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Novartis Research and Development

LJN452/LIK066

Clinical Trial Protocol CLJN452D12201C / NCT04065841

# A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy and each monotherapy, compared with placebo for treatment of adult participants with nonalcoholic steatohepatitis (NASH) and liver fibrosis (ELIVATE)

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| Document type: | Amended Protocol Version |
| EUDRACT number: | 2019-002324-32 |
| Version number: | 02 (Clean) |
| Clinical Trial Phase: | IIb |
| Release date: | 30-Apr-2021 |

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## List of abbreviations

| | |
|---|---|
| ADME | absorption, distribution, metabolism, and excretion |
| AE | adverse event |
| AESI | adverse event of special interest |
| AHA | American Heart Association |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AMA | Anti-mitochondrial antibodies |
| ANA | Anti-nuclear antibodies |
| ANCOVA | analysis of covariance |
| ANIT | Alpha-naphthylisothiocyanate |
| APTT | Activated Partial Thrombin Time |
| ARFI | Acoustic Radiation Force Impulse |
| APRI | AST to Platelet Ratio Index |
| ASMA | Anti-smooth muscle antibody |
| AST | aspartate aminotransferase |
| ATC | anatomical therapeutic chemical |
| ATZ | Atazanavir |
| [redacted] | |
| AUDIT | Alcohol Use Disorders Identification Test |
| BA | bio-availability |
| BCRP | breast cancer resistance protein |
| BfArM | Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices |
| BMI | body mass index |
| BSL | Baseline |
| BUN | blood urea nitrogen |
| [redacted] | |
| CDT | carbohydrate deficient transferrin |
| CFR | Code of Federal Regulation |
| CK | Creatine kinase |
| [redacted] | |
| Cmb | Combo |
| CO | Country Organization |
| COVID-19 | Coronavirus disease |
| CRF | Case Report/Record Form (paper or electronic) |
| CRN | Clinical Research Network |
| CRO | Contract Research Organization |

| | |
|---|---|
| [redacted] | |
| CSR | clinical study report |
| CTA | Clinical Trial Application |
| [redacted] | |
| CYP | cytochrome P |
| DBP | diastolic blood pressure |
| DDI | drug-drug interaction |
| DILI | drug-induced liver injury |
| DLT | Dose limiting toxicity |
| DNA | Deoxyribo Nucleic Acid |
| DMC | Data Monitoring Committee |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| eCRF | electronic case report form |
| EDC | Electronic Data Capture |
| [redacted] | |
| EOS | end of study |
| EOT | end of trial |
| eSAE | electronic serious adverse event |
| FAS | full analysis set |
| FCS | fully conditional specification |
| FDA | Food and Drug Administration |
| FGF19 | fibroblast growth factor 19 |
| [redacted] | |
| FIH | first in human |
| FSH | follicle stimulating hormone |
| FXR | farnesoid X receptor |
| GCP | Good Clinical Practice |
| GGT | Gamma - Glutamyl transferase |
| GI | Gastrointestinal |
| GLP | glucagon-like peptide |
| GSH | glutathione |
| HA | Health Authority |
| HAV | Hepatitis A Virus |
| HbA1c | hemoglobin A1c |
| HBsAg | Hepatitis B surface Antigen |
| HCP | health care provider |
| HCV | Hepatitis C Virus |
| HDL | High Density Lipoprotein |
| HDL-C | High Density Lipoprotein cholesterol |
| HIV | Human immunodeficiency virus |
| HOMA-IR | Homeostatic Model Assessment of Insulin Resistance |
| IB | investigator brochure |

| | |
|---|---|
| IL | interleukin |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IFN | Interferon |
| IgM | Immunoglobulin M |
| IMP | Investigational Medicinal Product |
| IND | Investigational New Drug |
| INR | International normalized ratio |
| IQR | Interquartile range |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| ITT | intent-to-treat |
| IUD | intrauterine device |
| IUS | intrauterine system |
| LC-MS/MS | liquid chromatography coupled to tandem mass spectrometry |
| LDH | lactate dehydrogenase |
| LDL | low-density lipoprotein |
| LDL-C | low-density lipoprotein cholesterol |
| LFT | Liver function test |
| LLN | Lower limit of normal |
| LLOQ | Lower Limit of Quantification |
| MELD | Model For End-Stage Liver Disease |
| MCAR | Missing Completely at Random |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MDRD | Modification of Diet in Renal Disease |
| MHRA | Medicines and Healthcare products Regulatory Agency |
| MI | multiple imputation |
| MAR | missing at random |
| MRI | Magnetic Resonance Imaging |
| MRI-PDFF | Magnetic Resonance Imaging Proton Density Fat Fraction |
| NAS | NAFLD Activity Score |
| NASH | non alcoholic steatohepatitis |
| NAFLD | non alcoholic fatty liver disease |
| NMR | Nuclear Magnetic Resonance |
| NOAEL | no observed adverse effect level |
| OATP | organic anion transporting polypeptide |
| OCA | obeticholic acid |
| OGTT | oral glucose tolerance test |
| [redacted] | |
| PBC | primary biliary cholangitis |

