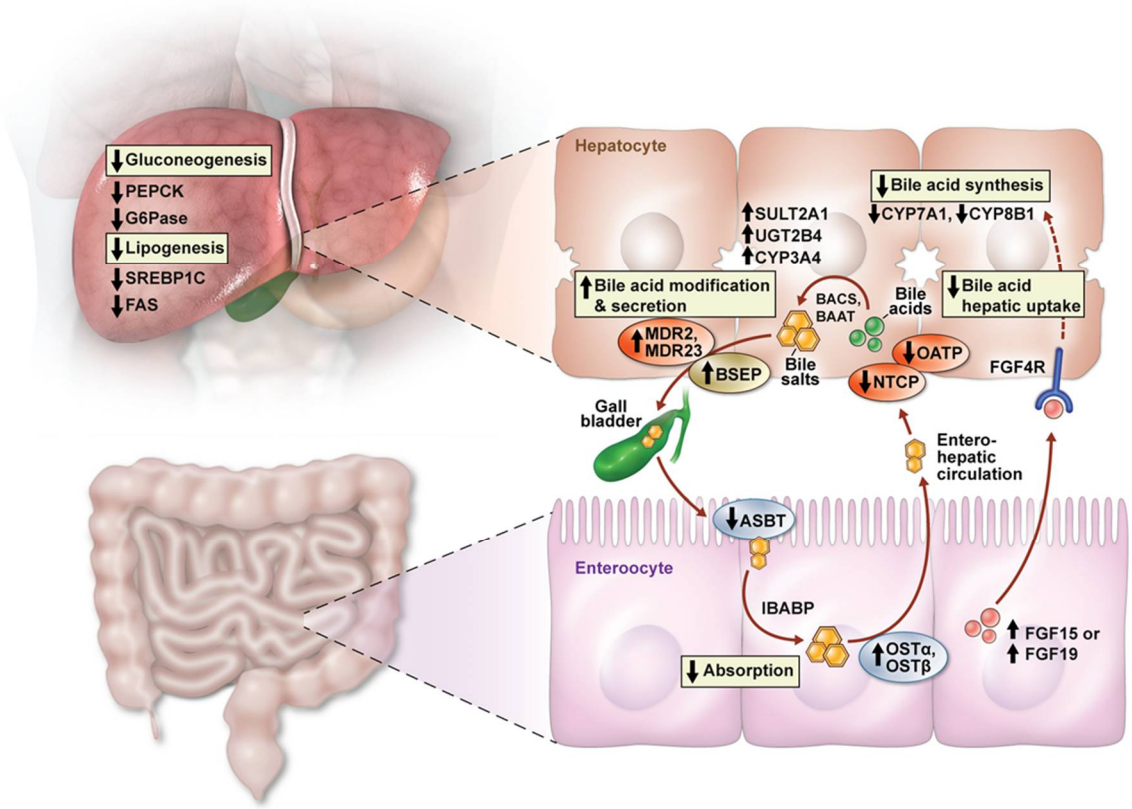
gluconeogenesis and lipogenesis (Figure 1-1) (Pattni et al 2012, Walters et al 2015). In the liver, FXR agonism modulates bile acid synthesis and detoxifying metabolism. FXR agonist increases expression of genes involved in canalicular and basolateral bile acid efflux and bile acid detoxifying enzymes 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).

Figure 1-1 Co-ordinated effects of FXR on metabolism



FXR regulates bile acid metabolism through multiple mechanisms in the liver and intestine. The processes regulated by FXR are shown in rectangular boxes. Genes are shown with up or down arrows to indicate the direction of regulation by FXR agonists. Arrows are used to show the flow of bile acids in the enterohepatic circulation or the movement of FGF15 (rodents) or FGF19 (human) from the enterocyte to the hepatocyte. In normal physiology, FXR detects increased levels of bile acids and responds by decreasing bile acid synthesis and bile acid uptake while increasing bile acid modification and secretion in the liver. In the intestine, FXR detects increased bile acid levels and decreases bile acid absorption and increases secretion of FGF15 or FGF19. The net result is a decrease in the overall levels of bile acids (Figure adapted from Calkin and Tontonoz 2012).

Clinical validation of a FXR agonist for the treatment of NASH has been shown in clinical trials with obeticholic acid (OCA), a semi-synthetic variant of the natural bile acid chenodeoxycholic acid. In a small study in patients with NAFLD and type 2 diabetes mellitus

[redacted]

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-Tetri et al 2015).

Tropifexor

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 early phase healthy subject and patient studies. The Investigator's Brochure (IB) provides a detailed review of the pre-clinical and clinical information on tropifexor available to date.

In vitro pharmacology studies demonstrate that tropifexor is a potent human FXR agonist with an EC50 of 0.2 nM and 0.3 nM in a cell-based FXR reporter gene assay and in a biochemical co-activator interaction assay, respectively, 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.

Human safety and tolerability, pharmacokinetic and pharmacodynamic data are available from the First-in-Human study CLJN452X2101 (see also Section 3.3). In healthy volunteers administered tropifexor once daily for up to 14 days the treatment was generally well tolerated but isolated asymptomatic and reversible elevations in ALT were observed at higher doses. No significant findings in physical exam, vital signs or ECGs have been related to tropifexor; no adverse events related to itch, a common adverse event for bile acid-derived FXR agonists, were observed in CLJN452X2101. Pharmacokinetic data were consistent with once daily dosing (see also Section 3.3). Human pharmacodynamic data show that after single doses in healthy volunteers, there were dose-dependent increases in FGF19 from 10 µg to 3000 µg tropifexor. After multiple doses, a maximal mean serum FGF19 of 592 pg/ml (range 462- 847 pg/ml) was observed at 6 hours after administration of 60 µg tropifexor consistent with likely pharmacological effect. In healthy volunteers administered tropifexor once daily for up to 14 days the treatment was generally well tolerated but isolated asymptomatic and reversible elevations in ALT were observed at higher doses. At the 60 µg dose 2/6 patients had isolated ALT/AST elevations; one at 2X ULN and one just above the ULN. The ALT/AST peaked on Day 7 and fully resolved with uninterrupted dosing of tropifexor. At the 100 µg dose one patient had an isolated ALT/AST elevation of 5X ULN: one patient had an elevation slightly greater than 3X ULN. These elevations were noted by Day 7 and resolved quickly after discontinuation of therapy. No significant findings in physical exam, vital signs or ECGs have been related to tropifexor; no adverse events related to itch, a common adverse event for bile acid-derived FXR agonists, have been observed in CLJN452X2101 to date.

Currently patients are receiving tropifexor in ongoing studies CLJN452X2201 (Primary Biliary Cholangitis (PBC)) and CLJN452X2202 (primary Bile Acid Diarrhea (pBAD)).

[redacted]

This study is the first study of tropifexor in patients with phenotypic or biopsy-confirmed NASH (see Section 4.1), and it aims to assess safety and tolerability as well as efficacy after daily dosing for 12 weeks in Parts A and B and for 48 weeks in Part C.

1.2 Purpose

The purpose of this study is to assess the safety and tolerability profile of tropifexor and to determine the early hepatic response to different doses of tropifexor in patients with phenotypic non-alcoholic steatohepatitis (NASH). Data from this study will be used to support further development of tropifexor in the treatment of patients with NASH.

2 Study objectives and endpoints

Primary objective(s)

To determine safety and tolerability of different doses of tropifexor

To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH (ALT and AST)

To determine the dose-response relationship of tropifexor on liver fat content by changes in quantitative MRI determined fat

Secondary objective(s)

To determine the effect of different doses of tropifexor on anthropometric assessments (weight, BMI, waist-to-hip (WTH) ratio) after 12 weeks of treatment

To determine the dose-response relationship of tropifexor on FGF19 over time, a marker of FXR target engagement in the gut, and C4, a marker of hepatic target engagement

To determine the dose-response relationship of tropifexor on markers of liver fibrosis commonly available such as Fibroscan® (in a subset of patients), enhanced liver fibrosis panel (ELF), and fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®)

To determine the dose-response relationship of tropifexor on GGT, a marker of cholestasis

To determine the effect of tropifexor on fasting lipid profile

To determine the pharmacokinetics (PK) of tropifexor

To determine the effect of tropifexor compared to placebo with respect to occurrence of potential itch based on a visual analog scale (VAS) rating scale

To determine effects of tropifexor on primary endpoints in the subset of patients who have historical biopsy data, both overall and by subsets defined by fibrosis score and/or NAS score as feasible (based on the extent of available data)

Additional Secondary Objectives in Part C only:

To demonstrate the efficacy of tropifexor in patients with NASH and F2/F3 fibrosis as assessed by histological improvement from baseline after 48 weeks of treatment compared to placebo

[redacted]

To determine safety and tolerability of different doses of tropifexor by monitoring adverse events up to the end of the study.

To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH by changes in ALT and AST from baseline to Week 48.

To determine the dose-response relationship of tropifexor on liver fat content by changes from baseline to Week 48 in quantitative MRI determined fat

[redacted]

2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective	Endpoint	Unit of measure	Time Frame	Stat Analysis Section
Primary				
To determine safety and tolerability of different doses of tropifexor	Occurrence of SAE, AE resulting in discontinuation of study treatment and/or dose reductions, and AE of special interest	Adverse events monitoring	up to End of Study	Section 9.4
To determine the dose-response relationship of tropifexor on markers of hepatic inflammation in NASH (ALT and AST)	Change from baseline to Week 12	Clinical chemistry	up to Week 12	Section 9.4
To determine the dose response relationship of tropifexor on liver fat content by changes in quantitative MRI determined fat	Relative change from baseline to Week 12 in % of fat in the liver assessed using MRI	% of fat	baseline, Week 12	Section 9.4
Secondary				
To determine the effect of different doses of tropifexor on anthropometric assessments (weight, BMI, waist-to-hip (WTH) ratio) after 12 weeks of treatment	Changes from baseline to Week 12	kg, kg/m^2	up to Week 12	Section 9.5
To determine the dose-response relationship of tropifexor on FGF19 over time, a marker of FXR target engagement in the gut, and C4, a marker of hepatic target engagement	Changes from baseline to Week 12	Lab variables	up to Week 12	Section 9.5
To determine the dose-response relationship of tropifexor on markers of liver fibrosis commonly available such as Fibroscan®, enhanced liver fibrosis panel (ELF), and	Changes from baseline to Week 12	kPa, Clinical chemistry	up to Week 12	Section 9.5

[redacted]

Objective	Endpoint	Unit of measure	Time Frame	Stat Analysis Section
fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®)				
To determine the dose-response relationship of tropifexor on GGT, a marker of cholestasis	Changes from baseline to Week 12	Clinical chemistry	up to Week 12	Section 9.5
To determine the effect of tropifexor on fasting lipid profile	Changes from baseline to Week 12	Fasted clinical chemistry	up to Week 12	Section 9.5
To determine the pharmacokinetics (PK) of tropifexor	Ctrough, C_{2h}	ng/mL	up to Week 12	Section 9.5
To determine the effect of tropifexor compared to placebo with respect to occurrence of potential itch based on a visual analog scale (VAS) rating scale	The score (distance from left) on the VAS will be recorded by the patient marking with a line. The distance marked will be converted to a score between 0 and 10	VAS score between 0-10	up to Week 12	Section 9.5
To determine effects of tropifexor on primary endpoints in the subset of patients who have historical biopsy data, both overall and by fibrosis score and/or NAS score subsets as feasible (based on the extent of available data)	Subgroup analysis with respect to: occurrence of SAE, AE resulting in discontinuation of study treatment and/or dose reductions, and AE of special interest, relative change from baseline to Week 12 in % of fat in the liver assessed using MRI, and change from baseline to Week 12 of ALT and AST and GGT	Adverse events monitoring % of fat Clinical chemistry	up to Week 12	Section 9.5
Additional Secondary Endpoints for Part C: To demonstrate the efficacy of tropifexor in patients with NASH and F2/F3 fibrosis as assessed by histological improvement from baseline after 48 weeks of treatment compared to placebo	Proportion of patients who have at least a one point improvement in fibrosis without worsening of steatohepatitis at Week 48 compared to baseline Proportion of patients with resolution of steatohepatitis without worsening of fibrosis at Week 48 compared to baseline	NAS, NASH CRN scoring system and NAFLD fibrosis score	up to Week 48	

[redacted]

Objective	Endpoint	Unit of measure	Time Frame	Stat Analysis Section
To determine the effect of tropifexor on markers of hepatic inflammation in NASH (ALT and AST) in Part C	Change from baseline to Week 48	Clinical chemistry	up to Week 48	Section 9.5
To determine the effect of tropifexor on liver fat content by changes in quantitative MRI determined fat in Part C	Relative change from baseline to Week 48 in % of fat in the liver assessed using MRI	% of fat	baseline, Week 48	Section 9.5
To determine safety and tolerability of different doses of tropifexor, adjusted for length of exposure	Exposure adjusted incidence of SAE, AE resulting in discontinuation of study treatment and/or dose reductions, AE of special interest and other AE	Adverse events monitoring	up to Week 52	Section 9.5

[redacted]

3 Investigational plan

3.1 Study design

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group, dose finding, 3-part, adaptive, study to assess the safety, tolerability and efficacy of six doses of tropifexor as compared to placebo in patients with non-alcoholic steatohepatitis (NASH).

Patients can be included if they have either histologic evidence of NASH or phenotypic diagnosis of NASH (In Parts A & B), as further specified in Section 4.1. Histologic evidence of NASH (with fibrosis stage 2 or 3), per central read, during the Screening period or within 6 months of randomization is required for all patients in Part C. The composite criterion for phenotypic diagnosis has been shown to be nearly as precise as locally read liver biopsy which can be frequently re-read as 'non-NASH' (Neuschwander-Tetri et al 2015).

The study will start with screening and enrolling patients for Part A. Screening will continue without pause, even after all patients for Part A have been enrolled, but randomization for Part B will not start until after the first interim analysis in Part A. When ≥ 90% of the patients in Part A have completed 8 weeks of treatment, an interim analysis will be performed using all available data to allow for the DMC to recommend dose selection for the arms in Part B (see Section 3.5 and Section 9.7). The treatment arms of Part A are planned to be completed without adaptation. In addition, a second interim analysis of Part A data collected up to Week 16 will be performed.

Randomization for Part B will only be started after the DMC recommendations on the dose(s) to be used in Part B are implemented by the Sponsor.

Part C was introduced as a result of the DMC recommendation to pursue doses > 90 µg after the planned interim analysis and DMC review of the Part A data, as well as the preclinical and pharmacokinetic data described in Section 3.3. Randomization into Part C will commence after Part B randomization is complete.

Each patient will be randomized into only one Part of the study. Patients may be screened for more than one study Part as appropriate and randomized into the Part for which all eligibility criteria are met.

Study Periods

The total planned duration of the study for each patient in either Part A or Part B is up to 16 weeks from randomization to the last follow up visit (Figure 3-1); study treatment is taken for 12 weeks. In Part C, the total planned duration for each patient is 52 weeks from randomization: 48 weeks of treatment and a 4 week follow up period.

Screening period:

PART A

The duration of the screening period will be 14 to 35 days during which study eligibility will be confirmed. Screening will consist of two consecutive visits. During the first screening visit

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(maximum -5 weeks prior to baseline/randomization), patients will be assessed for eligibility to participate in the trial. Patients' potential entry into the study will be determined when the majority of screening procedures including inclusion and exclusion criteria are assessed. Laboratory assessments required for eligibility during the screening period should not be repeated unless the sample is compromised rendering testing impossible or is otherwise reasonably suspected of being inaccurate (e.g. a nonsensical value). If liver biopsy results are available prior to randomization, the results will be reviewed prior to MRI (to be done at 2nd screening visit) to confirm they are consistent with NASH and without the diagnosis of other chronic liver diseases. If potential eligibility is confirmed, patients will proceed to the second screening visit (-2 weeks prior to baseline/randomization) at which a qualifying quantitative MRI will be performed to assess their liver fat percentage for entry into the study. MRI should only be scheduled to occur within 2 weeks of the expected date of randomization. The MRI assessment will be forwarded to a central MRI laboratory for evaluation. Patients with liver fat ≥ 10% as determined by the central MRI laboratory will be eligible for randomization into the study. The investigator will be notified whether the patient qualifies for the study and will be informed of any other safety findings that would influence the participation of the patient in the study; however he/she will be blinded to the actual liver fat percentage until after the study is completed.

PART B

There may be a variable duration of screening (5 weeks to approximately 8 months) during which study eligibility will be confirmed; screening will consist of two visits. During the first screening visit (visit duration will be dependent on time needed for the first interim analysis and dosing recommendations from Part A), patients will be assessed for eligibility to participate in the trial. Patients' potential entry into the study will be determined when the majority of the screening procedures including inclusion and exclusion criteria are assessed. If liver biopsy results are available prior to randomization, the results will be reviewed prior to MRI (to be done at 2nd screening visit) to confirm they are consistent with NASH without cirrhosis and without the diagnosis of other chronic liver diseases. Laboratory assessments required for eligibility during the screening period should not be repeated unless the sample is compromised rendering testing impossible or is otherwise reasonably suspected of being inaccurate (e.g. a nonsensical value). If the period between the first screening visit and the expected date of randomization for a subject in Part B is greater than 2 months, certain assessments of screening visit 1 will be repeated at screening visit 2 (see Table 6-1 and Section 6.2.8). If randomization into Part B can occur within 2 months after screening visit 1, the repeat of these assessments is not needed. In either case, potentially eligible patients will proceed to screening visit 2 (-2 weeks prior to baseline/ randomization) at which a qualifying quantitative MRI will be completed to assess their liver fat percentage for entry into the study and repetition of selected screen 1 assessments, when applicable (Table 6-1 and Section 6.2.8). MRI should only be scheduled to occur within 2 weeks of the expected date of randomization. The MRI assessment will be forwarded to a central MRI laboratory for evaluation. Patients with liver fat ≥ 10% as determined by the central MRI laboratory will be eligible for randomization into the study. The investigator will be notified whether the patient qualifies for the study and will be informed of any other safety findings that would influence the

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participation of the patient in the study; however he/she will be blinded to the actual liver fat percentage until after the study is completed.