| | |
|---|---|
| PCR | protein to creatinine ratio |
| PD | pharmacodynamic(s) |
| PDFF | Proton Density Fat Fraction |
| [redacted] | |
| Plc | Placebo |
| PK | pharmacokinetic(s) |
| PIIINP | amino-terminal pro-peptide of procollagen type III |
| [redacted] | |
| PTH | parathyroid hormone |
| QMS | Quality Management System |
| RAN | randomized analysis set |
| RBC | red blood cell(s) |
| RNA | Ribonucleic acid |
| SAE | serious adverse event |
| SAF | Safety analysis set |
| SAP | statistical analysis plan |
| SBP | systolic blood pressure |
| SCR | screened analysis set |
| sCR | serum creatinine |
| SGLTs | sodium glucose co-transporters |
| SHP | small heterodimer partner |
| SMQ | Standardized MedDRA Query |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TBL | total bilirubin |
| T2DM | Type-II Diabetes Mellitus |
| TFQ | Trial Feedback Questionnaire |
| TIMP | tissue inhibitor of metalloproteinases |
| TNF | Tumor necrosis factor |
| TT | Thrombin Time |
| UDCA | Ursodeoxycholic Acid |
| UG | Unblinded at the Group level |
| UGTs | uridine 5'-diphosphoglucuronosyltransferases |
| UI | Unblinded to Individual participant treatment codes |
| ULN | upper limit of normal |
| US | United States |
| VLDL | very low-density lipoprotein |
| WBC | white blood cell(s) |
| WHR | waist-to-hip ratio |
| WoC | withdrawal of consent |
| WOCBP | women of child bearing potential |
| WHO | World Health Organization |

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study |
| Coded Data | Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code. |
| Cohort | A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed up or traced over time |
| Control drug | A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug. |
| Discontinuation from study | Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data. |
| Discontinuation from study treatment | Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data. |
| Dosage | Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day) |
| Electronic Data Capture (EDC) | Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care |
| End of the clinical trial | The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol |
| Enrollment | Point/time of participant entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol). The action of enrolling one or more participants. |
| Estimand | As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint), as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable. |
| Healthy volunteer | A person with no known significant health problems who volunteers to be a study participant |
| Intercurrent events | Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. |
| Investigational drug | The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”. |
| Investigational treatment | All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage. |

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| Medication number | A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system. |
| Mis-randomized participant | Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study |
| 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 participants with established disease and in those with newly-diagnosed disease. |
| Participant | A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection |
| Participant number | A unique number assigned to each participant upon signing the Informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc. |
| [redacted] | |
| Period | A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Personal data | Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples. |
| Premature participant withdrawal | Point/time when the participant exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned. |
| Randomization | The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias. |
| Randomization number | A unique identifier assigned to each randomized participant, corresponding to a specific treatment arm assignment |
| Re-screening | If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol |
| Remote | Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location |
| Screen Failure | A participant who did not meet one or more criteria that were required for participation in the study |
| Stage | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Study completion | Point/time at which the participant came in for a final evaluation visit or when study drug was discontinued whichever is later. |
| Study drug discontinuation | When participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation |
| Study drug/treatment | Any drug or combination of drugs or intervention administered to the participant as part of the required study procedures; includes investigational drug (s), control (s) or background therapy. |

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| Study treatment discontinuation | When the participant permanently stops taking study treatment prior to the defined study treatment completion date |
| Treatment arm/group | A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. |
| Variable (or endpoint) | The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event. |
| Withdrawal of consent (WoC)/ Opposition to use of data /biological samples | Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation.<br>Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent. |

## Amendment 02 (30-Apr-2021)

**Amendment Rationale**

**The key purposes of this amendment are to:**

- Introduce the tropifexor single 140 µg hard gelatin capsule as a replacement for 3 lower dose hard gelatin capsules that made up this dose (one each of 10 µg, 30 µg and 100 µg).
- Correct the definition of "no worsening of NASH" to align with definitions in the following guidance documents. Details of these definitions will be included in the study Statistical Analysis Plan.
    - FDA Draft Guidance for Industry in *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment*: December 2018 and
    - EMA *Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases* (PBC, PSC, NASH) 15 November 2018.
- Include additional emerging guidance for study conduct in the context of the COVID-19 or other public health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster.
- Make editorial clarifications throughout and align with Novartis' Clinical Trial Protocol Template Version 4.0 (15-Feb-2021).

## Changes to the Protocol

| Protocol Section | Change | Rationale for change |
|---|---|---|
| List of abbreviations<br>Glossary of terms<br>Protocol summary | **Editorial changes** | To align with Novartis' Clinical Trial Protocol Template Version 4.0 (15-Feb-2021). |
| Section 1.1.3 | **Text Added**<br>During the course of this ongoing CLJN452D12201C study tropifexor (and its matching placebo) has been offered in two forms; a) initially as 3 hard gelatin capsules containing 10, 30 and 100 µg tropifexor (or matching placebo) and b) to reduce the pill burden for the participants, as a single hard gelatin capsule containing 140 µg tropifexor (or matching placebo). This change in capsule number is not expected to alter the absorption of tropifexor since the same formulation principle is used for all dose strengths (10, 30, 100 and 140 µg): dry blend in hard gelatin capsule using the same excipients. [redacted] | Use of the tropifexor single 140 µg hard gelatin capsule to replace 3 hard gelatin capsules; one each of 10 µg, 30 µg and 100 µg, will reduce the participant burden from 6 to 4 pills daily and will eliminate the production challenges of the 10 µg tropifexor capsule. |
| Section 2 and Section 12<br><br>Table 2-1 and Table 12-1<br>Objectives and related Endpoints | **Primary endpoint modified**<br>**From:**<br>Whether the participant achieves at least one stage of improvement in fibrosis without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared to baseline<br>**To:**<br>Whether the participant has at least a one stage improvement in fibrosis without worsening of NASH at Week 48 compared to baseline<br><br>**Key secondary objective was modified**<br>**From:**<br>To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint.<br>**To:**<br>To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint after 48 weeks of treatment.<br><br>AND<br><br>**From:** | To align with NASH endpoint definitions according to FDA and EMA Guidance documents |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | To evaluate improvement in fibrosis by at least one stage.<br>**To:**<br>To evaluate improvement in fibrosis by at least one stage after 48 weeks of treatment.<br>**Key secondary endpoint was modified**<br>**From:**<br>Whether the participant achieves resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared with baseline.<br>**To:**<br>Whether the participant achieves resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH at Week 48 compared with baseline.<br>  | |
| Section 2.1 and Section 12.4 | **Changed the summary measure of first primary estimand**<br>**From:**<br>Proportion of the participants with at least one stage improvement in fibrosis without worsening of NASH at Week 48 compared with Baseline.<br>**To:** | To clarify that odds ratio is the summary measure of pairwise comparisons for the primary estimand. |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | Odds ratio of the participants achieving at least one stage improvement in fibrosis without worsening of NASH, at Week 48 compared with Baseline, of the two treatments for each pairwise comparison.<br><br>**Changed the summary measure of second primary estimand**<br>**From:**<br>Proportion of the participants with resolution of NASH and no worsening of fibrosis at Week 48 compared with Baseline.<br>**To:**<br>Odds ratio of the participants obtaining resolution of NASH and no worsening of fibrosis, at Week 48 compared with Baseline, of the two treatments for each pairwise comparison.<br><br>**Changed the summary measure in analysis of the of primary endpoints(s)/estimand(s)**<br>**From:**<br>Proportion of participants achieving histological response at Week 48 for the following comparisons for each primary endpoint: combination vs. placebo, monotherapies vs. placebo, and combination vs. monotherapies.<br>**To:**<br>Odds ratio of participants achieving histological response at Week 48 for the following comparisons for each primary endpoint: combination vs. placebo, monotherapies vs. placebo, and combination vs. monotherapies. | |
| Section 4.6<br>Section 6.7<br>Section 8.4 | **Text Added**<br>During a public health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and should be permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate. | Emerging guidance has been added allowing mitigation procedures for study conduct in the context of the COVID-19 or other public health emergency as declared by Local or Regional authorities |

<table>
<tr><th>Protocol Section</th><th>Change</th><th>Rationale for change</th></tr>
<tr><td>Section 5.2<br>Exclusion 3 and<br>Exclusion 13</td><td>From:<br>3. Weight change > 5% compared to Baseline since qualifying liver biopsy.<br>To:<br>3. Weight at Baseline changed by > 5% since qualifying liver biopsy.<br><br>From:<br>13. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:<br>To:<br>13. History or current diagnosis of ECG abnormalities based on Central ECG report indicating significant risk of safety for participants participating in the study such as:</td><td>Text updated for clarity.<br><br>Clarification that ECG eligibility is determined by the central reader</td></tr>
<tr><td>Section 6.1.1 and<br>Section 6.1.3</td><td>Text Added<br>The 140 µg dose of tropifexor and its matching placebo are each now available as a single hard gelatin capsule. Participants participating at the time of availability of the single tropifexor/placebo capsule, may continue on the 3-capsule tropifexor (100 µg + 30 µg + 10 µg) or matching placebo regimen described in protocol v01 until the available 3-capsule supply is depleted. After the 3-capsule supply is depleted, participants will take one 140 µg tropifexor or matching placebo capsule daily as described in Table 6-1. No change has been made to licogliflozin dosing.<br><br>Table 6-1 Modified<br>From:<table><tr><td>Tropifexor (LJN452) 140 µg</td><td>10 µg, 30 µg and 100 µg hard gelatin capsules</td></tr><tr><td>Placebo Tropifexor (LJN452) 140 µg</td><td>Hard gelatin capsules matching to tropifexor (LJN452) 10 µg, 30 µg and 100 µg</td></tr></table>To:<table><tr><td>Tropifexor (LJN452) 140 µg</td><td>140 µg hard gelatin capsule</td></tr><tr><td>Placebo Tropifexor (LJN452) 140 µg</td><td>Hard gelatin capsule matching to tropifexor (LJN452) 140 µg</td></tr></table></td><td>Use of the tropifexor single 140 µg hard gelatin capsule to replace 3 hard gelatin capsules; one each of 10 µg, 30 µg and 100 µg will reduce the participant burden from 6 to 4 pills daily and will eliminate the production challenges of the 10 µg tropifexor capsule</td></tr>
</table>