PART C

The duration of the screening period will be 14 to 70 days during which study eligibility will be confirmed. Screening will consist of two consecutive visits. During the first screening visit (10 weeks prior to baseline/randomization), patients will be assessed for eligibility to participate in the trial. Patients' potential entry into the study will be determined when the majority of screening procedures including inclusion and exclusion criteria performed at Screening Visit 1 are assessed. Laboratory assessments required for eligibility during the screening period should not be repeated unless the sample is compromised rendering testing impossible or is otherwise reasonably suspected of being inaccurate (e.g. a nonsensical value). If potential eligibility is confirmed, patients will proceed to the second screening visit (-2 weeks prior to baseline/randomization) for histology and hepatic fat assessments. If liver biopsy was performed within 6 months of planned randomization, slides must be prepared as required by, and sent to, the central reader to confirm eligibility. If tissue from a liver biopsy within 6 months of randomization is not available, a liver biopsy must be performed during the Screening Period (and may be performed prior to SV2 to allow sufficient time for central review and site notification prior to baseline) after other eligibility is confirmed. Patients whose biopsy results are consistent with NASH (with Fibrosis scoring F2 or F3), as determined by the Central Reader will be eligible for Randomization into the study. A qualifying quantitative MRI will also be performed at Screening Visit 2 to assess liver fat percentage for entry into the study. MRI should be scheduled to occur within 2 weeks prior to the expected date of randomization. The MRI assessment will be forwarded to a central MRI laboratory for evaluation. Patients with liver fat ≥ 10% as determined by the central MRI laboratory will be eligible for randomization into the study. The investigator will be notified whether the patient's liver biopsy and MRI qualify for the study and will be informed of any other safety findings that would influence the participation of the patient in the study. However investigators will remain blinded to the actual histology findings and liver fat percentage until after the study is completed.

Treatment period

PART A (12 weeks)

In Part A, approximately 75 patients whose eligibility is confirmed will be randomized at the baseline visit (BSL) to tropifexor (10 µg, 30 µg, 60 µg or 90 µg) or placebo in a 1:1:1:1:1 ratio (Arms A, B, C, D and E). Tropifexor or matching placebo will be administered once daily for 12 weeks in a blinded manner.

After ≥ 90% of the patients from Part A have completed 8 weeks of treatment, the first interim analysis for all Part A patients will be done and all available data will be evaluated by a Data Monitoring Committee who will recommend the treatment arms to be used in Part B.

PART B (12 weeks)

In Part B, approximately 120 patients, whose eligibility is confirmed, will be randomized at baseline to tropifexor (anticipated 2 doses as recommended by the DMC) or placebo in a

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15:4:5 ratio (Arms F, G and H). Tropifexor or matching placebo will be administered once daily for 12 weeks in a blinded manner.

In August 2017, the DMC recommended one tropifexor dose, 90 µg (safe and efficacious) to be evaluated in 75 patients in Part B. Therefore, per protocol, one of the other originally planned active treatment arms, 60 µg (next highest dose), will continue with a smaller sample size (20 patients) to confirm the earlier findings of this dose observed in Part A. In this scenario, 90 µg will be tested in approximately 90 patients, 60 µg in 35 patients, and placebo in 40 patients in the combined Parts A and B. If only one arm was deemed safe, the DMC may have recommended only one active dose to be pursued in Part B, along with matched placebo.

PART C (48 weeks)

In Part C approximately 150 patients, whose eligibility is confirmed, will be randomized at baseline to 140 µg or 200 µg tropifexor or placebo in a 1:1:1 ratio (Arms I, J and K). Tropifexor or matching placebo will be administered once daily for 48 weeks in a blinded manner. Part C dose selection is detailed in Section 3.3.

Post treatment follow-up period (4 weeks) – Follow up 1 period

All patients in all parts will be followed up for 4 weeks after the last dose of study treatment (Follow up 1 period).

Post treatment follow-up period (flexible period) – Follow up 2 period

Patients who develop medically important laboratory abnormalities or medically important AEs that are considered related to study drug and which are not resolved or stabilized at the Follow up 1 visit (Visit 299) will be followed, beyond the planned post treatment follow-up period, until these events have resolved or stabilized.

The following will be considered as medically important:

i. severe AEs CTCAE (Common Terminology Criteria for Adverse Events) grade ≥3,
ii. serious AEs,
iii. hepatic and renal AEs,
iv. elevated liver enzymes (ALT, AST or alkaline phosphatase >2x ULN and >1.5x baseline) (see Section 9.5.2.5 for definition of baseline levels)

These patients will be monitored frequently by the investigator and have unscheduled visits to collect safety and/or laboratory data. It is advised that the first follow up of these patients with such events will be scheduled approximately 4 weeks after the completion of the Follow up 1 period, or sooner based on investigators discretion; if events are not resolved or stabilized at this time point, further follow up will be scheduled at the investigators discretion and unscheduled visits will be used to collect safety and/or laboratory data. As soon as the event is resolved and/or stabilized, and as long as there are no additional medically important events from the treatment period ongoing, the final follow-up visit to complete the follow-up 2 period needs to be performed (EOS).

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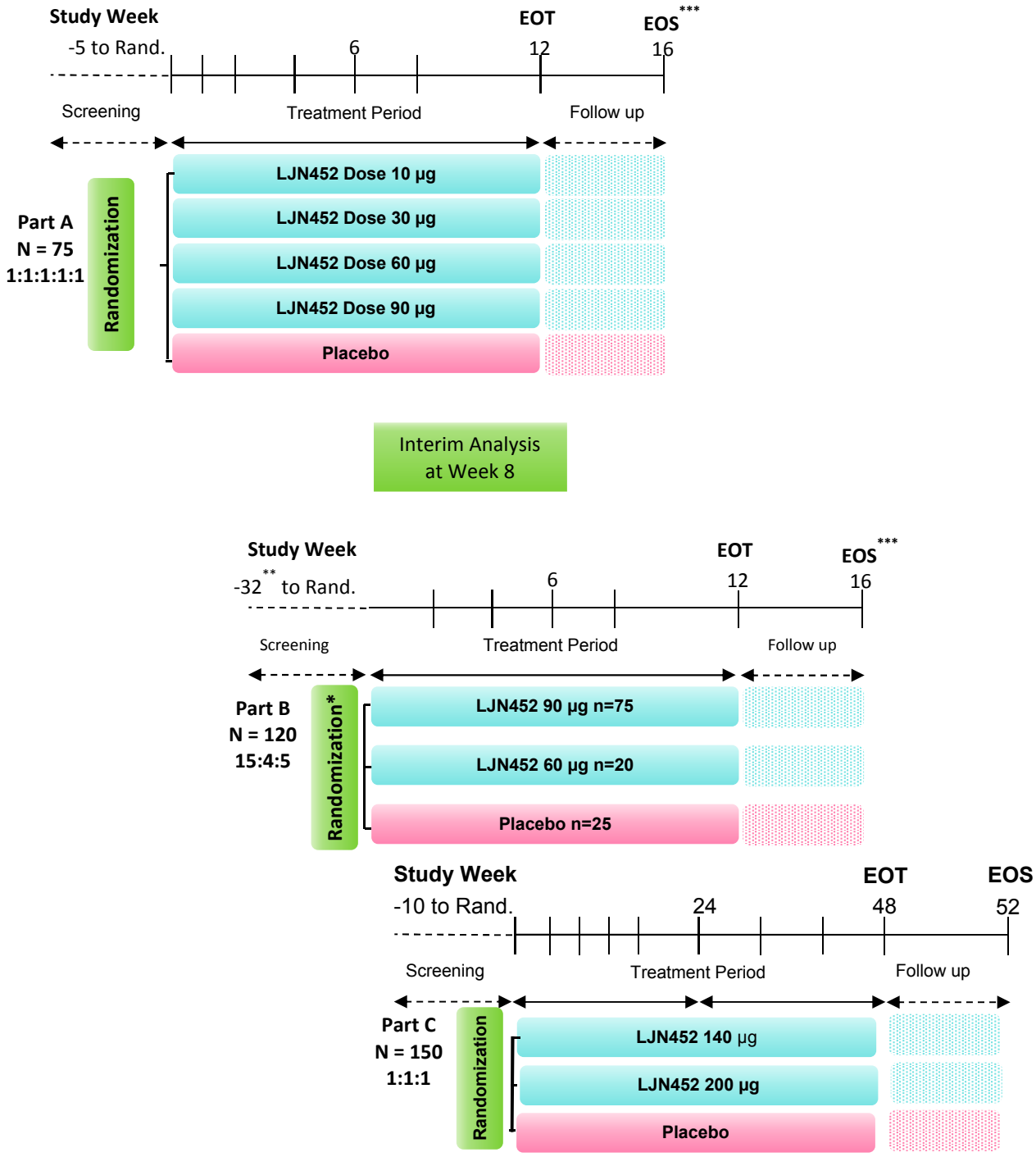
Figure 3-1 Study design



* As planned in all versions of this protocol, in the event that the DMC interim analysis selects only one active dose to be tested in 75 patients in Part B (90 µg), one of the other originally planned active treatment arms (60 µg) will continue with a smaller sample size (20 patients) to confirm the earlier

[redacted]

findings of this dose observed in Part A. In this scenario, Dose A will be tested in a total of 90 patients, Dose B in a total of 35 patients, and placebo in a total of 40 patients.

** Screening period for Part B can take up to approximately 32 weeks depending on the availability of the IA results to confirm the doses for Part B.

***Patients who develop medically important laboratory abnormalities or medically important AE that are considered related to study drug will be followed as described in Section 3.1.

3.2 Rationale for study design

This randomized, multi-center, double-blind, 3 part, adaptive, placebo-controlled study is designed to assess the safety and tolerability and early hepatic response to tropifexor in the dose range of 10 µg to 200 µg relative to placebo in patients with NASH. Longer term response, assessed by histology in a subset of patients (Part C), will also be examined. The principle of an FXR agonist treating NASH has been demonstrated in a Phase 2b trial of obeticholic acid, a bile acid FXR agonist (Neuschwander-Tetri et al 2015). Therefore, this trial will focus on identifying the appropriate doses of tropifexor, a potent non-bile acid FXR agonist. Expansion in Part B, followed by Part C will develop a larger safety data base for two doses of tropifexor (60 µg and 90 µg) in Part B which demonstrated early biochemical response and no safety concerns, and two higher doses in Part C (140 µg and 200 µg), to further enable the dose finding objectives of this study. Non-clinical toxicity data, the DMC Interim Analysis, and exposure data predicted by pharmacokinetic modeling of Part A data, support the study of the 140 µg and 200 µg doses (Section 3.3). The longer term non-clinical data support increasing treatment duration to 48 weeks, allowing addition of a histological endpoint in Part C.

Multiple sites are necessary due to low diagnosis rate of this prevalent disease, the high number of competing trials, and the historically slow accrual rate to date in publicly disclosed trials of NASH (e.g. FLINT trial: Neuschwander-Tetri et al 2015). No known quantitative differences exist in regional criteria for the diagnosis of NASH, except that phenotypic NASH has been defined by a lower BMI criteria for Asian patients. There may be a greater number of patients with "non-obese" NASH in some Asian countries but this entity is difficult to diagnose without liver biopsy and is not being studied in this trial.

Although an elevated ALT is frequently associated with NASH, in patients with other phenotypic elements of NASH there is a wide overlap of ALT values in those with simple fatty liver (52±34) and those with NASH (81±60; Bazick et al., 2015). This issue is further complicated by the fact that while there is little technical variation in measuring ALT and AST between laboratories, the posted 'normal' values often do not correspond to true normal values and are gender specific. Based on an extensive review of this subject (Liu et al., 2014) the upper limits of normal for ALT are 38 IU in males and 28 IU in females. The ACG Clinical Guideline (Kwo et al 2017) suggests ALT levels above 29 to 33 IU/L for males and 19 to 25 IU/L for females should be assessed. Additionally, there is a large cadre of NASH patients with normal ALT. The strength of the phenotypic determination of NASH used in Parts A and B of this trial rests on the combination of type 2 diabetes mellitus, obesity, and high hepatic fat fraction. Based on this information, the population to be studied in this trial is patients with elevated ALT values who have type 2 DM, obesity, and HFF greater than 10%. ALT values in these patients have the potential for reduction to true normal values. Several other measures of efficacy, including reduction of hepatic fat, are measured in this trial. The

[redacted]

issue of diagnostic specificity will be approached in three ways: 1) an analysis of the sub-group of patients in Parts A and B with a histologic diagnosis of NASH, 2) an analysis of patients with higher ALT values on entering the trial, and 3) verification of NASH using a) more complex published formulas which utilizing other variables captured in this trial (Bazick et al., 2015) and b) the use of novel biomarkers in development such as the metabolomic/lipidomic signatures developed by OWL Metabolomics (Alonso et al., In Press)

In order to maintain the scientific integrity of the study, the Investigator, the patient and Novartis study personnel will remain blinded to their treatment allocation. For the purposes of data presentation to the DMC, non-study Novartis personnel may be unblinded to the study data. These people will be documented in the DMC charter.

The current study will follow an adaptive design as the accumulating data from the first part will be used to guide to which treatment group(s) additional patients will be added. This approach will allow for minimizing the overall number of patients required to study a new treatment while allowing enlargement of promising treatment regimens in order to increase the precision of the treatment effects estimates for further decision making to inform the design of future studies.

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

The duration of 12 weeks of therapy in Parts A and B was supported by GLP-toxicology studies of 13 weeks in duration. Subsequently, longer term GLP-toxicology 26 weeks rat and 39 weeks dog studies allow for longer term treatment. As a result, patients will be treated for 48 weeks in Part C. In addition to longer term safety and efficacy follow up, 48 week treatment also provides the opportunity for evaluation of histological improvement by paired biopsies at Baseline and Week 48, which will be included in Part C.

The patient population is described in more detail in Section 4 below.

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

The initial range of doses of 10 µg to 90 µg tropifexor studied in Part A was 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 (Investigator's Brochure). The use of doses up to 200 µg in Part C is supported by 1) additional preclinical toxicity and efficacy data (animal models of NASH, 26 week rat and 39-week dog toxicity studies),2) Safety and tolerability data in NASH patients (Part A), and DMC dose recommendation, and 3) Pharmacokinetic modeling.

3.3.1 Pre-Clinical Animal Studies

In non-clinical studies in rodents, tropifexor was well tolerated with no exacerbation of transaminase release in the elevated ALT cholestasis model (ANIT) or fatty liver disease model.

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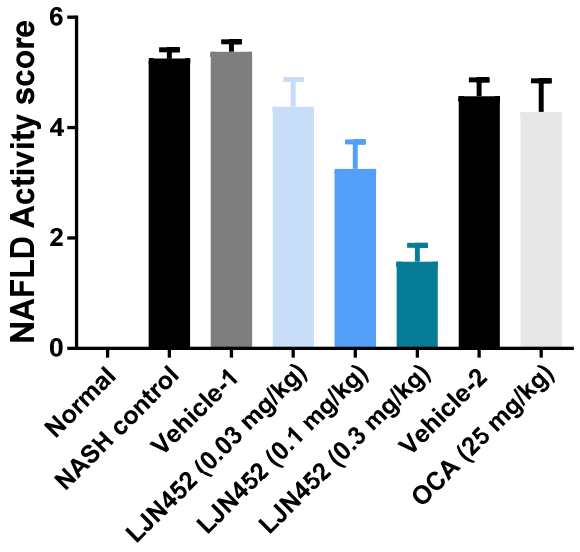
Additional Preclinical studies evaluating higher exposure levels than those currently used in Parts A and B of this trial demonstrate that greater FXR activation is possible (both *in vitro* and *in vivo*) suggesting that increased level of FXR activation would result in greater efficacy. In a NASH mouse model higher dosing resulted in lower NAFLD Activity Score and reduced fibrosis (Figure 3-2). A dose of 0.3 mg/kg in mice provides exposure of 129 ng*h/mL, which is higher than the predicted exposure of 200 µg daily in NASH patients of approximately 80 ng•hr/ml.

Figure 3-2 NAS score (mouse NASH model)



The safety profile of tropifexor was further evaluated in oral gavage toxicity studies conducted in rats for up to 26 weeks and in dogs for up to 39 weeks.

The direct pharmacological effects of clinical relevance from these studies include decreases in bile acids; alterations in cholesterol and triglycerides; increases in fibrinogen (with shortening of PT or APTT), BUN and ALP (intestinal and hepatic isoforms) at most dose levels. These alterations in serum chemistry parameters were reversible and not adverse in their magnitude.

Hepatic effects included hepatocellular hypertrophy along with minimal increases in ALT. Hepatocellular hypertrophy was only adverse in animal models at exposures (e.g in dogs, Mean AUC0-24h of 898 and 507 ng*h/mL in males and females respectively) well above those expected in NASH patients (80 ng*h/mL at 200 µg) for the doses planned in this study. Hepatocellular hypertrophy represents an adaptive response to the high hepatic concentrations of enzyme-inducing drugs and has limited clinical relevance.

The proposed NOAEL of 0.03 mg/kg/day is based on the results of the 26-week rat and 39-week dog toxicity studies. Systemic exposures in terms of AUC0-24h were 27.1 ng*h/mL in rats (16.5 ng*h/mL in males and 37.7 ng*h/mL in females) and 274 ng*h/mL in dogs (210 ng*h/mL in males and 338 ng*h/mL in females).

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Overall, the nature (mechanism, reversibility, monitorability) of the non-clinical safety findings support the dog as the most relevant animal species for risk assessment. Based on the systemic exposures (274 ng*h/mL) at the dog NOAEL, the highest proposed daily dose of 200 µg ($AUC_{0\text{-}24h}$ ~80 ng*h/mL), for Part C is not considered to pose an additional safety risk to patients.