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Section 6.1.3.1 | **Text Modified**<br>Until 3 capsule tropifexor (100 µg + 30 µg + 10 µg) and matching placebo is replaced by the 140 µg hard gelatin single capsule, in order to maintain the blind, placebo capsules matching tropifexor (LJN452) 10, 30 and 100 µg and placebo tablets matching licogliflozin (LIK066) 10 mg will be given to participants as indicated in Table 6-5, so that all participants will receive 3 capsules and 3 tablets per day. One capsule from each of the 3 bottles, and 3 tablets from the blister pack should be taken close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal or no more than 30 minutes after consuming the evening meal and at about the same time each day. | Updated to clarify dosing process while tropifexor 3-capsule supply is used after availability of single capsule supply. |
| Section 6.1.3.2 | **Text Added**<br>After tropifexor and matching placebo is replaced by the 140 µg hard gelatin single capsule, in order to maintain the blind, placebo capsules matching tropifexor (LJN452) 140 µg and placebo tablets matching licogliflozin (LIK066) 10 mg will be given to participants as indicated in Table 6-6, so that all participants will receive 1 capsule and 3 tablets per day. One capsule from the bottle, and 3 tablets from the blister pack should be taken close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal, or no more than 30 minutes after consuming the evening meal and at about the same time each day. | Text added to reflect dosing regimen when the tropifexor 140 µg hard gelatin single capsule replaces the 3-capsule regimen. |
| Section 6.1.2, Section 6.2.1.1 and Table 6-2 2 | **Text Added**<br>There are no restrictions related to COVID-19 vaccines, and these are allowed throughout study participation as permitted by local regulations.<br><br>**Clarification**<br>Clarified in Table 6-2 that only phenothiazines, not all psychotropic medications, must be at a stable dose | To acknowledge and confirm no restriction to the ongoing COVID-19 vaccination campaigns implemented globally<br><br>Psychotropic medications were required to be stable in early studies with tropifexor out of an abundance of caution. However, no DDI or other issues have been identified for these compounds or the indications treated, so restrictions regarding stable dosing no longer apply. However, phenothiazine compounds are |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | | associated with substantial weight gain, and so these compounds must be at a stable dose and expected to remain stable from screening visit 1 onwards. |
| Table 6-3 | **Text Added**<br><br>Drugs approved in any market for treatment of NASH — Stop at least 6 months prior to baseline | As drugs gain approval in select markets for NASH (e.g. Saroglitazar in India) it is necessary to prohibit these confounders prior to, and during, study participation. |
| Section 6.4<br>Table 6-4 | **Text Added**<br>2a. The randomization codes will be disclosed to an independent analysis team to prepare safety and efficacy reports for the DMC. The independent analysts will keep randomization data confidential until data base lock. Data will be shared with the study team under blinded conditions.<br><br>Unblinding a single participant's treatment at a site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result the participant should be discontinued from the study treatment.<br>[redacted]<br>At the time of safety review, the DMC will review unblinded reports created by an independent analysis team. More details will be provided in the DMC charter.<br><br>**Modifications**<br>Abbreviations for blinding and unblinding terminology updated. | Clarifications to the unblinding process implemented to align with Novartis' Clinical Trial Protocol Template Version 4.0 (15-Feb-2021). |
| Section 6.7.2 | **Text Added**<br>Once the protocol amendment v02 is approved and after the tropifexor (LJN452) 10, 30 and 100 µg and matching placebo hard gelatin capsule supply is depleted, the participant will receive 9 blister packs in a box (10 mg licogliflozin or matching placebo tablets) and 1 bottle of 140 µg hard gelatin capsules (replacing | [redacted] |

| Protocol Section | Change | Rationale for change |
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| | the 10, 30 and 100 µg tropifexor or matching placebo capsules) for each 4 week period every 4 weeks through Week 20. At the Week 24, Week 32 and Week 40 visits 2 sets of 4 week supplies of study medication will be distributed to accommodate the 8 weekly visit schedule (Table 8-1). The participants will take **3 tablets** from the blister pack and **1 capsule** from the bottle daily as described above.<br><br>**Text Added**<br>[redacted]<br><br>At site dosing – Baseline and Week 4:<br>• Participants should take study drug either just prior to (within 5 minutes) consuming the morning meal, or no more than 30 minutes after consuming the morning meal.<br>• Participants should be instructed to swallow whole capsules and not to chew or open them.<br>• If vomiting occurs during the course of treatment, participants should not take the study treatment again before the next scheduled dose.<br>• No evening dose should be taken on the days of the Baseline and Week 4 visits as the daily dose is taken at the site on those 2 days. | |
| Section 6.7.2.1 | **Text Added**<br>The 140 µg dose of tropifexor and its matching placebo are each available as a single hard gelatin capsule. Participants on the study at the time of availability of the single tropifexor/placebo capsule, may continue on the 3-capsule tropifexor (100 µg + 30 µg + 10 µg) or matching placebo regimen, as shown in Table 6-5, until the available 3 capsule supply is depleted.<br><br>After the 3-capsule supply is depleted, participants will take 1-capsule of 140 µg tropifexor or matching placebo daily as described in Table 6-6. No change is made to licogliflozin dosing.<br><br>IMPORTANT: Please ensure that the date of the change, and the number of capsules (from 3 capsule to 1 capsule) is accurately captured in the eCRF Change in Dosing log for each participant. | Use of the tropifexor single 140 µg hard gelatin capsule to replace 3 hard gelatin capsules; one each of 10 µg, 30 µg and 100 µg will reduce the participant burden from 6 to 4 pills daily. |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Table 6-6 | **Table Added**<br>Table 6-6 Dosing with single capsule (140 µg) tropifexor supply | Table 6-6 provides guidance and clarification for dosing with the single tropifexor 140 µg hard gelatin capsule |
| Table 8-1<br>Footnote # 4<br><br>Section 8.3.1.10 | **Text Modified**<br>**From:**<br>4. Baseline MRI should be done at least 4 weeks after biopsy.<br>**To:**<br>4. Screening MRI should be done only in participants who are scheduled for liver biopsy. MRI should be acquired at any time during the screening period after Screening 1 eligibility has been confirmed. Every effort should be made to perform Screening MRI before liver biopsy (exception: historical liver biopsy not performed during the screening period). If not possible to obtain the MRI before a biopsy performed during the screening period, MRI should be performed 3 weeks or more after the liver biopsy. | This provision has been added to allow sites sufficient flexibility to schedule the MRI with external facilities during the screening period, while providing sufficient time to avoid artifacts due to biopsy from appearing on the MRI. |
| Section 8.3.1.8 | **Text Modified**<br>**From:**<br>Participants will have paired liver biopsies (Screening and EOT, after 48 weeks of treatment). Fibrosis staging and NAFLD Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment will be determined by a Study Central Reader<br>**To:**<br>Participants will have paired liver biopsies (Screening and EOT, after 48 weeks of treatment). Fibrosis staging and NAFLD Activity Score (NAS) based on steatosis, lobular inflammation, and hepatocyte ballooning assessment will be determined by a Study Central Reader, at the time of submission of each biopsy (Screening and EOT) and again, as a pair, temporally blinded, at the completion of the trial. | Clarity around the paired biopsy at the completion of trial |
| Section 8.4.2 | **Text Added**<br>Local lab collection may be used during a public health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits.<br>If participants cannot visit the site for protocol specified safety lab assessments, an alternative local lab, collection site or relevant clinical facility that are certified for lab diagnostics may be used. | Emerging guidance has been added allowing mitigation procedures for study conduct in the context of the COVID-19 or other public health emergency as declared by Local or Regional authorities |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | Safety samples (specifically hematology, clinical chemistry and coagulation panels) that can be collected locally will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory.<br>Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE, if central laboratory results are unevaluable, inconclusive or cannot be obtained due to public health emergencies, or when the treating physician cannot wait for central laboratory results for decision making.<br>The results of the local laboratory will be recorded in the eCRF | |
| Section 8.4.4.1 | **Text Added**<br>Determination of eligibility will be based on the ECG report from the central ECG review, not on the ECG machine-generated report.<br><br>**Text Added**<br>Local ECG collection may be used during a public health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits.<br>If participants cannot visit the site for protocol specified safety ECG assessments, an alternative local facility, collection site or relevant clinical facility that are certified for ECG collection may be used. | Clarification that ECG eligibility is determined by the central reader<br><br>Emerging guidance has been added allowing mitigation procedures for study conduct in the context of the COVID-19 or other public health emergency as declared by Local or Regional authorities |
| Section 9 | Updates to definitions of Discontinuation and completion | Align with Novartis' Clinical Trial Protocol Template Version 4.0 (15-Feb-2021). |
| Section 9.1.1 | **Text Added**<br>Discontinuation from study treatment is required in cases of serious COVID-19 infection requiring hospitalization. | Recommended by DMC |
| Section 12.4.2 | **Mentioned**<br>While the model used for primary analyses will be the typical logistic regression in most cases, it should be set as the Firth logistic regression if some arm (such as the placebo) has a low response rate. | Typical logistic regression returns biased results from data with rare events. |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Table 16-2 | **Text Added**<br>**From:**<br>ALT and/or AST<br>> 3 × ULN but ≤ 5 × baseline<br>**To:**<br>ALT and/or AST<br>> 3 × ULN but ≤ 5 × baseline<br>AND<br>total bilirubin > 2 × ULN<br>(in Gilbert's syndrome, see footnote[f]) | Clarification of conditions requiring dosing interruption in the context of Gilbert's syndrome. |
| | **Text Added**<br>Potential DILI cases defined as [AST or ALT > 2 x baseline] OR [AST or ALT >7 × ULN] whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] | Definition added for conditions requiring dosing interruption in the context of elevated transaminase values at baseline. |

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 Informed Consent has been adapted accordingly to reflect the above changes.

No additional risks related to COVID-19 pandemic were identified, and therefore the benefit risk is unchanged.

# Summary of Previous Amendments

## Amendment 01 (18-Sep-2020)

### Amendment rationale

**The key purposes of this amendment are to:**

- Implement commitments and recommendations received from individual national regulatory authorities which were initially implemented as country specific amendments.
- Include a placebo arm to minimize sources of bias and to ensure reliable inference with respect to the safety and effectiveness of the treatments as prompted by:
  - Strong recommendation from the study Data Monitoring Committee (DMC) and Health Authorities (HAs) during the initial review of the protocol
  - Recent trials which have shown unexpectedly high placebo response rates, raising concerns about the interpretability of outcomes in a non-placebo controlled trial.
- Increase sample size to accommodate addition of placebo arm, change of hypothesis tests, update in response rate assumptions and to increase statistical power.
- Provide guidance for study conduct in the context of the COVID-19 or other pandemic
- Update where applicable relevant sections as per the latest version of the Investigator Brochure (IB).
- Implement editorial changes throughout the document to align with Novartis' Clinical Trial Protocol Template Version 3.0 (31-Jan-2020). Notably, 'participant' replaces 'patient'.

At the time of preparation of this protocol amendment (V01) document, 225 participants have been screened and 27 participants randomized as of 18-Sep-2020.