3.3.2 CLJN452X2101 – Healthy Volunteers

Tropifexor has been studied in healthy subjects in single doses up to 3000 µg and in multiple doses up to 100 µg for up to 2 weeks. To date, over 63 healthy subjects have been treated with tropifexor. Data from study CLJN452X2101 has demonstrated the following:

- In single ascending dose (SAD) (Part 1, 6 cohorts of 8 subjects, each with 6 subjects on active and 2 on placebo), a single drug-related AE (Grade 1) of nausea was reported in a single subject at 300 µg. The highest exposures tested in healthy subjects were Cmax 54.2 ng/mL and AUCinf 944 ng*h/mL in the 3000 µg single dose cohort.
- In multiple ascending dose (Part 2, with cohorts of 8 subject, each with 6 subjects on active and 2 on placebo) with a treatment duration of 14 days, 4 SAEs were reported in 3 subjects of which 1 SAE was suspected to be related to study drug. Transient non-adverse elevation of ALT was noted in 2 subjects at 60 µg (Cmax 1.6 ng/mL and AUCtau 25.3 ng*h/mL) (2x ULN and <1.2x ULN) and returned to normal limits without cessation of study drug. At 100 µg tropifexor (Cmax 3.47 ng/mL and AUCtau 50.2 ng*h/mL) , 1 subject had an increase of ALT > 5x ULN and 1 subject had an ALT increase of slightly greater than 3x ULN. In both cases AST was also elevated to a lesser degree and elevated transaminase levels were not associated with symptoms or signs of hepatic dysfunction or elevation of bilirubin. Since study drug was discontinued it is not known if ALT/AST would have normalized with continued therapy as it did at the 60 µg dose, however liver enzymes normalized soon after study drug discontinuation. Based on the findings at the 60 µg dose, this isolated ALT/AST increase is consistent with a metabolic adaptation of the liver to tropifexor.
- Results from the First-in-Human study CLJN452X2101 also showed that when tropifexor was taken with a high-fat meal, median Tmax was delayed from 4 h to 9 h, and mean Tropifexor Cmax and AUCinf increased by approximately 60% compared to the fasted state. Individual Tropifexor fed vs. fasted exposure ratios ranged from 1.17 to 2.27-fold for Cmax and from 1.24 to 1.94-fold for AUCinf. To avoid variability in drug exposure, it is recommended that throughout the treatment period, patients will be directed to take study drug at home with ~240 mL (8 ounces) of water in the morning in a fasting state, at least 30 min prior to the first beverage apart from water and 60 min prior to first meal of the day, preferably at the same time of the day. For each daily dose, one capsule should be taken from each of the 3 bottles dispensed.
- The pharmacodynamic marker, FGF19 continues to rise with increasing tropifexor doses up to 3000 µg in the SAD study. The 30 µg/day dose resulted in FGF19 elevations consistent with likely pharmacological activity in NASH (Neuschwander-Tetri et al 2015).

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3.3.3 Dose Selection

The DMC will closely follow safety data and liver enzymes of this study.

3.3.3.1 Part A

Initial Exposure cap (AUCtau,ss) - 70 ng•hr/ml was based on 13 week animal toxicity studies. Therefore, the doses in Part A have been chosen based on the following:

- The 10 µg dose of tropifexor to explore if the lowest dosage form is efficacious as well as to fully explore the lower part of the dose response curve
- The 30 µg dose has FGF19 elevation consistent with likely pharmacological activity in NASH and comparable to FGF19 elevations observed with the OCA dose of 25 mg. This dose has shown efficacy in a Phase II trial (Neuschwander-Tetri et al 2015)
- The 60 µg dose to result in larger FGF19 elevations; there were no persistent ALT/AST elevation in healthy subjects at this dose
- The 90 µg dose to explore a dose with greater FGF19 elevations; based on data at 100 µg, this dose is expected to lead to isolated ALT/AST elevation in some patients. It is expected that any isolated ALT/AST elevations at this dose will also normalize during therapy (as seen at the 60 µg dose) in the first few weeks of therapy. All patients will be followed closely for safety in conjunction with the DMC. Patients in Part A of the trial are monitored for LFTs at weeks 1 and 2 (and further as per schedule), when such potential elevations are expected.
- The longer term animal toxicity studies confirm that the exposure in NASH patients at a dose of 90 µg maintains a < 1-fold safety margin to the rat NOAEL (slightly > 1-fold against the previous cap of 70 ng•hr/ml) but of >2-fold safety margin to the dog NOAEL

3.3.3.2 Part B

Two doses will be selected for Part B based on DMC recommendations after review of a formal interim analysis of the safety and efficacy data after ≥ 90% of patients from Part A have completed Week 8. See Section 3.5 for further details. DMC selected use of 90 µg tropifexor in Part B. Therefore, as described in Section 3.1, Part B will include 3 treatment arms: 75 patients will be treated with 90 µg, 20 patients with 60 µg tropifexor and 25 patients with placebo.

3.3.3.3 Part C

The rationale for investigating tropifexor doses > 90 µg in Part C is supported by the need to explore the pharmacological effect at a broader dose range of tropifexor. The current non-clinical safety profile of tropifexor, preclinical data (see Section 3.3.2), and the DMC's recommendation upon review of LJN452A2202 Part A safety, and pharmacokinetic data, all support the investigation of tropifexor doses of > 90 µg.

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Summary

The duration of 12 weeks of therapy is a suitable timeframe to test primary endpoints in the study. Reduction of hepatic fat content has been demonstrated in studies of similar length in response to surgical and pharmacologic therapies. Biochemical response to therapy approaches a maximum (i.e. lowest GGT or ALT level) at Week 12, and is detected as soon as Week 4, with treatment with another FXR agonist (Neuschwander-Tetri et al 2015, Sanyal et al 2009). The availability of longer term non-clinical toxicology data (Section 3.3.1) allows for addition of longer term (48 week) treatment and inclusion of paired biopsies in Part C.

Isolated ALT and AST elevation in the single/multiple ascending dose studies of tropifexor were seen in less than 2 weeks of therapy and resolved within 7 days of continued therapy or drug discontinuation; a 12-week study is thus sufficient to allow assessment of the magnitude of effect and whether it resolves during continuing treatment. Planned DMC review of the Part A data identified no safety concerns. The DMC recommendation, supported by Part A pharmacokinetic modeling and completed non clinical toxicology studies, support exploring doses > 90 µg and specifically 140 and 200 µg in Part C.

Overall, the considerable safety data published for OCA (Neuschwander-Tetri et al 2015, Hirschfield et al 2015) gives a robust starting point for the safety of the FXR class of drugs in regards to on-target effects. In comparison to OCA, this non-bile acid FXR agonist is expected to have fewer off-target effects due to: 1) greater specificity; ~300× more potent with no TGR5 effects, 2) the lack of enterohepatic recirculation, low dosing and hepatic first pass metabolism leading to a predicted lower systemic exposure. Nonetheless safety will be monitored closely and frequently in conjunction with the DMC. The DMC findings upon review of the Part A interim analysis data support these assumptions. Statistical considerations regarding the evaluation of safety are provided in Section 9.8.1.

3.4 Rationale for choice of comparator

Currently there is no treatment approved for patients with NASH. A placebo will be used as a comparator in this study to examine the effects of Tropifexor beyond that achieved with a placebo.

3.5 Purpose and timing of interim analyses/design adaptations

The first planned interim analysis (IA) of available data will be performed to assess safety and biochemical response (surrogate of efficacy) after ≥ 90% of patients from Part A have completed assessments up to and including Week 8. The purpose of this interim analysis is to select the dosing for Part B. The timing of Week 8 is based on earlier results seen in the FLINT study (Neuschwander-Tetri et al 2015) in which the t½ of ALT reduction was already seen at 6 weeks on OCA treatment. It is further supported by findings from the First-in-Human studies with Tropifexor in which healthy volunteers had ALT or AST elevations within the first 7 days of treatment which were all resolved in the next 7 days. Therefore, 8

[redacted]

weeks seems an appropriate timing to select the treatment arms for enrichment in Part B of this study.

Unblinded interim analysis of safety, efficacy and PK results will be reviewed by an external Data Monitoring Committee (DMC). The DMC will make recommendations concerning the dosing arms for Part B. The DMC will be asked to identify the highest safe (and effective) dose and the lowest effective (and safe) dose for further study in Part B. Part B of the trial will also be conducted as double blind placebo controlled and similar to Part A the doses investigated will be known, but the individual treatment allocation will remain blinded.

The details for decision rules that will be used to guide the DMC on the dose selection in Part B will be specified in a separate DMC charter.

It was expected that several of the doses selected for study in Part A would be both safe and efficacious. As pre-specified, in the event that the DMC selected only one active dose to be tested in 75 patients in Part B, one of the other originally planned active treatment arms would continue with a smaller sample size (20 patients) to confirm the earlier findings of this dose level observed in Part A. The DMC selected 90 µg to be tested in Part B (75 patients). As pre-specified in the protocol, in this case, another dose, 60 µg, will be tested in 20 patients in Part B. If only one 'safe' dose had been identified, then only one tropifexor dose (and placebo arm) would be advanced in Part B.

Additional information is presented in Section 9.

The DMC will review safety, including AEs and laboratory parameters, on a regular basis. In particular, in the event that more than 3 patients develop an AE of CTCAE (Common Terminology Criteria for Adverse Events) grade ≥3 or higher in the same system organ class, the DMC chairman will be alerted. Further details regarding relevant data and actions will be specified in the separate DMC charter.

A second analysis of Part A data, collected up to Week 16, will be performed. The purpose of this analysis is for internal decision making by the sponsor (Novartis) and discretionary DMC review.

A third analysis of complete Part A and Part B data will be performed when all patients randomized to Part B have completed the Week 16 EOS visit (Visit 299) or prematurely discontinued from the study.

An interim analysis of Part C data (fourth planned reporting event) will be performed when all patients have completed the Week 12 visit or prematurely discontinued from the study prior to week 12. Part C patients will continue through Week 52, so Novartis and CRO associates involved with continued direct study site conduct will not be unblinded at the time of the Part C Week 12 Interim Analysis. Novartis and CRO associates involved in data management, analysis and reporting, and Novartis management will be unblinded at this Interim Analysis. Site personnel, patients and Novartis and CRO field force associates will remain blinded.

The final data analysis will be performed when all patients randomized to Part C have completed the Week 52 visit (Visit 299) or prematurely discontinued from the study. This final analysis will include all data from Part C plus data from Parts A and B as appropriate. If an extension trial is available at the end of Part B, data for patients from Parts B and C who rollover into the extension will be available through EOT only.

[redacted]

Data collected during the follow-up 2 period (i.e., after week 16) will be reported in a subsequent separate report.

3.6 Risks and benefits

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

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

Isolated increases in transaminases ALT and AST were observed at higher doses of tropifexor in healthy subjects in study CLJN452X2101 as detailed in Section 3.3. These changes normalized spontaneously at the 60 µg dose and were not observed at the 30 µg dose. It is not known if the isolated ALT or AST elevations noted in healthy volunteers at the 100 µg/day would have resolved on continued therapy, however, they did normalize soon after discontinuation of study drug. These findings are consistent with hepatic adaptation to higher doses of drug. Nonetheless patients' liver function tests will be followed closely, especially early in therapy, in conjunction with the DMC, including frequent checks of a liver safety panel and drug dosage dose reduced or discontinued if necessary.

Pruritus and LDL elevations have been noted in clinical trials with a bile acid FXR agonist, but have not been noted in a first-in-human study with tropifexor, a non-bile acid FXR agonist. Both pruritus and serum lipids will be closely monitored in this study.

A maximum of 400 mL of blood is planned to be collected from each patient in Parts A and B and 900 mL in Part C as part of the study. Additional samples for monitoring of any safety findings may be required, and would be in addition to this volume. Over the course of the 4 to 12 months study period, this is not considered to be a concern for this population.

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

Paired liver biopsies (baseline and Week 48) are required for patients participating in Part C. Baseline biopsies will confirm the diagnosis of NASH (steatosis, lobular inflammation, hepatocyte ballooning) and presence of fibrosis. The primary risk of liver biopsy is bleeding from the site of needle entry into the liver, although this occurs in less than one per cent of patients. Other possible 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 Parts A and B, might have reductions in hepatic fat; it is possible that this is a clinical benefit. However, 12 weeks treatment is unlikely to be sufficient to provide benefit in reducing hepatic fibrosis. For this reason, paired liver biopsies in Part C with 48 weeks of treatment have been included in this study providing evaluation of longer-term

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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.

4 Population

The study population will consist of adult male and female patients with EITHER histologic evidence of NASH on liver biopsy within 2 years (within 6 months for Part C) prior to randomization and elevated ALT, OR phenotypic diagnosis of NASH based on elevated ALT, Type 2 diabetes mellitus or elevated HbA_{1c} and increased BMI, in both cases accompanied by liver fat ≥ 10% on centrally-read MRI. The phenotypic definition of NASH will not be used for eligibility in Part C. All patients participating in Part C must meet the histologic criteria for NASH as determined by the biopsy central reader. See Section 4.1 for full details.

The study will include a total of approximately 345 patients of which approximately 75 patients will enroll in Part A, approximately 120 patients in Part B, and approximately 150 in Part C.

The study will be conducted in approximately 35 to 90 centers worldwide. Since a 60% screening failure rate is expected, approximately 850 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)
3. Presence of NASH as demonstrated by **ONE** of the following:
   - **In Parts A & B:** Histologic evidence of NASH based on liver biopsy obtained 2 years or less before randomization with a diagnosis consistent with NASH, fibrosis level F1, F2 or F3, (i.e. fibrosis in the absence of established cirrhosis) no diagnosis of alternative chronic liver diseases
   - **Part C (All patients)**: Adequate liver biopsy sample for evaluation by Central Reader to confirm Histologic evidence of NASH based on liver biopsy obtained during the Screening period or within 6 months before randomization with a diagnosis consistent with NASH, fibrosis level F2 or F3, and no diagnosis of alternative chronic liver diseases. Permitted therapies must be stable as outlined in Table 5-5 (from 1 month prior to biopsy up to and including screening)

     AND (all Parts)

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

   OR in Parts A and B only

   - Phenotypic diagnosis of NASH based on presence of ALL **THREE** of the following:
     - ALT ≥ 43 IU/L (males) or ≥ 28 IU/L (females) **AND**
     - BMI ≥ 27 kg/m^2 (in patients with a self-identified race other than Asian) or ≥ 23 kg/m^2 (in patients with a self-identified Asian race) **AND**

[redacted]

- Diagnosis of Type 2 diabetes mellitus by having either:
  - $HbA_{1C} \geq 6.5\%$ or
  - Drug therapy for Type 2 diabetes mellitus (See Section 5.5.8)

4. Liver fat ≥ 10% at screening as determined by the reading of the central MRI laboratory of locally produced images
5. Patients must weigh at least 40 kg (88 lb) and no more than 150 kg (330 lb) to participate in the study. Inclusion of patients with higher weights up to 200 kg (440 lbs) may occur if a MRI scanner with a suitable table weight of 200 kg (440 lbs) is available. Patients must not have ≥ 4.5 kg (10 lb) weight loss within the last 6 months prior to screening
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study

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 the study drug or its excipients or to drugs of similar chemical classes
3. Previous exposure to FXR agonists (including tropifexor)
4. Patients taking medications prohibited by the protocol. See Section 5.5.8 for further details
5. Patients taking the following medicines UNLESS on a stable dose (within 25% of baseline dose) for at least 1 month before randomization: (for Part C patients, dose must be stable for at least 1 month prior to biopsy through Screening as defined in Table 5-5) anti-diabetic medications, insulin, beta-blockers, thiazide diuretics, fibrates, statins, niacin, ezetimibe, vitamin E (if doses > 200 IU/day; doses > 800 IU/day are prohibited), thyroid hormone, psychotropic medications, estrogen or estrogen containing birth control
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 5 days (= 5 times the terminal half-life of tropifexor) after stopping of study treatment. Highly effective contraception methods include:
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy, total hysterectomy or tubal ligation) at least six weeks before taking

[redacted]

study treatment. In case of oophorectomy alone, the sterile reproductive status of the woman must have been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

9. Sexually active males must use a condom during intercourse while taking study medication and for 5 days after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid
10. Current or history of significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening (significant alcohol consumption is defined as more than 20 g/day in females and more than 30 g/day in males, on average) and/or a score on the AUDIT questionnaire ≥8
11. Inability to reliably quantify alcohol consumption based upon local study physician judgment
12. 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
13. Prior or planned (during the study period) bariatric surgery (eg, gastroplasty, roux-en-Y gastric bypass)
14. Uncontrolled diabetes defined as $HbA_{1c} \geq 9.5\%$ within 60 days prior to enrollment
15. Presence of cirrhosis on liver biopsy or clinical diagnosis
16. Platelet count $< 120 \times 10^9/L$
17. Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities:
    - Serum albumin < 32 g/L
    - INR > 1.3
    - Direct bilirubin > 13 mg/L
    - ALT or AST > 5× ULN
    - Alkaline phosphatase > 3× ULN

[redacted]

- History of esophageal varices, ascites or hepatic encephalopathy
- Splenomegaly

18. Previous diagnosis of other forms of chronic liver disease:
    - Hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg)
    - Hepatitis C as defined by presence of hepatitis C virus (HCV) RNA
    - Evidence of ongoing autoimmune liver disease as defined by compatible liver histology
    - 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
    - Wilson's disease as defined by ceruloplasmin below the limits of normal and compatible liver histology
    - Alpha-1-antitrypsin (A1AT) deficiency as defined by diagnostic features in liver histology (confirmed by alpha-1 antitrypsin level less than normal; exclusion at the discretion of the study physician)
    - History of hemochromatosis or iron overload as defined by presence of 3+ or 4+ stainable iron on liver biopsy or iron saturation levels interpreted as hemochromatosis.
    - Drug-induced liver disease as defined on the basis of typical exposure and history
    - Known bile duct obstruction
    - Suspected or proven liver cancer
    - Suspected or confirmed Gilbert's syndrome
    - Any other type of liver disease other than NASH
19. Calculated eGFR less than 60 mL/min (using the MDRD formula)
20. History of biliary diversion
21. History of liver transplantation or current placement on a liver transplant list
22. Known positivity for Human Immunodeficiency Virus (HIV) infection
23. Active substance abuse including inhaled or injection drugs in the year prior to screening
24. Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study
25. Chronic (> 3 months) use of excessive doses of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as evaluated by investigator
26. New use of GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide within 3 months of screening.
27. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:

[redacted]

- Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
- History of familial long QT syndrome or known family history of Torsades de Pointes

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

ALT, platelets, INR and eGFR values must always meet the requirements listed in the inclusion and exclusion criteria. For other laboratory values, patients with a single lab value outside of the value required for eligibility may be considered eligible for enrolment, as long as that value is within 10% of the value required for eligibility. All other eligibility requirements must be met.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Tropifexor

Dosage form: 10 µg, 30 µg, and 100 µg capsules.