### Changes to the Protocol

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Protocol title | From:<br>A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy, compared to each monotherapy, for treatment of adult patients with nonalcoholic steatohepatitis (NASH) and liver fibrosis (ELIVATE)<br><br>To:<br><br>A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy, and each monotherapy, compared with placebo for treatment of adult participants with nonalcoholic steatohepatitis (NASH) and liver fibrosis (ELIVATE) | A Placebo treatment group has been added to the study and the title change reflects that all active treatment groups will be compared to placebo. |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| List of abbreviations | New abbreviations added or deleted | Updated to align with the revised protocol |
| Protocol Summary | Updates made to all sections of the summary. Details and rationale for each change in the summary can be found in the respective sections of this Amendment summary. | To align with the changes made to the body of the protocol. |
| Section 1.1.3 | Updated text:<br>CLJN452A2202 (FLIGHT-FXR) is an adaptive 3-part Phase 2 study of tropifexor in participants with phenotypic or biopsy-confirmed NASH, 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. In Parts A and B of study CLJN452A2202, one hundred fifty two participants received tropifexor at doses ranging from 10 to 90 µg daily for 12 weeks. [redacted] ALT, hepatic fat fraction by MRI-PDFF, and body weight also improved in a dose dependent manner compared to placebo. These early changes were confirmed at Week 48 with a clinically meaningful dose response in reducing ALT, a sustained reduction of GGT, clinically meaningful reduction in Hepatic Fat Fraction, and dose dependent and continued reduction in body weight versus placebo for both 140 µg and 200 µg tropifexor.<br>Tropifexor was generally well tolerated at all dose without safety signals of concern. Pruritus was reported in the 60 µg, 90 µg, 140 µg, 200 µg, and placebo arms and the frequency was dose dependent. The majority of pruritus events were Grade 1 (mild) in severity. Dose-related increases in LDL-C and decreases in HDL-C were observed by Week 12 with no subsequent worsening. Tropifexor did not affect triglyceride levels. | Update summary of available FLIGHT-FXR data to align with tropifexor IB Edition 11 |
| Section 1.1.4 | Updated text:<br>CLIK066X2204 study tested licogliflozin at doses of 30 and 150 mg for 12 weeks in NASH participants. Results from full study population confirmed that treatment with licogliflozin at 150 mg and 30 mg per day resulted in dose-dependent improvements in markers of liver injury (ALT, AST and GGT) and liver fat content. (LIK066 IB Edition 12) The study clinical report is currently in preparation. Both doses of licogliflozin led to significant placebo adjusted weight loss at the 150 mg and 30 mg doses respectively (LIK066 IB). Licogliflozin treatment also improved glycemic and insulin sensitivity markers; HbA1c and HOMA-IR at both doses. The most common AE was diarrhea, reported by similar number of participants in the placebo and 30 mg groups but at a higher rate in the 150 mg dose group. As in previous studies with licogliflozin, diarrhea was mostly mild in the participants who had it. Only one participant in the 150 mg dose group discontinued treatment as a result of diarrhea.<br>In summary, in clinical studies, licogliflozin has been well tolerated to date, resulting in improvements in markers of liver injury, hepatic fat, and weight loss with doses tested up to 150 mg orally in the CLIK066X2204 study. | Update summary of available CLIK066X2204 data to align with licogliflozin IB Edition 12 |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Section 1.1.6.1 | Text added:<br>A clinical study (CLJN452A2103) assessing the effect of strong CYP3A4 inhibitors and inducers on tropifexor PK has been completed after initiation of this trial and confirmed the expected interaction: the strong CYP3A4 inhibitor itraconazole increased the AUC of tropifexor by 47%; the strong CYP3A4 inducer rifampin decreased the AUC of tropifexor by 77-79%. | CYP3A4 interaction study CLJN452A2103 recently completed. |
| Section 1.1.6.3 | Text added:<br>The pharmacokinetic drug interaction between tropifexor (140 ug) and licogliflozin (50 mg) was investigated in study CLJN452E12101. Preliminary data from this study confirm the absence of a clinically relevant pharmacokinetic drug interaction between these 2 drugs. In the presence of licogliflozin, mean peak plasma concentration (Cmax,ss) of tropifexor decreased by 15% and total exposure (AUCtau,ss) decreased by 13%. In the presence of tropifexor, mean peak plasma concentrations of licogliflozin increased by 8% and total exposure increased by 12%. The small observed changes are within the 0.8-1.25 range and therefore below the effect generally considered a weak drug interaction. | DDI study CLJN452E12101 recently completed. |
| Section 2<br><br>Table 2-1<br>Primary Objective and Endpoint | Primary Objective modified<br>From:<br>To demonstrate the efficacy of tropifexor + licogliflozin as assessed by histologic improvement after 48 weeks of combination treatment compared to each monotherapy treatment in patients with NASH and stage 2 or 3 fibrosis.<br><br>To:<br><br>To evaluate the efficacy of tropifexor + licogliflozin in combination therapy and each monotherapy treatment, as assessed by histologic improvement after 48 weeks compared to placebo in participants with NASH and stage 2 or 3 fibrosis.<br><br>Primary endpoint modified<br>From:<br>Proportion of participants with resolution of NASH and no worsening of fibrosis OR Improvement in fibrosis by at least one stage without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared with baseline<br><br>To:<br><br>-Whether the participant has at least a one stage improvement in fibrosis without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared to baseline | Aligned with guidance from Regulators. |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | - Whether the participant achieves resolution of steatohepatitis without worsening of fibrosis at Week 48 compared to baseline | |
| Section 2<br><br>Table 2-1<br>Key Secondary Objectives and Endpoints | Two secondary Objectives were changed<br>From:<br><br>Improvement in fibrosis by at least one stage with no worsening of NASH after 48 weeks of treatment<br><br>Resolution of NASH with no worsening of fibrosis after 48 weeks of treatment<br><br>To<br><br>To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint<br><br>Two secondary Endpoints were changed<br>From:<br>Key secondary endpoint: Proportion of patients who have at least one stage improvement in fibrosis without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared with baseline<br><br>Key secondary endpoint: Proportion of patients with resolution of NASH and no worsening of fibrosis at Week 48 compared with baseline<br><br>To:<br><br>Key secondary endpoint: Whether the participant achieves resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH (no worsening of hepatocellular ballooning or lobular inflammation) at Week 48 compared with baseline. | These objectives and associated endpoints were replaced with the original primary endpoint (the single composite endpoint). |
| Section 2 | Preface Primary and Secondary Objective definitions with ‘to evaluate’<br><br>Added timeframe for objective evaluation for secondary and [redacted] objectives to be assessed ‘after 48 weeks of treatment’ | Harmonize language used in primary and secondary objective definitions.<br><br>Clarification of timeframe for objective evaluation. |

| Protocol Section | Change | Rationale for change |
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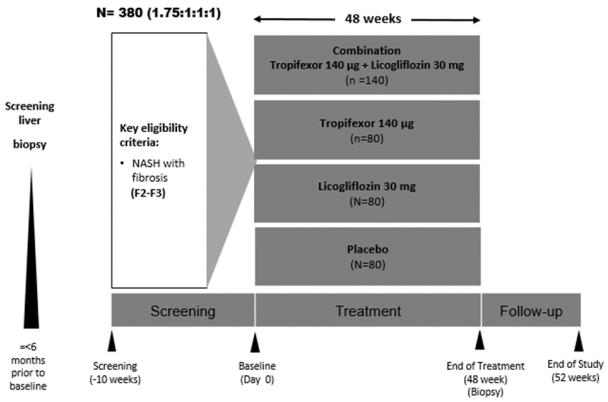
| [redacted] | | |
| Section 2.1 | Primary estimands Section added | To clearly define the primary estimand under the estimand framework described in ICH E9R1 |
| Section 3 | Updated first paragraph as follows:<br>This is a randomized, double-blind, parallel-group, multiple-arm study to assess the efficacy, safety and tolerability of tropifexor and licogliflozin combination therapy, and each monotherapy compared with placebo as well as the combination therapy compared to each monotherapy, in participants with NASH and fibrosis.<br><br>Study design updated as follows:<br>Approximately 380 participants with NASH (NAS ≥4) and fibrosis stage 2 or 3 will be randomly assigned to one of the following treatments:<br>Arm A: Combination therapy Arm - (N=140): tropifexor 140 µg + licogliflozin 30 mg, once daily.<br>Arm B: Tropifexor monotherapy Arm - (N=80): tropifexor 140 µg (+ placebo matching licogliflozin), once daily.<br>Arm C: Licogliflozin monotherapy Arm - (N=80): licogliflozin 30 mg (+ placebo matching tropifexor), once daily.<br>Arm D: Placebo Arm – (N=80): placebo matching tropifexor + placebo matching licogliflozin once daily. | Include a placebo arm to minimize sources of bias and to ensure reliable inference with respect to the safety and effectiveness of the treatment as prompted by:<br>1. Strong recommendation from DMC and HAs during the initial review of the protocol<br>2. Recent trials which have shown unexpectedly high placebo response rates, raising concerns about the interpretability of outcomes in a |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | | non-placebo controlled trial.<br><br>Increase sample size to accommodate addition of placebo arm, change of hypothesis tests, update in response rate assumptions and to increase statistical power. |
| Figure 3-1Study Design | New figure:<br>  <br> | Figure updated to reflect new sample size and study design, including addition of placebo treatment group, increase in sample size from 210 to 380, and randomization ratio change from 1:1:1 to 1.75 (combination) : 1 (tropifexor) : 1 (licogliflozin) :1 (placebo). |
| Section 3 | Deleted the following text: “Additional monotherapy treatments, and potential combination arms may become available after the start of this study and may be considered to be added to this study via protocol amendments. This would only be proposed if situationally and scientifically justifiable, and with a full scientific biological rationale and supportive data packages. This is a theoretical consideration at this time. If additional arms are anticipated the appropriate guidance for platform studies will be considered.” | Deletion requested by the United Kingdom’s Medicines and Healthcare Products Regulatory Agency (MHRA) during CTA review. |
| Section 4.3 | Rationale for choice of control drugs (comparator/placebo) or combination drugs<br>Updated text:<br>Currently there is no drug established as standard of care for participants with NASH. Combination of tropifexor and licogliflozin and each of these | Rationale updated to reflect use of placebo as comparator. |