Presentation: Bottle

Expiry date: Mentioned on the labels.

Placebo

Dosage form: capsules

Presentation: Bottle

Expiry date: Mentioned on the labels.

Novartis Drug Supply Management (DSM) will provide sufficient supplies of tropifexor and placebo to last each patient between visits (or more).

[redacted]

5.1.2 Additional treatment

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

5.2 Treatment arms

Patients in **Part A** will be assigned at the baseline visit to one of the following 5 treatment arms in a ratio of 1:1:1:1:1 in a blinded manner. Placebo capsules will be given in each treatment arm where necessary to maintain blinding:

Arm A: Once daily (morning, fasting) treatment with 10 µg tropifexor for 12 weeks

Arm B: Once daily (morning, fasting) treatment with 30 µg tropifexor for 12 weeks

Arm C: Once daily (morning, fasting) treatment with 60 µg tropifexor for 12 weeks

Arm D: Once daily (morning, fasting) treatment with 90 µg tropifexor for 12 weeks

Arm E: Once daily (morning, fasting) treatment with matching placebo capsules for 12 weeks

Patients in **Part B** will be assigned at the baseline visit to one of the following 3 treatment arms in a ratio of 15:4:5 in a blinded manner. The doses to be used in Part B were decided based on data from the first interim analysis and DMC consultation. Placebo capsules will be given in each treatment arm where necessary to maintain blinding.

Arm F: Once daily (morning, fasting) treatment with 90 µg tropifexor as determined after DMC review of first Part A interim analysis data for 12 weeks

Arm G: Once daily (morning, fasting) treatment with 60 µg tropifexor as determined after DMC review of first Part A interim analysis data for 12 weeks

Arm H: Once daily (morning, fasting) treatment with matching placebo for 12 weeks

Patients in **Part C** will be assigned at the baseline visit to one of the following 3 treatment arms in a ratio of 1:1:1 in a blinded manner. The doses used in Part C were determined based on preclinical toxicology data, pharmacokinetic modeling and DMC recommendations based on Part A data (Section 3.3). Placebo capsules will be given to maintain blinding.

Arm I: Once daily (morning, fasting) treatment with 140 µg tropifexor for 48 weeks

Arm J: Once daily (morning, fasting) treatment with 200 µg tropifexor for 48 weeks

Arm K: Once daily (morning, fasting) treatment with matching placebo for 48 weeks

In order to maintain the blind, placebo capsules matching tropifexor 10, 30 and 100 µg capsules will be given to patients as indicated in Table 5-1, so that all patients will receive 3 capsules per day. One capsule from each of the 3 bottles dispensed should be taken in the morning after an 8 hour fast.

[redacted]

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

Treatment arm	Placebo capsules	10 µg capsules	30 µg capsules	100 µg capsules
Placebo	3	-	-	-
10 µg	2	1	-	-
30 µg *	0 OR 2	3 OR 0	0 OR 1	-
60 µg	1	-	2	-
90 µg	-	-	3	-
140 µg	-	1	1	1
200 µg	1	-	-	2

* Patients in the 30 µg arm will either receive 3 x 10 µg capsules OR 1 x 30 µg capsule AND 2 x placebo capsules

In case of necessary dose reductions due to ALT and/or AST elevation (see Section 5.5.5), the patient will return his original treatment to the clinic and will receive 3 new bottles assigned via Interactive Response Technology (IRT) to keep the blind.

5.3 Treatment assignment and randomization

At the baseline visit, all eligible patients will be randomized via 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.

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

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

Stratification

Part A: Randomization will be stratified in Part A by BMI at baseline (<30 kg/m^2 or ≥ 30 kg/m^2 for patients with an Asian race or < 35 kg/m^2 or ≥ 35 kg/m^2 for all other patients). The race is based on the race the patient self-reports as captured on the demography eCRF.

Part B: Randomization will be stratified in Part B by BMI at baseline (<30 kg/m^2 or ≥ 30 kg/m^2 for patients with an Asian race or < 35 kg/m^2 or ≥ 35 kg/m^2 for all other patients). The race is based on the race the patient self-reports as captured on the demography eCRF. Randomization in Part B will also be stratified by Japanese or non-Japanese, Japanese defined as patients residing in Japan.

[redacted]

Part C: Randomization in Part C will be stratified by Fibrosis level (F2/F3) as determined in the Screening biopsy by the Central Reader and by Type 2 Diabetes status (yes/no) as reported on the Medical History eCRF. To ensure balance of patients in Japan among the 3 treatment arms, the following stratum levels will be implemented (Japanese subgroup is too small for additional stratification):

1. Japan
2. Non-Japan, F2, T2D=No
3. Non-Japan, F2, T2D=Yes
4. Non-Japan, F3, T2D=No
5. Non-Japan, F3, T2D=Yes

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 study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. Additional placebo capsules will be given in active treatment groups when needed to maintain blinding. One capsule from each of the 3 bottles dispensed should be taken daily.

As an interim analysis will be performed at Week 8 in Part A, there will be a database lock / freeze when ≥ 90% of patients of Part A have completed their Week 8 assessments. A selected Novartis team not involved in the clinical conduct of the study will be unblinded to the Week 8 results and will support and advise the DMC (see Section 8.4). Part B of the trial will also be conducted as double blind placebo controlled and similar to Part A the doses investigated will be known, but the individual treatment allocation will remain blinded.

Further, as indicated in Section 3.5, the DMC will review safety, including AEs and laboratory parameters, on a regular basis.

A second analysis of Part A data, for all patients collected up to Week 16, will be performed. (See Section 3.5). At that time, Novartis and CRO associates will be unblinded to data from Part A, only.

A third analysis will include Part B data collected up to Week 16. At that time Novartis and CRO associates will be unblinded to data from Part B.

An interim analysis of Part C data (fourth planned reporting event) will be performed when all patients have completed the Week 12 visit or prematurely discontinued from the study prior to week 12. Part C patients will continue through Week 52, so Novartis and CRO associates involved with continued direct study site conduct will not be unblinded at the time of the Part C Week 12 Interim Analysis. Novartis and CRO associates involved in data management, analysis and reporting, and Novartis management will be unblinded at this Interim Analysis. Site personnel, patients and Novartis and CRO field force associates will remain blinded. The final database lock for the end-of-study analyses will occur when all patients have completed the study. This will include data through EOT (Week 12 for Parts A and B, Week

[redacted]

48 for Part C) visit for any patients continuing therapy in an extension protocol (if available), or EOS (Week 16 visit for Parts A, and B, or Week 52 for patients in Part C) for all other patients, unless prematurely discontinued from the study.

The Novartis clinical trial team (or delegates), patients, investigator, site personnel performing the assessments, and monitors will remain blinded to individual treatment allocation for patients randomized in Part A until after the second Interim Analysis for Part A (data through Week 16), until after the Part B database lock (through Week 16) for patients randomized in Part B, and likewise blinded to individual treatment for patients randomized to Part C, until the Part C database lock. After all patients complete (EOS Visit) of Part C, designated Sponsor and CRO associates will be unblinded to all study data.

The bioanalyst will have access to the randomization list to facilitate analysis of the PK/PD samples (i.e. to avoid the unnecessary analysis of placebo samples).

Whenever needed or requested by the clinical team or the DMC, the bioanalyst, supported by an independent programmer, will share information from PK measurements before clinical database lock in a blinded fashion with the pharmacokineticist, pharmacometrician and pharmacometrics programmer. The PK results for each study Part will remain blinded to the Novartis clinical team until the analysis is completed at the end of each study part respectively. If available, the summary and individual PK results may be shared with the DMC through a non-study/independent Novartis representative.

Unblinding will only occur for select individuals, in the case of patient emergencies (see Section 5.6), at the time of the interim analyses (see Section 9.7), for DMC review, at the time of the second Part A interim analysis, at the time of the end of Part B analysis and at the conclusion of the study. A Novartis programmer not involved in the clinical conduct (see above) will facilitate the data extract for each interim analysis to be forwarded for analysis by the 3rd party independent team. Patient data collected subsequent to each interim analysis will remain blinded. During study conduct, DMC members may request patient treatment assignments from Cenduit, the Interactive Voice Response vendor.

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 patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator (e.g. [redacted]). Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site must select the CRF book with a matching Subject Number from the EDC system to enter data.

[redacted]

If the patient fails to be treated for any reason, the IRT must be notified within 2 days that the patient was not treated. The reason for not being treated will be entered on the Screening epoch Study Disposition CRF.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the "n" treatment arms and a [specific visit or dose/dose level]. 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.

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.

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 or remotely and at the completion of the trial. Patients will be asked to return all unused study treatment and packaging at the end of the study 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, at approximately the same time each day, except on the days where there are study visits at which time the patients should take their doses at the clinic. On the baseline day, patients will

[redacted]

be instructed to take 3 capsules each day during the duration of the study. One capsule, from each of the 3 bottles dispensed, should be taken each day as directed.

Dosing recommendations:

- Patients should be fasted for at least 8 hours prior to each dose and should refrain from drinking anything but water for at least 30 min post dose. A light breakfast may be taken after 60 minutes.
- Tropifexor is to be taken by mouth with a glass of ~240 mL water and consumed over as short a time as possible.
- 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.

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

The patients will also be instructed to bring back unused medication and empty bottles at selected time-points for drug accountability checking.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

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

5.5.4.1 Dietary restrictions

- No alcohol consumption is allowed for 8 hours before dosing and each study visit until Study Completion evaluation.

All patients will fast (i.e. no food and liquid except water) for at least 8 hours prior to each dose and should refrain from drinking for at least 30 min post dose, and refrain from eating for at least 60 min post dose. A light breakfast may be taken after 60 minutes.

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 equivalent if there is a country specific recommended diet (see 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 patients who experience significant isolated ALT and/or AST elevations, dose reductions are permitted in order to allow the patient to continue on study treatment. The guidance for the modification of study treatment is outlined below. In case of significant ALT and/or AST elevations, the guidance should be followed. However, in the short term management of an

[redacted]

individual patient, not related to significant ALT and/or AST elevations, investigators must use their medical judgments in regards to what they deem as the best interest of the patient.

In the event of a significant ALT and/or AST elevation, dose reduction to the next lower dose level is permitted, see further instructions below and in Table 5-2 and Table 5-3; this will allow an evaluation of whether such dose reductions are useful in patient management. The ability to reduce dose is clinically relevant when a possible adverse event is a laboratory finding that can be easily monitored. In the context of a Phase II trial exploring different dose levels, discontinuation of study treatment is not considered optimal as data generated after dose reduction will further inform on e.g. the tolerability and safety of tropifexor.

Study medication dose can be reduced one level in all study Parts as indicated on Table 5-3. In Parts A and B one cycle of dose reduction is allowed. If, despite being on a reduced dose, a patient has persistent or new significant ALT and/or AST elevations, he must be discontinued from study treatment. Increasing the dose to the original level is not permitted for patients in Parts A and B, but is permitted in the longer-duration Part C. After returning to the original randomized dose, a subsequent 1 level dose reduction for patients in Part C is allowed.

Significant isolated ALT and/or AST increase

If the patient has symptoms or other LFTs are also elevated (in particular bilirubin and/or PT/INR), please refer to Section 7 and Section 14 for appropriate actions.

A **significant ALT** and/or AST **increase** is defined as: 2× Baseline value (see Section 9.5.2.5 for definition of baseline levels).

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

Patients with a significant increase of ALT and/or AST will be instructed to return to the clinic for an additional laboratory evaluation to confirm these results. The laboratory tests to be repeated are ALT, AST, GGT, alkaline phosphatase, total bilirubin, and albumin (LFT) and PT/INR. Please refer to Table 5-2 for the next actions.

[redacted]

Table 5-2 Isolated ALT/AST Elevations

ALT and/or AST increase[4]	First Action	Result	2nd Action	Result	3rd Action
>2× baseline[5] AND ≤ 5× ULN	Repeat tests[1] within 48 – 72 hours[1]	Persistent elevation[2] of ALT and/or AST	Repeat tests[1] within 48 – 72 hours[1]	Persistent elevation[2] of ALT and/or AST	Repeat tests[1] within 48 – 72 hours if no improvement or within 1 week if improved. Continue testing[1] until 2 weeks after start original elevation. If after 2 weeks ALT and/or AST are persistently elevated reduce dose (Table 5-3). Continue testing[1] within 48 – 72 hours if no improvement and within 1 week if improved until ALT and AST <3x ULN. If ALT and AST levels remain ≥3x ULN three weeks after dose reduction, discontinue study treatment
				Decreasing ALT and AST[3]	Continue assigned study treatment as per protocol
		Decreasing ALT and AST[3]	Continue assigned study treatment as per protocol	--	--
>2× baseline[5] AND >5× ULN but ≤8× ULN	Repeat tests[1] within 48 – 72 hours[1]	Persistent elevation[2] of ALT and/or AST	Repeat tests[1] within 48 – 72 hours if no improvement or within 1 week if improved. Continue testing[1] until 1 week after start original elevation. If after 1 week ALT and/or AST are persistently elevated, reduce dose (Table 5-3). Repeat tests[1] within 48 – 72 hours[1] if no improvement and within 1 week if improved	Persistent elevation[2] of ALT and/or AST	Repeat tests[1] within 48 – 72 hours if no improvement or within 1 week if improved. Continue testing[1] until 2 weeks after start original elevation. If after 2 weeks ALT and/or AST are persistently elevated, discontinue study treatment
				Decreasing ALT and AST[3]	Continue with reduced dose. Continue testing[1] within 48 – 72 hours if ALT/AST not improving and weekly if improving until ALT and AST <3x ULN. If ALT and AST levels remain ≥3x ULN three weeks after dose reduction, discontinue study treatment
		Decreasing ALT and AST[3]	Continue assigned study treatment as per protocol	--	--

[redacted]

ALT and/or AST increase[4]	First Action	Result	2nd Action	Result	3rd Action
>2× baseline[5] AND >8× ULN	Repeat tests[1] within 48 hours	Persistent elevation of ALT and/or AST[2]	Discontinue study treatment	--	--
		Decreasing ALT and AST[3]	Repeat tests[1] within 48 – 72 hours[1] if no improvement or within 1 week if improved.	Persistent elevation of ALT and/or AST[2]	Dose reduction (Table 5-3). Continuetesting[1] within 48 – 72 hrs if ALT/AST not improving and weekly if improving until ALT and AST <3x ULN. If ALT and AST levels remain ≥3x ULN three weeks after dose reduction, discontinue study treatment
				Decreasing ALT and AST[3]	Follow as per table

[1]Tests: PT/INR and LFT: Liver function test: ALT, AST, GGT, alkaline phosphatase, total bilirubin, and albumin (see Section 6.4.2); these repeats must be performed using the central laboratory if possible and captured via the unscheduled lab CRF. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. If tests are performed at local laboratory, results will be captured in source documents only. In all cases, a physical examination should be performed and recorded in source documents.

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

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

[4]Please also refer to Section 14, Appendix 2, Table 14-2 for additional actions

[5]Please see Section 9.5.2.5 for definition of baseline values.

[redacted]

If the additional laboratory evaluation confirms a significant increase of ALT and/or AST values, the study treatment will be reduced to the next dose level in **a blinded manner** (Table 5-3). The investigator must contact the IRT to register the patient's dose reduction.

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

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

Table 5-3 Dose reduction

Original treatment (daily dose)	Reduced treatment (daily dose)
200 µg	140 µg
140 µg	90 µg
90 µg	60 µg
60 µg	30 µg
30 µg	10 µg
10 µg	Placebo

Second dose reductions are not permitted in Parts A and B. Returning to the original treatment is not permitted in Parts A and B. In Part C, returning to the original dose is allowed upon resolution of the lab abnormality and at the investigator's discretion. Subsequent dose reduction cycles are allowed in Part C as necessary after returning to the original dose. Dose can only be reduced by one dose level in all Parts of the protocol.

Patients with a persistent or second cycle of significant ALT and/or AST increase while being on a reduced dose will be instructed to return to the clinic for an additional laboratory evaluation within 1 week or 2 days, depending on the elevation, to confirm these results. If the additional laboratory evaluation confirms the significant increase of ALT and/or AST values, the patient will discontinue study treatment, and will enter the follow up period. If the additional laboratory evaluation does not confirm the significant increase of ALT and/or AST values, the patient will continue with the assigned (reduced) treatment. Data handling rules for patients in Part C who experience dose reductions will be described in the Analysis Plan.

Treatment discontinuations: The investigator must contact the IRT to register the patient's discontinuation from study treatment. Further, all study treatment discontinuations must be recorded on the eCRF. After discontinuation for a liver-related event, LFT and clinical monitoring should continue until the event is resolved (see Table 14-2 in Appendix 2).

5.5.6 Rescue medication

Use of rescue medication is not allowed during the 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

[redacted]

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

Medication or herbal remedies likely to have a significant impact on tropifexor metabolism by inhibiting UGT1A1 are prohibited in the study from the first dosing until the end-of-study visit Week 16 (visit 299 or visit 399 in relevant patients (see Section 3.1)) has been conducted.

These include: atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine and zafirlukast and *Silybum marianum (milk thistle)* and *Valeriana officinalis (valerian)*. The non-selective UGT inhibitors diclofenac, probenecid and valproic acid are also prohibited.

Alcohol consumption is to be strongly discouraged, and should not exceed 20 g/day in females and 30 g/day in males.

An overview of the prohibited medication is given in Table 5-4, and the summary of permitted medication if on stable dose is in Table 5-5.

Patients on medications specified in Table 5-5 can be included if these medications are medically necessary, the dose has been stable for at least 1 month, and the investigator feels the dose will remain stable for the duration of the double-blind treatment period. A stable dose is defined as a dose within 25% of the baseline dose. No new use of these medications is allowed after entering the study with the exception of drugs to control medically significant elevations in LDL-cholesterol which have been confirmed upon repeat testing

Table 5-4 Prohibited medication

Medication	Prohibited
Specific UGT1A1 inhibitors:atazanavir, gemfibrozil, indinavir, itraconazole, ketoconazole, manidipine, and zafirlukast	Any use from first drug intake to end-of-study visit
Herbal remedies inhibiting UGT1A1:: Silybum marianum (sylamarin, milk thistle) and Valeriana officinalis (valerian)	Any use from first drug intake to end-of-study visit
Non-selective UGT inhibitors:: diclofenac, probenecid, valproic acid	Any use from first drug intake to end-of-study visit
Vitamin E	Doses >800 IU/day
GLP-1 agonists such as liraglutide, exenatide , lixisenatide, albiglutide or dulaglutide^	Newly initiated use within 3 months prior to randomization
^For patients in Part C, these medications must be stable for at least 1 month prior to qualifying baseline biopsy through the Screening period.	

[redacted]

Table 5-5 Medications permitted only if dose is stable (within 25 percent of baseline dose) for at least 1 month prior to randomization and expected to remain stable through the double-blind treatment period

Medication
Oral anti-diabetic medications such as (metformin and/or sulfonylureas)^
Insulin*
Beta-blockers and thiazide diuretics
Fibrates**^, statins**, niacin**^, ezetimibe**
Vitamin E*** ^
Thyroid hormone
Psychotropic medications (phenothiazines or second generation antipsychotics)
Estrogen or estrogen containing birth control
* unless adjustment is required due to intercurrent illness; **unless required to treat medically significant increases in LDL-cholesterol that have been confirmed upon repeat testing ***Only applicable for patients taking >200 IU/day; doses >800 IU/day are prohibited ^ For patients in Part C, these medications must be stable for at least 1 month prior to qualifying baseline biopsy through the Screening period.

5.5.9 Emergency breaking of assigned treatment code

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

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

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

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

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.

[redacted]

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 12 weeks of treatment may include:

- Enrollment in an extension study, if any, to allow for therapy beyond 12 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 299) should be conducted 4 weeks after last treatment (EOT, Week 12 in Parts A, B and Week 48 for patients in Part C). The information to be collected at this follow up visit includes concomitant medications, adverse events, and laboratory samples, as detailed on Table 6-1.

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 (see Section 6.5.6 and Section 7.6)
- Use of prohibited treatment as per recommendations in 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
  - For ALT, AST, total bilirubin and/or alkaline phosphatase elevations mandating study treatment discontinuations, please refer to Section 7.3 and Table 14-2 for further instructions and monitoring.
  - For specified renal events, please refer to Section 7.4 and Table 15-1 for further instructions and monitoring.
  - Other CTCAE grade 3 that are related to study drug,
  - Other CTCAE grade ≥4 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.

[redacted]

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 eCRF. The investigator must determine the primary reason for the patient's premature discontinuation of study treatment and record this information on the eCRF. The investigator must also contact the IRT to register the patient's discontinuation from study treatment.

After study treatment discontinuation, at a minimum, the following data should be collected at abbreviated clinic visits or by telephone visits:

- 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 planned End of Treatment (EOT) (Week 12 in Parts A and B, Week 48 in Part C) and planned End of Study (EOS) (Week 16 in Parts A and B, Week 52 in Part C) visits must be performed. The follow up 2 visit should be performed in relevant patients (see Section 3.1).

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

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

5.6.3 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Note that a patient choosing to discontinue study treatment is not usually withdrawing consent to participate in the study, and such patients should continue follow up as described in Section 5.6.2.

Withdrawal of consent from the study is defined as when a patient:

- Does not want to participate in the study anymore

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

and

- Does not allow analysis of already obtained biologic material

[redacted]

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the patient's decision to withdraw his/her consent and record this information.

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

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

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.

5.6.4 Loss to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient cannot be considered as lost to follow-up until the time point of his/her scheduled 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 withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing 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. In particular for **Part A**, every effort should be made to respect the time frame for the Week 8 visit.

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 study treatment 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 (EOT visit). At this final visit, all dispensed study treatment should be reconciled and the adverse event and concomitant medications reconciled on the CRF. See also Section 5.6.2.

[redacted]

Patients will visit the site for a follow up visit 4 weeks following the last administration of study treatment (EOS visit); some patients will have a further visit 4 weeks later.

Recommended Visit windows

Treatment period:

- ±2 days for Weeks 1 to 12 visits
- ± 7 days for Weeks 16 - 48

For patients who discontinue study treatment prematurely before the end of the treatment period for any reason other than withdrawal of informed consent, the planned End of Treatment (EOT) and End of Study (EOS) visits must be performed. The follow up 2 visit should only be performed in relevant patients (see Section 3.1).

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.

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. See Section 3.1 for what is considered as medically important.

[redacted]

Table 6-1 Assessment schedule Parts A and B

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
Screening												
Informed consent	X											
[redacted]												
Inclusion / Exclusion criteria	X	X	X									
Demography	X											
Serum Pregnancy test[12]	X	X[2]										Urine pregnancy test during study treatment and follow up
Medical history/ current medical conditions	X	X[2]										
Protocol solicited medical history	X	X[2]										
Assessments												
Physical examination[11]	S	S	S			S		S	S	S		
Prior and concomitant medication	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	
Alcohol history / compliance	X[16]		X	X	X	X	X	X	X	X	X	

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
Smoking history	X											
Body height, weight, waist circumference, hip circumference	X		X	X	X	X	X	X	X	X		Height only at screening, waist/hip circumference only at Screening and Week 12
Vital signs	X		X	X	X	X	X	X	X	X		
12-lead ECG[14]	X								X			
MRI[5] (Quantitative liver fat)		X[5]							X[5]			Screening visit 2 including MRI only if provisional eligibility is confirmed
Review of Liver biopsy report (only if available), NAS score (only if available)	X											Data on liver biopsy/ NAS score only collected if results are available in source documents

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
Fibroscan[15]			X						X[15]			Optional, see Section 6.2.6.2
Adverse Events / Serious AE / Liver, Renal Event review	X	X	X	X	X	X	X	X	X	X	X[4]	
AUDIT questionnaire		X	C	C	C	C	C	C	C	C		Full questionnaire (X) at screening, short questionnaire (C) at other visits
VAS (Visual Analog Scale) for itch			X				X		X	X		
[redacted]												
Randomization via IRT			S									

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
Contact IRT	X	X	X			X		X	X			
Drug dispensing			S			S		S				
Drug administration record			X	X	X	X	X	X	X			
Drug compliance				S	S	S	S	S	S			
AHA Diet Review			S				S		S	S		
Diet Compliance			X				X		X	X		
Exercise assessment			X				X		X	X		
Blood collection												
Hepatitis serology	X[6]											
Liver function tests	X	X[2]	X	X	X	X	X	X	X	X	X[4]	
Serum BUN and Creatinine	X		X			X	X	X	X	X	X[4]	
Coagulation panel	X		X				X		X			
Fibrosis biomarker test[13]	X		X						X			
ELF Panel Including TIMP1, HA, PIIINP	X		X						X			
Fibrosis markers and scores	X		X				X		X			
NAFLD fibrosis score	X		X						X			
Fasting lipids	X		X		X		X		X	X		
[redacted]												
Hematology	X		X				X		X	X	X[4]	

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
Clinical chemistry panel	X[7, 16]		X				X		X	X	X[4]	
HbA_{1c}	X								X[19]			
[redacted]												
PK blood collection[10]				X	X[3]	X	X	X	X			
Urine												
Dipstick / routine Urinalysis with Reflex Micro	X		X	X	X	X	X	X	X	X		
Urine pregnancy test[12]			X			X		X	X	X		Serum pregnancy at screening
Drug screen	X	X[2]	X									
Period completion forms												
Screening completion	X	X										
Treatment completion									X			
Study completion										X[4]	X[4]	

TD: treatment discontinuation; PSW: Premature study withdrawal; X and C: assessment to be recorded on clinical database; S: assessment to be recorded on source documentation; C: Short AUDIT questionnaire

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

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	

2: Part B only: Assessments marked with "2" are only to be done in case period between screening visit 1 and anticipated baseline visit > 2 months. All other assessments for screening visit 2 are to be done as listed

3: Part A only: Visit 102/ Week 1. In Part B no Week 1 visit is to be done

4: 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 planned post treatment follow-up 1 period until these events have resolved or stabilized. See Section 3.1 for the definition of medically important events that need this follow up, and for the scheduling of these follow ups. Data will be collected via unscheduled CRFs. The follow up 2 period visit/ EOS visit/399 visit should be completed only when these events are resolved or stabilized.

5: MRI should only be scheduled to occur within 2 weeks of the expected date of randomization. Assessment at visit 199 not to be done in case of premature treatment discontinuation unless the patient has received ≥ 8 weeks of therapy.

6: Not needed if available within 5 years from screening, unless risk factors for viral hepatitis are present after last serologic testing.

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]

9: Optional. A separate informed consent needs to be signed before sample collection. Sample can be collected at BSL visit or any subsequent visit

10: Part A: Week 1: pre-dose and 2 hrs post dose. Week 2, 4, 6, 8 and 12: pre-dose. Part B: Week 2: pre-dose and 2 hrs post dose. Week 6: pre-dose and 4 hours post dose (the last activity of the visit): Week 4, 8 and 12 pre-dose

11: Full physical examination at screening visit 1, baseline and Week 12

12: Only for pre-menopausal women who are not surgically sterile

13: Fibrosis biomarker test originally called Fibrotest / Fibrosure

14: For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding

15: Assessment at visit 199 not to be done in case of premature treatment discontinuation unless the patient has received ≥ 8 weeks of therapy.

16: 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.

[redacted]

Parts A and B	Screening		Randomized Treatment							Post Treatment Follow Up 1	Post Treatment Follow Up 2[4]	Notes
Week	**-5 to -2**	**-2 to BSL[1,2]**	**BSL**	**1[3]**	**2**	**4**	**6**	**8**	**12 TD**	**16 / PSW**	**≥20 [4]**	
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**	
[redacted]												

19: HbA_{1c} to be tested at Week 12 for patients enrolled in Part B.

[redacted]

Table 6-2 Assessment schedule Part C

Part C	Screening		Randomized Treatment													Post Treatment F/U 1	Post Treatment F/U 2
Week	**-10 to -2**	**-2 to BSL[1,2]**	**BSL**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48 TD**	**52**	**>=56**
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**
Screening																	
Informed consent	X																
[redacted]																	
Inclusion / Exclusion criteria	X	X	X														
Demography	X																
Serum Pregnancy test[12]	X	X[2]															
Medical history/ current medical conditions	X	X[2]															
Protocol solicited medical history	X	X[2]															
Assessments																	
Physical examination[11]	S	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	X	X	X	X
Surgical and medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[redacted]

Part C	Screening		Randomized Treatment													Post Treatment F/U 1	Post Treatment F/U 2
Week	**-10 to -2**	**-2 to BSL[1],[2]**	**BSL**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48 TD**	**52**	**>=56**
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**
Alcohol history / compliance	X[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking history	X																
Body height, weight, waist circumference, hip circumference[20]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[14]	X											X			X		
MRI[5] (Quantitative liver fat)		X[5]							X[5]			X[5]			X[5]		
Liver biopsy[19]		X[19]													X[19]		
Fibroscan[15]			X						X			X			X		
Adverse Events / Serious AE / Liver, Renal Event review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]	
AUDIT questionnaire[3]		X	C	C	C	C	C	C	C	C	C	C	C	C	C	C	
VAS (Visual Analog Scale) for itch			X		X		X		X			X			X	X	
[redacted]																	

[redacted]

Part C	Screening		Randomized Treatment													Post Treatment F/U 1	Post Treatment F/U 2
Week	**-10 to -2**	**-2 to BSL[1],[2]**	**BSL**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48 TD**	**52**	**>=56**
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**
[redacted]																	
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	S			
Drug administration record			X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug compliance				S	S	S	S	S	S	S	S	S	S	S	S	S	
AHA Diet Review			S				S		S	S	S	S	S	S	S	S	
Diet Compliance			X				X		X			X			X	X	
Exercise assessment			X				X		X			X			X	X	
Blood collection																	
Hepatitis serology	X[6]																
Liver function tests	X	X[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[4]

[redacted]

Part C	Screening		Randomized Treatment													Post Treatment F/U 1	Post Treatment F/U 2
Week	**-10 to -2**	**-2 to BSL[1],[2]**	**BSL**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48 TD**	**52**	**>=56**
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**
Serum BUN and Creatinine	X		X			X	X	X	X	X	X	X	X	X	X	X	X[4]
Coagulation panel	X		X				X		X			X			X		
Fibrosis biomarker test[13]	X		X						X			X		X	X		
ELF Panel Including TIMP1, HA, PIIINP	X		X						X			X			X		
Fibrosis markers and scores	X		X				X		X			X		X	X		
NAFLD fibrosis score	X		X						X			X			X		
Fasting lipids	X		X		X		X		X		X	X		X	X	X	
[redacted]																	
Hematology	X		X				X		X		X	X		X	X	X	X[4]
Clinical chemistry panel	X[7, 16]		X				X		X		X	X		X	X	X	X[4]
HbA_{1c}	X								X						X		
[redacted]																	

[redacted]

Part C	Screening		Randomized Treatment													Post Treatment F/U 1	Post Treatment F/U 2
Week	**-10 to -2**	**-2 to BSL[1],[2]**	**BSL**	**1**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**32**	**40**	**48 TD**	**52**	**>=56**
Visit number/ Visit name	**1**	**2**	**101**	**102**	**103**	**104**	**105**	**106**	**107**	**108**	**109**	**110**	**111**	**112**	**EOT / 199**	**EOS / 299**	**EOS[4] / 399**
[redacted]																	
PK blood collection[10]							X	X	X			X		X	X		
Urine																	
Dipstick / routine Urinalysis with Reflex Micro	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[12]			X			X		X	X	X	X	X	X	X	X	X	
Drug screen	X	X[2]	X														
Period completion forms																	
Screening completion	X	X															
Treatment completion															X		
Study completion																X[4]	X[4]

[redacted]

TD: treatment discontinuation; PSW: Premature study withdrawal; X and C: assessment to be recorded on clinical database; S: assessment to be recorded on source documentation; C: Short AUDIT questionnaire

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

2: Assessments marked with "2" are only to be done in case period between screening visit 1 and anticipated baseline visit > 2 months. All other assessments for screening visit 2 are to be done as listed

3: Full questionnaire AUDIT (X) at screening, short questionnaire (C) at other visits

4: 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 planned post treatment follow-up 1 period until these events have resolved or stabilized. See Section 3.1 for the definition of medically important events that need this follow up, and for the scheduling of these follow ups. Data will be collected via unscheduled CRFs. The follow up 2 period visit/ EOS visit/399 visit should be completed only when these events are resolved or stabilized.

5: MRI should only be scheduled to occur within 2 weeks of the expected date of randomization and subsequently at Weeks 12, 24 and 48. Assessment at visit EOT not to be done in case of premature treatment discontinuation unless the patient has received ≥ 8 weeks of therapy.

6: Not needed if available within 5 years from screening, unless risk factors for viral hepatitis are present after last serologic testing.

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]

10: pre-dose and post-dose as the last activity of the visit at week 12, 24 and 48, post-dose as the last activity of the visit at week 6 and 40.

11: Full physical examination at screening visit 1, baseline and Weeks 12, 24, & 48.

12: Only for pre-menopausal women who are not surgically sterile. Serum pregnancy at screening - Urine pregnancy test during study treatment and follow up

13: Fibrosis biomarker test originally called Fibrotest / Fibrosure

14: For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding

15: Post baseline Fibroscan to be conducted at the same visits as MRI: Weeks 12, 24 and 48. Assessment at EOT not to be done in case of premature treatment discontinuation unless the patient has received ≥ 8 weeks of therapy.

16: 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.

[redacted]

[redacted]

[redacted]

19: Paired liver biopsies (=< 6 months and at least 2 weeks prior to baseline [redacted]) are required to confirm the diagnosis of NASH (steatosis, lobular inflammation, hepatocyte ballooning) and presence of fibrosis. Baseline Biopsy slides, prepared from biopsies performed during the screening period or =< 6 months prior to the randomization visit, will be sent to a Central Reader to determine eligibility

20: Height only at screening, waist/hip circumference only at Screening and Week 12

[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 Screening Phase Disposition CRF. In addition, the following CRFs should be completed: Informed Consent, Demography, Inclusion/Exclusion, 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 CRF 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 CRF 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 CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

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: year of birth, gender, race, ethnicity, source of referral, 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

[redacted]

recorded in the Medical History CRF. 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 CRF (see Section 7.1 for the timeframe to record AEs during the screening period of Part B). Whenever possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF 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 CRF. 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.

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.

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 Biopsy

For Parts A and B, if liver biopsy was done for the diagnosis of NASH within 2 years prior to randomization, the following information will be collected if available:

- Diagnosis
- Metavir, Ishak, Knodell, Ludwig Batts, or Kleiner-Brunt score, or a liver biopsy score by a country specific method
- NAS scoring on steatosis (0-3), ballooning degeneration (0-2), lobular inflammation (0-3), the NAS (NASH CRN NAFLD activity score) is the sum of the three component scores.

For Parts A and B, if a liver biopsy was done previously, and additional slides are available, the patient may be asked for additional consent to allow this material to be used for central reading of slides. Central reading of slides is only to be initiated if material from sufficient patients is available.

For Part C, 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

[redacted]

the Screening period, or within 6 months prior to randomization. For the biopsy to qualify as a baseline biopsy, the patient must have been on a stable permitted therapy for at least 1 month prior to the biopsy through the screening period (See Table 5-5). Five to eight Baseline Biopsy slides, unstained and prepared from biopsies performed during the screening period or =< 6 months prior to the randomization visit, will be sent to a Central Reader to determine eligibility. Patients in Part C will be treated for 48 weeks and an end of treatment biopsy will be performed and slides submitted to the Central Reader.

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

6.2.6.2 Transient Elastography (FibroScan®) (optional)

If sites have equipment available, a Transient Elastography (FibroScan®) will be done at baseline and at the Week 12 visit in Parts A and B and at baseline Weeks 12, 24 and 48 in Part C, aligned with the MRI assessments. (see Table 6-1). No other similar technology can be substituted. Week 12 assessment is not to be done if the patient prematurely discontinues treatment prior to Week 8.

The following information will be collected:

- Date and type of evaluation performed
- Liver stiffness: Score in kPa
- Probe type used
- Interquartile range (IQR)
- Corrected attenuation parameter (CAP) if available
- CAP IQR if available

The assessment at baseline is not needed if Transient Elastography (FibroScan®) is performed within 6 months prior to baseline and all required information is available. The results of such a previous scan are to be recorded in the database.

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, anthropometric assessments, past medical history record of HIV, Hepatitis B or C serology (not needed if available within 5 years from screening visit, unless risk factors for viral hepatitis are present after last serologic testing), Anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA) (these last 3 only if not historically available), iron, ferritin, transferrin saturation, Hemoglobin A_{1c} (HbA_{1c}), VAS scale for itch [redacted] A serum pregnancy test will be performed for women of child-bearing potential, [redacted]

[redacted]

Sample numbering for [redacted] biomarkers are shown in Appendix 4, Section 16.

6.2.8 Screening visit 2 – additional assessments

In Part A, Part B (if the first screening visit and anticipated randomization baseline date is within 2 months) and Part C, the second screening visit should only be conducted if eligibility is confirmed. Assessments for this visit include MRI, Liver biopsy for patients in Part C, and other non-lab assessments as indicated in Table 6-1.

In Parts B and C, if the period between screening visit 1 and the anticipated randomization / baseline visit is > 2 months: screening visit 2 should only be conducted if eligibility is confirmed. Assessments for this visit include MRI, liver biopsy in Part C, and other non-lab assessments as indicated in Table 6-1 and Table 6-2 AND a repeat of the liver function test 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

Dosing information for study medication will be collected on corresponding Dosage Administration Record eCRFs. Compliance will be assessed by the investigator and/or study personnel at each visit using capsule counts and information provided by the patient. This information should be captured in the source documents at each visit. All study treatment dispensed and returned must be recorded in the Drug accountability Log. Dietary compliance will also be assessed as indicated in Table 6-1 and recorded in the eCRF.

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.

Patient-reported outcomes

PROs should be performed in the following recommended order, prior to any investigator / lab assessments:

Part A:

- VAS for Itch
- [redacted]

Part B and Part C:

- VAS for Itch
- [redacted]

Efficacy assessments

The efficacy assessments should be completed in the following recommended order.

- MRI
- Liver Function Test
- Liver Histology
- Coagulation test
- Markers of liver fibrosis
- NAFLD Fibrosis score
- Fasting lipids
- [redacted]

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

6.4.1 Magnetic Resonance Imaging

Patients in Parts A and B will undergo magnetic resonance imaging two times during the course of the study to quantitate liver fat, [redacted] as outlined in the assessment schedule (Table 6-1). Week 12 assessment is not to be done if the patient prematurely discontinues treatment prior to Week 8. Patients in Part C will have an MRI at Baseline, Weeks 12, 24, and 48.

All MRI scans will be performed locally and sent to the central MRI laboratory for evaluation. They will remain blinded to the investigator, patient and sponsor until after the study (or study Part, respectively) has been completed and the database has been locked. However, incidental medically significant findings (e.g. tumor) not related to fat content can be disclosed by the radiologist obtaining MRI images at the investigative site during the course of conducting the clinical trial to the investigator as appropriate to the medical care of the patient. Detailed information can be located in the MRI manual.

6.4.2 Liver Function 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, 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 function 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.

[redacted]

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

6.4.4 Markers of liver fibrosis

- Fibroscan®: the following will be collected: Date and type of evaluation performed, number of (successful) measurements, liver stiffness (in kPa), probe type and Interquartile range (IQR) (optional assessment, only if sites have equipment available)
- Enhanced liver fibrosis Test (ELF) panel: the following will be assessed: hyaluronic acid (HA), tissue inhibitor of metalloproteinases (TIMP-1), and amino-terminal pro-peptide of procollagen type III (PIIINP)
- Fibrosis biomarker test, originally called Fibrotest®/ Fibrosure®. The following will be assessed: α2-macroglobulin, apolipoprotein A1, total bilirubin, haptoglobin, GGT, and ALT
- [redacted]

These markers will be assessed as indicated in Table 6-1.

6.4.5 NAFLD fibrosis score

The following formula will be utilized for the calculation of the NAFLD fibrosis score: -1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG (increased fasted glucose)/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet (×10^9/l) – 0.66 × albumin (g/dl). This score will be calculated programmatically and will not be available to investigators until after the database is locked. The fibrosis score will be assessed as listed in the Assessment schedule (Table 6-1).

6.4.6 Fasting Lipids

Blood samples will be collected for a fasting lipid panel, including total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, free glycerol and free fatty acids as per the assessment schedule (Table 6-1). Lipid measurements should be collected after an 8-hour (overnight) fast. Detailed information will be provided in the lab manual.

[redacted]

[redacted]

6.4.9 Liver Biopsy

In Part C, patients will have paired liver biopsies (Baseline and EOT, after 48 weeks of treatment). Fibrosis staging and scores of steatohepatitis markers (steatosis, lobular inflammation, and hepatocyte ballooning) 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. Components of the NAS Scoring are provided in Table 6-3. Additional details regarding liver biopsy requirements can be found in the accompanying central biopsy manual.

Table 6-3 NAS Components

Component	Score	Extent	Definition and Comment
Steatosis	0	<5%	Refers to amount of surface area involved by steatosis as evaluated on low to medium power examination; minimal steatosis (<5%) receives a score of 0 to avoid giving excess weight to biopsies with very little fatty change
	1	5-33%	
	2	>33-66%	
	3	>66%	
Lobular inflammation	0	No foci	Acidophil bodies are not included in this assessment, nor is portal inflammation
	1	<2 foci/200x	
	2	2-4 foci/200x	
	3	>4 foci/200x	
Hepatocyte ballooning	0	None	
	1	Few balloon cells	The term "few" means rare but definite ballooned hepatocytes as well as cases that are diagnostically borderline
	2	Many cells	Most cases with prominent ballooning also had Mallory's hyaline, but Mallory's hyaline is not scored separately for the NAS
NAS Score	Range: 0-8	N/A	Sum of the three components

6.4.10 Appropriateness of efficacy assessments

The primary and 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 as determined by magnetic resonance along with sustained improvement in alanine aminotransferase (ALT) is recommended as a valid endpoint for short-term phase 1 and 2 trials (Sanyal et al 2011). Part C secondary endpoints also include direct markers of

[redacted]

NASH measured by liver biopsy including fibrosis staging and scores of steatohepatitis markers.

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).

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 ≥140 mmHg and/or DBP ≥100 mmHg, or ≥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.

6.5.3 Anthropometric assessments

Height, body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes), and waist and hip circumference in centimeters (cm), and hip circumference (cm) will be measured as indicated in Table 6-1.

For the assessment of the waist and hip circumference, the patient should be standing upright during the measurements, with arms relaxed at the side, feet evenly spread apart and body weight evenly distributed.

[redacted]

The waist circumference should be measured on bare skin at the end of several consecutive natural breaths, at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid axillary line. The hip circumference should be measured on bare skin at a level parallel to the floor, at the largest circumference of the buttocks. For both measurements it is advised to use a stretch-resistant tape that is wrapped snugly around the patient, but not to the point that the tape is constricting (World Health Organization Dec 2008).

Waist-to-Hip ratio (WHR) will be calculated using the following formula:

- WHR = Waist circumference (cm) / Hip circumference (cm)

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]^2

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).

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. These stored samples will be destroyed 3 years after study end at the latest.

6.5.4.1 Hematology

Red blood cell (RBC) count, hemoglobin (Hb), hematocrit, mean corpuscular volume (MCV), 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 (additional assessments at Week 4 and Week 8), serum creatinine (additional assessments at Week 4 and Week 8), uric acid, creatine kinase, total protein, [redacted]haptoglobin and HbA_{1c}. 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: 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.

[redacted]

Liver function tests: see Section 6.4.2

Coagulation: see Section 6.4.3

For platelets, see Section 6.5.4.1

Fasting lipid profile: see Section 6.4.6

[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.

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.

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 should be labeled with the study number, patient initials, patient number, date and time, and kept in the source documents at the study site. For any ECGs with patient safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF page as appropriate.

6.5.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Screening Visit followed by a urine pregnancy test at Baseline Visit before study drug administration. The urine pregnancy test will be repeated every four weeks up to the follow up visit (see Table 6-1). The tests will be performed at the clinical center.

[redacted]

A positive test at Screening Visit and/or Baseline Visit is an exclusion criterion for participating in the study. 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.

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

6.6.1 Clinical Outcome Assessments (COAs)

6.6.1.1 Patient Reported Outcomes (PRO)

The impact of tropifexor on various aspects of patient's health status will be assessed by the following measures:

Part A:

- VAS for Itch

Part B and Part C:

- VAS for Itch

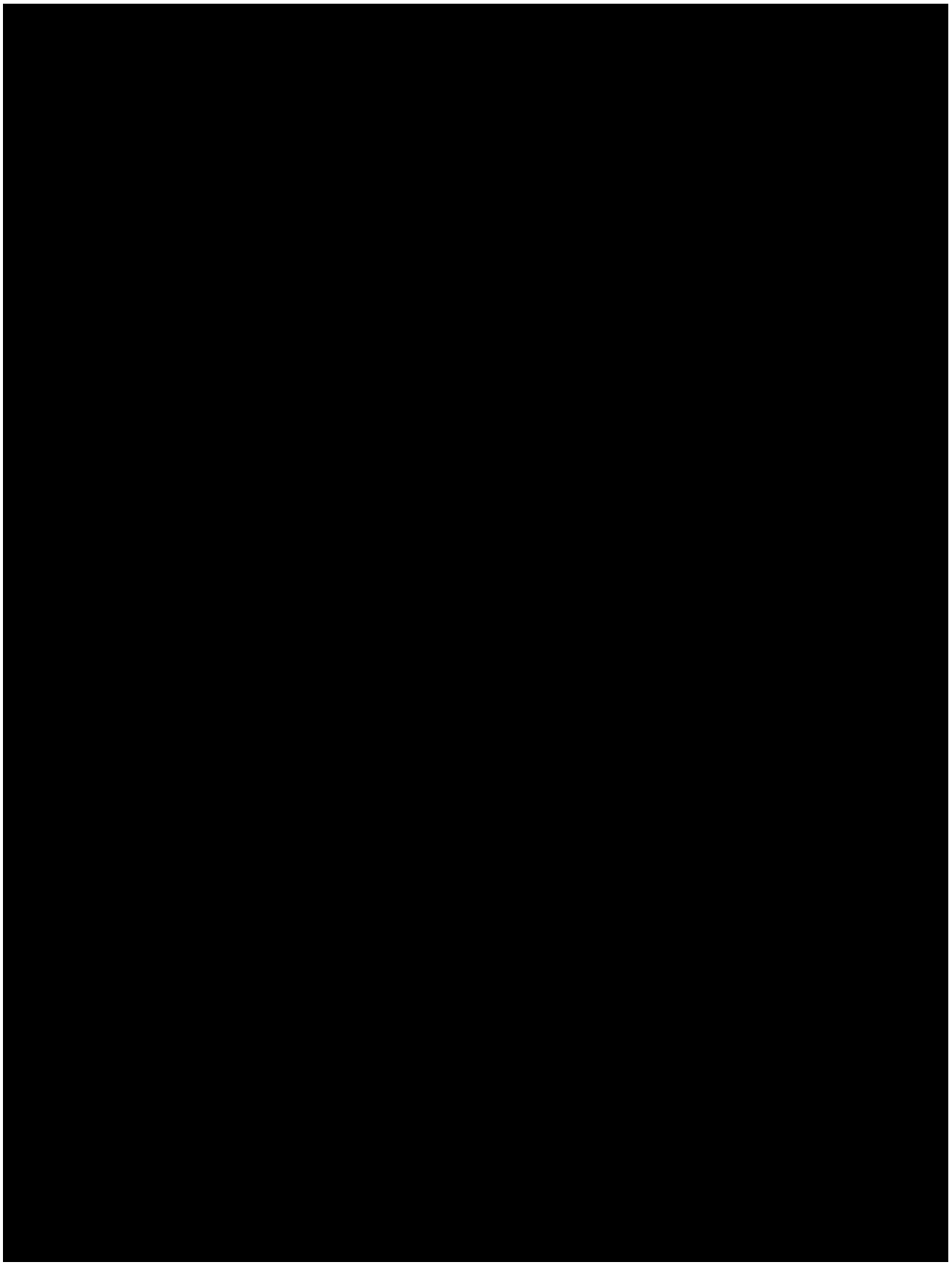
VAS for Itch

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

The questionnaire will be completed by patients as indicated in Table 6-1.

[redacted]

[redacted]



[redacted]

6.6.2 Resource utilization

Not applicable.

6.6.3 Pharmacokinetics

Peripheral blood samples for PK will be collected from all patients according to the schedule defined in Table 6-1 and Table 6-2 and further detailed below in Table 6-4. Further details on sample collection, numbering, processing and shipment can be found in the Laboratory Manual.

All samples will be given a unique sample number (as listed in Appendix 4, Table 16-1 (Part A) and Table 16-2 (Part B)).

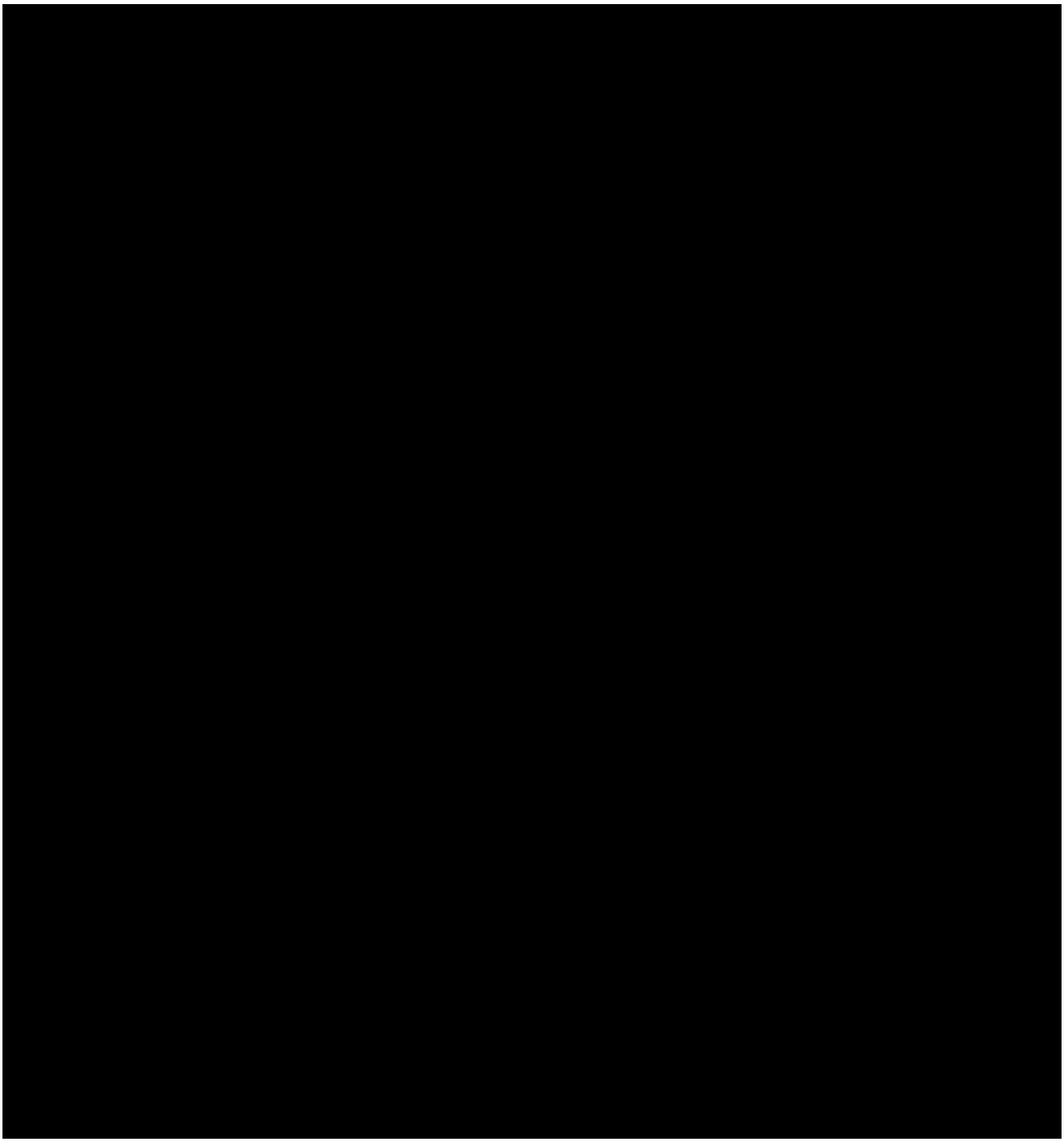
Table 6-4 Timing of PK samples

	Part A	Part B	Part C
Week 1	Pre-dose and 2 hrs post-dose	Not applicable	NA
Week 2	Pre-dose	Pre-dose and 2 hour post-dose	NA*
Week 4	Pre-dose	Post-dose as last activity	NA
Week 6	Pre-dose	Pre-dose and 4 hour post dose	Post-dose as last activity
Week 8	Pre-dose	Post-dose as last activity	NA
Week 12	Pre-dose	Post-dose as last activity	Pre-dose and post dose as last activity
Week 24	NA	NA	Pre-dose and post dose as last activity
Week 40	NA	NA	Post-dose as last activity
Week 48	NA	NA	Pre-dose and post dose as last activity

Tropifexor will be determined in plasma using a validated LC-MS/MS method (liquid chromatography coupled to tandem mass spectrometry). The lower limit of quantification (LLOQ) for tropifexor is 20 pg/mL or less for plasma. [redacted]

[redacted]

The dates and times (to the nearest minute) for all blood sample collections along with the dates and times (to the nearest minute) for study medication administration over at least the preceding 2 days shall be recorded in the source documents and on the CRF. Sampling problems will be noted in the Comments page of the eCRFs.



7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject. For part A, AE will be collected after providing written informed consent for participation in the study until the end of study visit. For patients participating in Part B, AEs will be collected after providing written informed consent and up to one month after the assessments of screening visit 1, and continued to be collected from screening visit 2 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 defined in Appendix 1.

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

- the Common Toxicity Criteria (CTC) AE grade

If CTCAE grading does not exist for an adverse event, use

1=mild

2=moderate

3=severe

4=life-threatening (see Section 7.2 for definition of SAE)

CTCAE Grade 5 (death) is not used, but is collected in other CRFs (Study Completion/Death).

There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- its relationship to the study treatment:

[redacted]

  - Yes
  - No
- 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 study treatment

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

- no action taken (e.g. further observation only)
- study treatment dosage increased/reduced
- study treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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 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 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

[redacted]

- 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 (specify what this includes)
  - 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 (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

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

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 after the last study visit must be reported to Novartis 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 if the investigator suspects a causal relationship to study treatment.

All SAEs reported up to the patient's last visit will be reported in the AE eCRF. SAEs beyond the last visit will only be recorded in the Novartis Drug Safety and Epidemiology database.

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

[redacted]

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 study treatment, 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 (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

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.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as (S)AE):

- Liver laboratory triggers, which will require repeated assessments of liver laboratory parameters
- Liver events, which will require close observation, follow-up monitoring and completion of the standard Liver CRF pages

Please refer to Table 5-2 in Section 5.5.5 for definition of significant ALT and AST triggers and required follow up actions, as well as to Table 14-1 in Appendix 2 for complete definitions of other liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 5-2 (Section 5.5.5) and Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Section 5.5.5 and Table 14-2 in Appendix 2.

For liver laboratory triggers:

[redacted]

- Repeat the liver function tests (LFT) after 48 to 72 hours if >2× baseline and no improvement on retest, or within 1 week if improved, unless a different time frame is stated, to confirm elevation.

These LFT repeats must be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event must be reported on the Liver CRF pages.

- If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For liver events:

- Repeat the LFT to confirm elevation as appropriate
- Discontinue the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event by consideration of possible alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed must be recorded on appropriate CRF pages, including the liver event overview CRF pages and on SAE forms when appropriate.

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; confirmed by doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable)
  - 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 (EMA definition).

[redacted]

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE (see Table 7-1).

Table 7-1 Treatment errors and appropriate actions

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes,	Yes, even if not associated with a SAE

7.6 Pregnancy reporting

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

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

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

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.

7.7 Monitoring for clinically significant LDL-cholesterol increases

LDL-cholesterol elevations have been noted in clinical trials with a bile acid FXR agonist (Neuschwander-Tetri et al 2015), but have not been noted in treatment with tropifexor, a non-bile acid FXR agonist.

Tests for monitoring fasted lipid levels (total cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, free glycerol and free fatty acids) are performed at regular time points during the study (see Table 6-1 and Table 6-2).

[redacted]

Patients with significant LDL-cholesterol increases that are confirmed upon repeat laboratory testing and not found to be due to dietary indiscretions and are deemed medically important should be managed according to local standards. Changes or initiation of therapy for increased LDL-cholesterol should be recorded in the CRF.

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 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 CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

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

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. 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 study

[redacted]

completion and final 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 staff [or CRO working on behalf of Novartis] review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. 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).

Diary data will be entered into an electronic diary by the patient. The system will be supplied by a vendor(s), who will also manage the database.

Patients will fill in their PRO data in a site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

MRI assessments will be processed 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 database will be sent electronically to Novartis (or a designated CRO).

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

The occurrence of 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. An interim analysis of Part A data collected up to Week 16 will be performed. The database will be locked at the end of Part B. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

[redacted]

[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. Further, the DMC will review available safety and efficacy data when ≥ 90% of the patients in Part A have completed the week 8 assessments prior to making a recommendation for the doses to use in Part B of the study.

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 an AE of CTCAE grade 3 or higher in the same system organ class, the DMC chairman will be alerted. Further details regarding relevant data and actions will be specified in the separate DMC charter.

The DMC may conduct a safety and efficacy review at the time of the second interim analysis when patients from Part A have finished the study.

8.5 Adjudication Committee

Not required.

9 Data analysis

The final (end-of-study) analysis will be conducted on all patient data collected up to the EOS Visit or the premature treatment discontinuation visit (i.e., EOT Visit for patients discontinuing during the treatment period or EOS (Visit for patients discontinuing during the Follow-up 1 period). For patients in Parts A and B, EOT is at week 12 and EOS is at Week 16. For patients in Part C, EOT is at Week 48 and EOS at Week 52.

Data collected during the Follow-up 2 period Visit will be described in a separate supplement to the primary CSR.

Data from Parts A and B will be pooled in each treatment arm for the analysis at the end of Part B. Placebo data from Part C might be pooled with placebo data from Parts A or B as

[redacted]

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

Interim analyses will be conducted 1) for DMC review at Week 8 in Part A, when ≥ 90% of patients in Part A have completed their Week 8 assessments, 2) at Week 16 in Part A. 3) when all patients have completed Week 16 in Part B, 4) when all patients in Part C have completed Week 12 and 5) the final analysis will be conducted when all patients have completed Part C.

9.1 Analysis sets

The following analysis populations will be defined for the statistical analysis:

- 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. Of note, in Parts A and B, patients with dose reduction due to AE will be analyzed according to the treatment they received up to the dose reduction. In Part C, patients with a dose reduction due to AE will be analyzed according to the treatment received >= 24 weeks.

* 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.

The number and percentage of patients in the randomized set who completed the study, who discontinued the study and the reason for discontinuation will be presented for each treatment group and all patients. The frequency (%) of patients with major protocol deviations as well as the criteria leading to exclusion from analysis sets will be presented in separate tables for the randomized 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.

[redacted]

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 1st 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 the SAF):

- Occurrence of SAE
- Occurrence of AE resulting in permanent discontinuation or dose reduction of study treatment
- Occurrence of AE of special interest

Efficacy (to be assessed in the FAS):

- Change from baseline to Week 12 in ALT
- Change from baseline to Week 12 in AST
- Relative change from baseline to Week 12 in percentage of fat in the liver assessed using MRI

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 and efficacy variables are outlined in Table 9-1.

Table 9-1 Primary variables and methods of analysis

Variable	Method of analysis
Occurrence of SAE	Summary table of absolute and relative frequency, overall and by preferred term
Occurrence of AE resulting in discontinuation or dose reduction of study treatment	Summary table of absolute and relative frequency, overall and by preferred term

[redacted]

Variable	Method of analysis
Occurrence of AE of special interest	Summary table of absolute and relative frequency, overall and by type of AE (risk definition as per SPP)
Change from baseline to Week 12 of ALT	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics
Change from baseline to Week 12 of AST	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics
Relative change from baseline to Week 12 in percentage of fat in the liver assessed using MRI	Baseline adjusted mean estimates and pairwise differences from ANCOVA, descriptive statistics

Summary tables will be presented by treatment group and visit (as applicable) using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables.

Repeated measures ANCOVA models will include time (visit) and treatment group as categorical explanatory variables. The stratification factor (BMI group) and the baseline assessment will be included as covariates. The interaction terms of time with baseline assessment and treatment will be included as well. An unstructured covariance matrix will be assumed for the within subject repeated measurements, and Kenward-Rogers type degrees of freedom will be used. 95% confidence intervals will be calculated for treatment differences (without adjustment for multiple comparisons). An ANCOVA model for the relative change in the percentage of liver fat will include baseline assessment and BMI stratification group as covariates, and treatment group as explanatory variable, with no interaction terms.

For ALT and AST and relative change in the percentage of liver fat, a multiple contrast test to confirm a general trend over placebo will be performed in addition. A one-sided p-value $\leq$ 0.05 will be considered as a confirmation of a dose-response relationship, without adjustment for multiple comparisons (due to testing more than one parameter). Contrast vectors will be derived from pre-specified alternative dose-response shapes using weights proportional to total sample sizes for each arm.

The multiple contrast test will be run on combined doses from Parts A, B and C after the completion of Part C Week 12.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for the efficacy variables in Table 9-1 will be accounted for by the use of repeated measures ANCOVA (MMRM), assuming data are missing at random (MAR). In case of dose reduction, any ALT and AST assessments after reduction will be set to "missing" for the respective analyses.

9.4.4 Sensitivity analyses

The missing data pattern will be explored graphically at the final analysis. If the exploration raises concerns about deviation from the MAR assumption, and/or the proportion of missing

[redacted]

data is large (e.g., >10%), the possible impact will be discussed. As there are no formal hypothesis tests and no confirmatory claims based on the results, no alternative analyses are pre-planned.

9.4.5 Supportive analyses of the primary variables

Primary variables will also be summarized, using descriptive statistics, in the subgroups defined by the stratification factors, and additionally in the subset of patients who have historical biopsy data, both overall and by fibrosis score and/or NAS score.

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
Absolute change from baseline to Week 12 in percentage of fat in the liver assessed using MRI	Baseline adjusted mean estimates and pairwise differences from ANCOVA, descriptive statistics
Weight, BMI, waist-to-hip (WTH) ratio	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from repeated measures ANCOVA
FGF19, C4	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from ANCOVA
Liver stiffness (in kPa) by Fibroscan®, enhanced liver fibrosis panel (ELF) score, and score of fibrosis biomarker test (originally known as Fibrotest®/ FibroSure®)	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from repeated measures ANCOVA
GGT	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from repeated measures ANCOVA
Fasting lipids (total cholesterol, trigylcerides, LDL-cholesterol and HDL cholesterol, free glycerol, free fatty acids)	Descriptive statistics (including geometric mean and CV) by visit (including %change and log transformed ratio to baseline), and pairwise ratio versus placebo with 95% CI from repeated measures ANCOVA (back transformed from log scale)
Itch VAS	Descriptive statistics by visit (including change from baseline), pairwise differences versus placebo with 95% CI from repeated measures ANCOVA
At least a one point improvement of fibrosis stage without worsening of steatohepatitis at Week 48 compared to baseline	Descriptive statistics (absolute and relative frequency), differences, odds ratio and relative risk reduction versus placebo with 95% CI
Proportion of patients who have at least a two point improvement in fibrosis without worsening of	Descriptive statistics (absolute and relative frequency), differences, odds ratio and relative

[redacted]

Variable	Analysis
steatohepatitis at Week 48 compared to baseline	risk reduction versus placebo with 95% CI
Resolution of steatohepatitis without worsening of fibrosis stage at Week 48 compared to baseline	
Change of NAS from baseline to Week 48	Descriptive statistics
Absolute and relative change from baseline to Week 48 in percentage of fat in the liver assessed using MRI	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics
Change from baseline to Week 48 of ALT and AST	Baseline adjusted mean estimates and pairwise differences from repeated measures ANCOVA, descriptive statistics

Summary tables will be presented by treatment group and visit (as applicable) using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables. All efficacy variables will be analyzed in the FAS and, with the exception of ALT and AST, assessments obtained after dose reduction will be included. Graphical displays will be provided as appropriate.

Repeated measures ANCOVA will be performed as described in Section 9.4.2.Standard ANCOVA for absolute change of liver fat to Week 12 will include baseline assessment and BMI stratification group as covariates, and treatment group as explanatory variable, with no interaction terms.

Binary biopsy based endpoints will be analyzed using logistic regression, including baseline fibrosis stage and BMI stratification group as covariates. Missing follow-up biopsy results will not be imputed, so that the primary analysis of these parameters will only be based on subjects with valid paired biopsies who have received >= 24 weeks of the baseline assigned treatment. However, additional supportive analyses addressing different estimands will be described in the analysis plan.

No adjustment of the type I error for multiplicity is planned. Any resulting p-values should only be considered descriptive.

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. Patients with dose reduction will be analyzed according to the treatment received before dose reduction. Assessments obtained after dose reduction will be included in safety summary tables.

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 (where placebo groups from Parts A and B will be combined, whereas the

[redacted]

placebo group from Part C will be reported as a separate group), the number and percentage of patients having experienced:

- any AE,
- any serious AE (SAE),
- any AE by primary system organ class (SOC),
- any AE by preferred term,
- any AE by severity (CTCAE grade),
- any AE possibly related to study treatment (investigator assessment),
- any AE resulting in dose reduction or discontinuation of study treatment ,
- any AE of special interest for tropifexor treatment.

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. Separate summaries will be provided for death.

To account for the longer duration of exposure to study treatment in Part C (48 weeks) compared to Parts A and B (12 weeks), exposure adjusted incidences for the types of events listed above will be presented additionally. The placebo groups from Parts A, B and C will be pooled for this type of analysis.

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.

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

9.5.2.3 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.

[redacted]

9.5.2.4 ECG

ECG data will be summarized by treatment and visit.

Notable QTc values and change from baseline will be summarized. A notable value is defined as a QTc interval of greater than 450 ms. The categories used for the change (increase) in QTc are - less than 30 ms, 30 to 60 ms and greater than 60 ms.

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

9.5.2.5 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 1 and Baseline visits (Screening 2 and Baseline if a test was performed during Screening 2 visit).

9.5.3 Resource utilization

Not applicable.

9.5.4 Pharmacokinetics

Plasma concentrations will be expressed in ng/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

Tropifexor plasma concentration data will be listed by part, cohort, treatment group, subject, and visit/sampling time point. Descriptive summary statistics will be provided by part, cohort, treatment group, and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. Any other PK analyses will be described in a separate report (e.g. a CSR addendum).

Due to the sparse blood sampling scheme, a population PK modeling approach will be used to estimate individual subject AUC within a dosing interval. Available data and analyses will be provided to the DMC as needed

[redacted]

[redacted]

9.5.6 Biomarkers

[redacted]

9.5.7 PK/PD

[redacted]

[redacted]

9.7 Interim analyses

Two interim analyses will be performed in the study. An interim analysis will be conducted when ≥ 90% of the patients in Part A have completed the Week 8 assessments. The analysis will, however, include all data available at the resulting data cutoff point. An independent DMC will review the safety profile, efficacy variables, and PK data. Estimates for the efficacy variables will also include time points beyond Week 8 (using a repeated measures ANCOVA) if sample sizes allow. Graphical displays will be used to support the data review.

Unblinded data analysis will be performed by a study independent statistician and programmer, and provided to the DMC. Semi-blinded analysis is not considered in this case

[redacted]

because tables and particularly graphs should display dose groups in ascending order to facilitate review.

Based on the results of the IA, the DMC will make recommendations on the treatment groups to be studied in Part B of the study. There are no strict quantitative rules for the DMC decision and no hypothesis tests. In brief, the DMC will determine which doses in Part A are safe, and among the safe doses, which are efficacious based on biomarker results (primarily ALT and AST). Target thresholds for desired biomarker response and further guidance will be provided in the DMC charter. Up to two of the doses are planned to be selected for Part B.

The DMC also provides recommendations for the range of doses > 90 µg to be considered for Part C dose selection.

As pre-specified, in the event that the DMC selected only one active dose (safe and efficacious) to be tested in 75 patients in Part B, one of the other originally planned active treatment arms (e.g. highest safe but inefficacious dose) was continued with a smaller sample size (20 patients) to confirm the earlier findings of this treatment arm observed in Part A. The DMC selected the 90 µg dose for Part B, so 60 µg will be tested in 20 patients. If only one dose was deemed safe then only one experimental group would have been studied in Part B.

If none of the doses is considered safe, or no sufficient efficacy is observed with safe doses, Part B may not be initiated. There is no adaptation of the type I error to account for this interim analysis. Further details will be described in the DMC charter.

In addition, the DMC will review safety, including AEs and laboratory parameters, on a regular basis. In the event that more than 3 patients develop an AE of CTCAE of grade 3 or higher in the same system organ class, the DMC chairman will be alerted. Further details regarding relevant data and actions will be specified in the separate DMC charter.

In addition to the interim analysis conducted for DMC review, a second analysis of Part A data collected up to Week 16 will be performed.

A third analysis will include Part B data collected up to Week 16. At that time Novartis and CRO associates will be unblinded to data from Part B.

An interim analysis of Part C data (fourth planned reporting event) will be performed when all patients have completed the Week 12 visit or prematurely discontinued from the study prior to week 12. Part C patients will continue through Week 52. Novartis and CRO associates involved in data management, analysis and reporting will be unblinded at the time of the Part C Week 12 Interim Analysis.

The final database lock for the end-of-study analyses will occur when all patients have completed the study. This will include data through EOT (Week 12 in Parts A and B, or Week 48 for Part C) visit for any patients continuing therapy in an extension protocol (if available), or EOS (Week 16 visit for Parts A and B or Week 52 for Part C) for all other patients, unless prematurely discontinued from the study.

9.8 Sample size calculation

The primary objective of the study is to determine a safe dose or dose range. However, the assessment will be made based on the whole safety profile and not on quantitatively

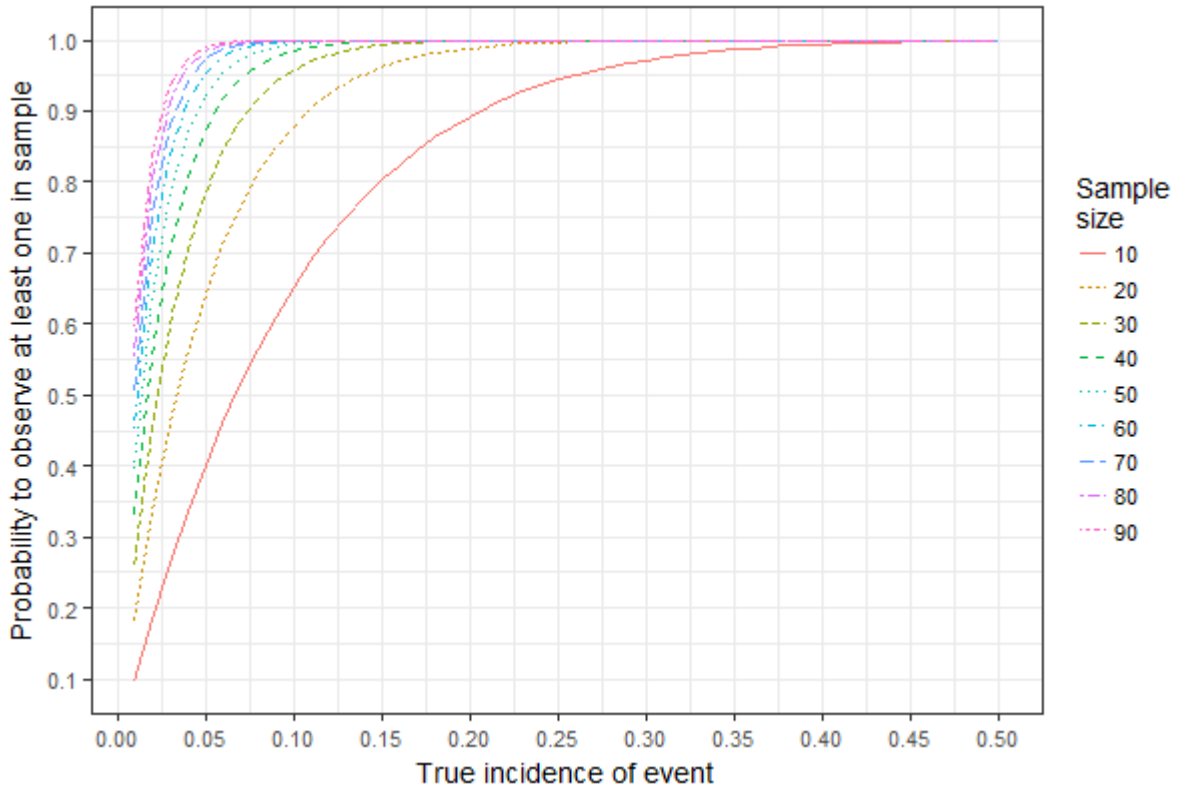
[redacted]

formulated hypotheses for distinct parameters. Therefore, the sample size is based on practicability with respect to expected speed of enrolment 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 observed with > 95% probability in samples of 10 and above. This would include, for example, the isolated ALT elevations observed at high doses in healthy volunteers. Events with true incidences below 10% down to 3% are still very likely to be observed in combined sample sizes from Parts A and B, and also each dose in Part C, while events are observed with less than 50% probability in Part A if the true incidence is less than about 4% (Figure 9-1). It is noteworthy, however, that a single patient constitutes 6.7% in a sample of 15.

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

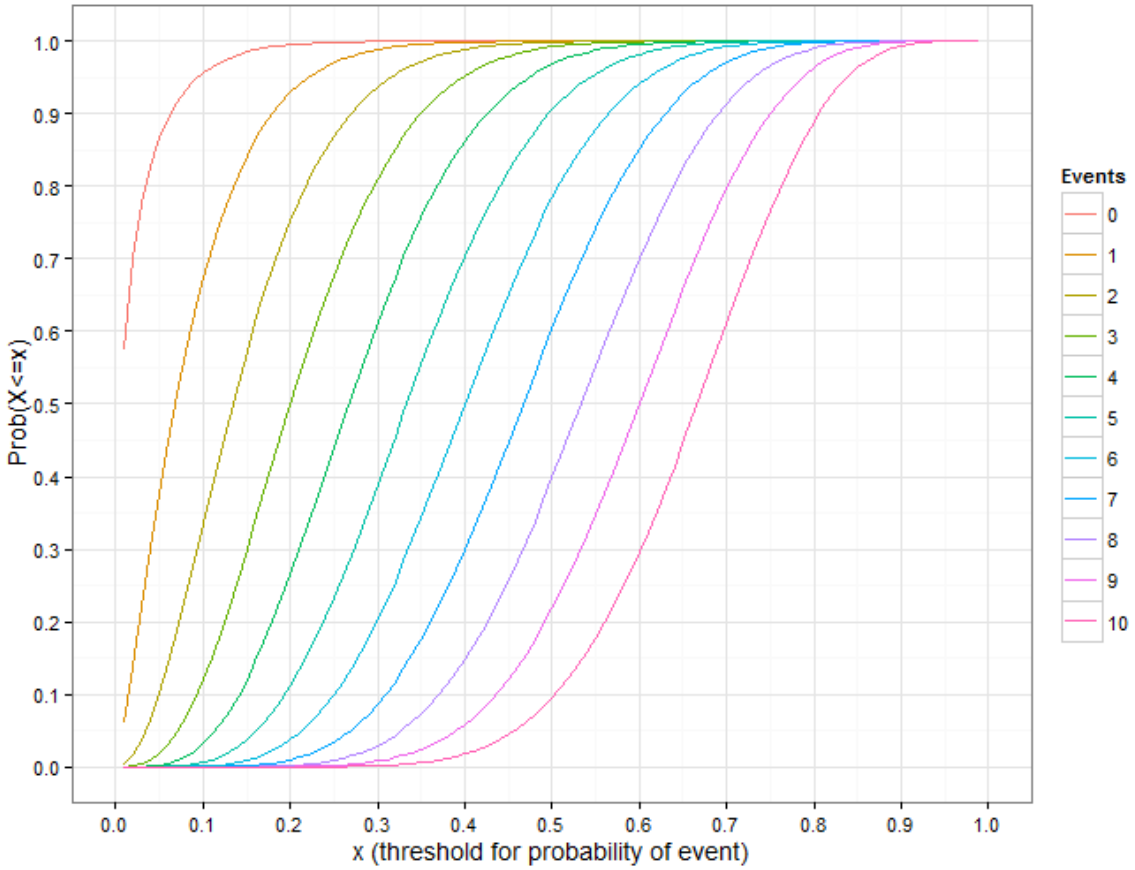


In the interim analysis, predictions of the probability of an event (incidence) will be based on the observed number of events, to support the decision to continue or drop a dose for Part B.

Probabilities of the incidence being below a certain threshold are plotted in Figure 9-2 for a sample size of 15 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 that the incidence is ≤ 5% would be 87%. If an event is observed in one patient, the probability that the incidence is ≤ 5% would be 38%. Similarly, if an event is observed in 5 patients (one third), the probability that the incidence is ≤ 50% would be 90%, but the probability that the incidence is ≤ 30% would be 39% (calculated using R function pbeta).

9.8.2 Power considerations with given sample size for efficacy assessment

A consideration for primary efficacy analyses is given in the following.

Neuschwander-Tetri et al (2015) reported a mean change of ALT from baseline to week 12 of -28 for obeticholic acid (OCA) and -11 for placebo, with standard deviations of 48 and 33, respectively. Assuming for simplicity a common standard deviation of 45, this translates into an effect size (mean difference / standard deviation) of approximately 0.38, which can be considered as a benchmark. The power for a t-test to compare two groups (1-sided type I error 0.05) based on such an effect size would be 63% (59%) with a sample size of 90 (50) in the active and 40 (50) in the placebo group. If the active dose were slightly better than OCA (-33 versus -11), the power would be 81% (78%) Numbers in parentheses refer to comparisons in Part C with 50 subjects in the active arm(s) and 50 in the placebo arm where no pooling with subjects in the placebo arms of Parts A and B is considered (calculations with NQuery

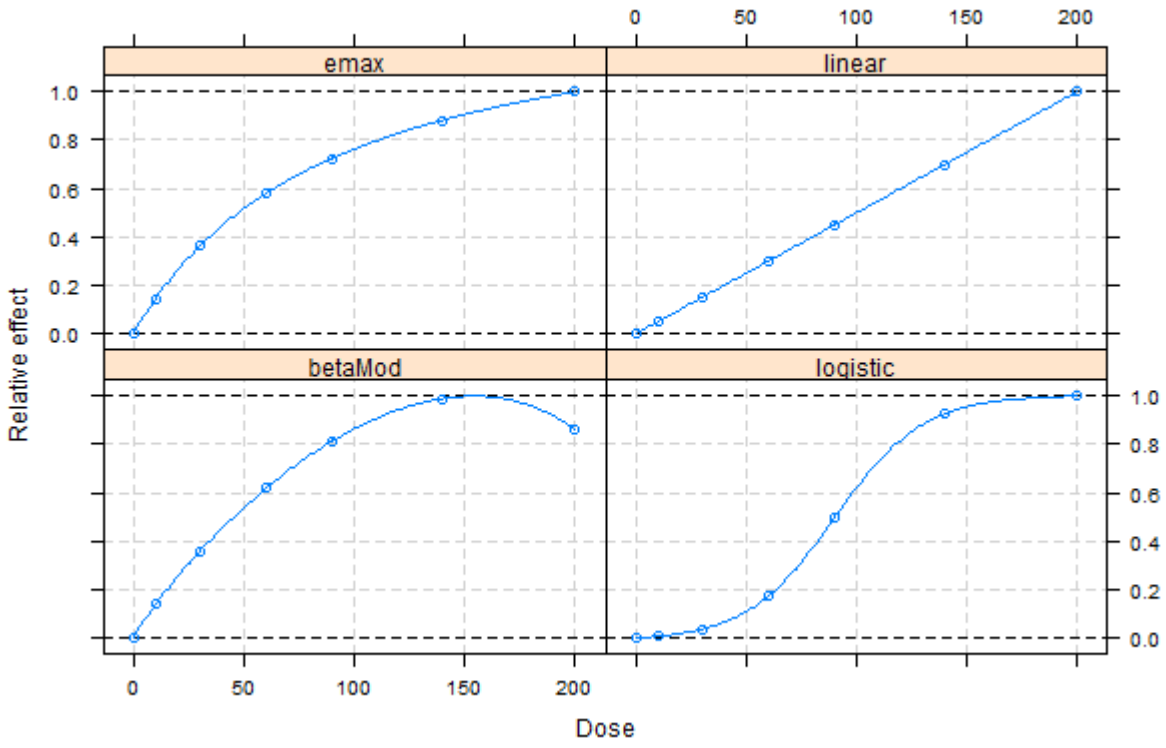
[redacted]

Advisor 7.0). Based on pre-clinical data for tropifexor and OCA, it is expected that the effect size achieved with an optimal dose of tropifexor maybe even larger, therefore resulting in a power above 80%.

For relative reduction of liver fat, no data are available for OCA. In the Novartis sponsored study CLCQ908A2216 in patients with NAFLD, with a baseline percentage of approximately 16%, the relative decrease after 12 weeks of treatment was about 2% in the placebo group and 21% in the highest active dose group, with a common standard deviation of approximately 30, resulting in an effect size of 0.63. If we assume a slightly smaller effect size of at least 0.5 for a tropifexor dose in the NASH study population, a power of ≥ 83% (79%) is achieved for pairwise comparisons with assumptions as described above.

Alternatively, we can consider the power of a multiple contrast test to demonstrate a trend over placebo across multiple dose arms, in this case 10 µg, 30 µg, 60 µg, 90 µg, 140 µg and 200 µg. We assume the dose-response curves in Figure 9-3. A beta shape is included as a possibility because the ALT elevations that may occur with high doses could, on average, interfere with the desired effect of ALT decrease.

Figure 9-3 Potential dose-response curves



[redacted]

Table 9-4 Power for multiple contrast test for trend over placebo

Sample size in Doses (µg)							Power for model (%)				
0	10	30	60	90	140	200	Emax	Linear	Beta	Logistic	Average
90	15	15	35	90	50	50	82 (98)	75 (89)	83 (96)	85 (99)	81 (95)

Contrasts for multiple contrast test are optimal for each model type and sample size; assumptions: placebo response: -11, maximal response: -28 (in brackets: -33), common standard deviation: 45, type I error: 0.05 (one-sided);
Only Part B and C sample sizes after DMC recommendation were considered.

The average power for this type of test is at least 81% for a pooled Week 12 analysis of all study parts:

- 50 subjects assigned to two doses (140 and 200 µg) and 50 to placebo in Part C,

An average power of ≥ 95% is achieved if the effect size is moderately better than that of OCA (Table 9-4, calculations using powMCT function of DoseFinding package in R). Power calculations for a multiple contrast test on relative reduction of liver fat were not performed, but are expected to be in a similar range based on the effect size considerations above.

As the first interim analysis will be conducted with only 13-15 patients per arm who have completed the Week 8 assessments, the power to compare the effect on ALT or AST reduction between groups will be considerably lower. Furthermore, only a certain percentage of the patients will have data up to Week 12 available at that time point, depending on the speed of enrollment. The assessment of efficacious doses in the interim analysis will therefore be primarily based on the relative size of the point estimates (mean changes) and the shapes of the curves over time for the liver enzymes in each group.

9.8.3 Power consideration for biopsy endpoints in Part C

The longer treatment duration in Part C is due to the DMC recommendation to include paired biopsy assessments. Therefore, the sample size in Part C is partly based on the following assumptions for biopsy based outcomes:

- Response parameter: Achievement of at least one stage improvement of fibrosis with no worsening of steatohepatitis at Week 48 compared to baseline (binary).
- Placebo response rate: 13%, based on interpolated results from Neuschwander-Tetri et al (2015). This assumes a linear improvement over time (a placebo rate of 19% was reported at week 72).
- Tropifexor response rate: 37% (best case assumption) with at least one of the doses.

For a 2-group continuity corrected χ^2 test of proportions with type error 0.05 (1-sided, no adjustment for multiple comparisons), a sample size of 50 per group results in a power of 82% (nQuery Advisor 7.0). The actual power might be smaller due to missing follow-up biopsies.

[redacted]

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 may only be included in the study after providing written (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. In cases where the patient's representative gives consent, the patient must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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, written informed consent form, consent form updates, patient recruitment procedures (e.g., advertisements) and any other written information to be provided to patients. Prior to study start, the investigator is required to sign a protocol signature page confirming

[redacted]

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.

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 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 should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

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 may be implemented immediately provided the health authorities are

[redacted]

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.

[redacted]

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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 are used to alert investigators to the results, and should not be used as reference ranges to establish a clinical diagnosis.

[redacted]

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

Table 14-1 Liver Event and Post Baseline Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• ALT or AST > 2× baseline value • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

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

Table 14-2 Follow Up Requirements for Post-Baseline Liver Events and Laboratory Triggers

Criteria	Actions required[d]	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, discontinue study treatment • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 – 72 hours • If elevation persists, reduce dose (Section 5.5.5), and continue follow-up monitoring • If with reduced dose elevation persists for more than 1 week, discontinue the study	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required[d]	Follow-up monitoring
	drug • Establish causality • Complete liver CRF	
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within 48 – 72 hours • If elevation is confirmed, initiate close observation of the patient, and repeat LFT within the next week • If elevation persists, reduce dose (Section 5.5.5), and continue follow-up monitoring • If with reduced dose elevation persists for more than 3 weeks, discontinue dose (Section 5.5.5) and continue follow up monitoring	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Complete liver CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Complete liver CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Complete liver CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.
[d]For elevated ALT and/or AST, please also refer to Table 5-2 (Section 5.5.5) for additional scenarios and actions

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions for Post Baseline Values

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 ≥3.4 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >17 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 CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or 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.	

16 Appendix 4: Sampling schedules and sample logs

Refer to the central laboratory manual for sample collection, preparation and shipping information.

Table 16-1 Blood collection log for pharmacokinetics – Part A

Week	Time point	PK sample number*	Dose reference ID
Week 1	Pre-dose	101	1
Week 1	2 hr post dose	102	1
Week 2	Pre-dose	103	2
Week 4	Pre-dose	104	3
Week 6	Pre-dose	105	4
Week 8	Pre-dose	106	5
Week 12	Pre-dose	107	6

* If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern 1001, 1002, 1003 etc

Table 16-2 Blood collection log for pharmacokinetics – Part B

Week	Time point	PK sample number*	Dose reference ID
Week 2	Pre-dose	101	1
Week 2	2 hr post dose	102	1
Week 4	Pre-dose	103	2
Week 6	Pre-dose	104	3
Week 6	4 hr post dose	107	3
Week 8	Pre-dose	105	4
Week 12	Pre-dose	106	5

* If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern 1001, 1002, 1003 etc

Table 16-4 Blood collection log for biomarkers – Parts A and B

Week*	**Time point**	[redacted]	**Fibrosis biomarker test[1]**	[redacted]
Screening Visit 1	--		501	
BSL	Pre-dose		502	
Week 6	Pre-dose		503	
	4 hours post dose			
Week 12	Pre-dose		504	

[1] Fibrosis biomarker test originally called Fibrotest/Fibrosure

* If other assessments listed in the protocol do require sample numbering, the sample numbers will follow the pattern 801, 802 etc for assessment 1, and 901, 902 for assessment 2, and if collected at an unscheduled visit, the sample numbers will follow the pattern 1801, 1802, or 1901, 1902 etc.

Table 16-5 Blood collection log for pharmacokinetics – Part C

Week	Time point	PK sample number*	Dose reference ID
Week 6	Post-dose as last activity	108	1
Week 12	Pre-dose and post dose as last activity	109, 110	2
Week 24	Pre-dose and post dose as last activity	111, 112	3
Week 40	Post-dose as last activity	113	4
Week 48	Pre-dose and post dose as last activity	114, 115	5

[redacted]

Table 16-6 Blood collection log for biomarkers – Part C

Week*	**Time point**	[redacted]	**Fibrosis biomarker test[1]**	[redacted]
Screening Visit 1	--		521	
BSL	Pre-dose		522	
Week 6	Pre-dose		523	
Week 6	4 hours post dose			
Week 12	Pre-dose		524	
Week 24	Pre-dose		525	
Week 40	Pre-dose		526	
Week 48	Pre-dose		527	

[1] Fibrosis biomarker test originally called Fibrotest/Fibrosure

* If other assessments listed in the protocol do require sample numbering, the sample numbers will follow the pattern 821, 822 etc. for assessment 1, and 921, 922 for assessment 2, and if collected at an unscheduled visit, the sample numbers will follow the pattern 1821, 1822, or 1921, 1922 etc.

[redacted]

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

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

AHA recommends the following:

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

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

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

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

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

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

Limit drinks and foods with added sugar.

[redacted]