| Protocol Section | Change | Rationale for change |
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| | compounds as monotherapy will be compared to placebo. Subsequently, the combination treatment will be compared to each of the monotherapies.<br>A placebo treatment group was added to improve the assay sensitivity and interpretation of the treatment effect given the wide variability observed in histological response in recent studies for those participants receiving standard of care. | |
| Section 4.5 Risks and Benefits | New text added:<br>When used as monotherapy, tropifexor and licogliflozin have been shown to have potential benefits in treating NASH. Based on the mechanisms of action of FXR agonists and SGLT1/2 inhibitors and the fact that the biologic pathways do not overlap, it is expected that they will complement each other and address the three main pathologic features of NASH, namely steatosis, inflammation and fibrosis.<br>Appropriate eligibility criteria as well as specific stopping rules, are included in this protocol. Recommended guidelines for supportive management of study drug induced adverse events are provided in Section 10.2.<br>The risk to participants in this trial is minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, stopping rules and periodic review of safety data by an independent DMC.<br>Toxicology of the combination is described in Section 1.1.9. All potential risks of each compound are described in the tropifexor and licogliflozin IBs. A brief summary of the benefits and risks of each compound follows: | Section added to explain the anticipated risks and benefits of tropifexor and licogliflozin in combination. |
| Sections 4.5.1, 4.5.1.1 and 4.5.1.2 | Tropifexor Benefits and Risks update to include emerging data. Updated to include additional details of hepatic effects of tropifexor in non-clinical (rats), healthy volunteers, and NASH participants studies. CYP3A4 inhibitor and inducer data from Study CLJN452A2103 added. | Non-clinical rat data requested by BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices) and the German Ethics Committee during the Clinical Trial Application (CTA) review. Additional data available. Risks split by population tested for ease of review. |
| Section 4.5.2.1 | Added text:<br>CLIK066X2204 study tested licogliflozin at doses of 30 and 150 mg for 12 weeks in NASH participants. Results from full study population confirmed that treatment with licogliflozin at 150 mg and 30 mg per day resulted in dose-dependent improvements in markers of liver injury (ALT, AST and | Aligned licogliflozin benefits section with data included |

| Protocol Section | Change | Rationale for change |
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| | GGT) and liver fat content (LIK066 IB edition 12). The clinical study report is currently in preparation. Both doses of licogliflozin led to significant placebo adjusted weight loss at the 150 mg and 30 mg doses respectively. (LIK066 IB). Licogliflozin treatment also improved glycemic and insulin sensitivity markers; HbA1c and HOMA-IR at both doses. | in other sections of the protocol. |
| Section 4.5.2.2 | Added text:<br>In study CLIK066X2204, the most common AE was diarrhea, reported by similar number of participants in the placebo and 30 mg groups but at a higher rate in the 150 mg dose group. As in previous studies with licogliflozin, diarrhea was mostly mild in the participants who had it. Only one participant in the 150 mg dose group discontinued treatment as a result of diarrhea.<br><br>Updated text:<br>Appropriate exclusion criteria are applied in this study and guidance is provided to mitigate the risks as per Section 10.2.3. It is recommended that bilateral foot exams be performed at screening to assess the presence of any foot deformity (including amputation), disease, and/or the presence of clinically significant neuropathy that may increase the risk of amputation. | Aligned licogliflozin risks section with data included in other sections of the protocol.<br><br>Bilateral foot exams, which may not be routine for hepatologists, recommended to identify clinically significant neuropathy. |
| Section 4.5.3 | Removed the text ‘and sexually active males’ from the following sentence:<br>Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. | Updated in tropifexor IB edition 10, Release date 10-Dec-2019,<br>(IB Section 7.2.1.4):<br>“Based on the FDA guidance on reproductive and developmental toxicities 2011 and after calculation of the safety margins based on potential amount of drug in semen<br>(IB Section 4.3.7): there is no requirement for male tropifexor |

| Protocol Section | Change | Rationale for change |
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| | | study participants to use a condom during sexual intercourse and no requirement for contraception in their female partners (FDA 2011)". |
| Section 5.1 | Inclusion Criterion 3 revised to specify that the NAFLD Activity Score (NAS) for eligible participants must be >= 4 with at least 1 point each in inflammation and ballooning on the screening histology assessment performed by the central reader. | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| Section 5.2 | Exclusion Criterion 4: updated as follows: History of hypersensitivity to either of the study drugs or their excipients or to drugs of similar chemical classes, or participants with hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption | Requested by BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices) and the German Ethics Committee during the Clinical Trial Application (CTA) review. |
| | Exclusion Criterion 5: Updated as follows:<br>Taking a permitted medication listed in Table 6-2 but who is NOT on a stable dose (within 25% of baseline dose) from the start of the screening. period and<br>a. for at least 3 months prior to the baseline visit for thyroid hormone, oral anti-diabetic medication, insulin, and GLP-1 agonists<br>b. for at least 6 months prior to baseline for Vitamin E | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| | Exclusion Criterion 6: revised to add "unit of alcohol", commonly used in some participating countries as follows:<br>Significant alcohol consumption is defined as more than 20 g/day (14 units/week) in females, or more than 30 g/day (21 units/week) in males, on average. A "unit" of alcohol is equivalent to one (12-ounce; 355 ml) beer, one glass (4-ounce; 120 ml) of wine, or 1 shot (ounce; 30 ml) of hard liquor. | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| | Exclusion Criterion 7: definition of uncontrolled type 2 diabetes reduced from HbA1c >= 9.5% to HbA1c >= 9.0% | Requested by the US Food and Drug |

| Protocol Section | Change | Rationale for change |
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| | | Administration (FDA) during the IND review. |
| | Exclusion Criterion 8: exclusionary value for platelets is < LLN (lower limit of normal) and refers to central laboratory normal range and not a specific numeric value. | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| | Exclusion Criterion 9: exclusionary values for albumin is < LLN, and total bilirubin and INR are > ULN (upper limit of normal) and refer to the central laboratory normal range and not a specific numeric value. Model For End-Stage Liver Disease (MELD) score >12 added as exclusion. In addition, ALT, AST, ALP and total bilirubin will be evaluated 2 times during the screening period and both values must meet eligibility criteria prior to randomization. | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| | Exclusion Criterion 10: added: presence of Immunoglobulin M (IgM) antibodies to Hepatitis A Virus (IgM anti-HAV). | Requested by the US Food and Drug Administration (FDA) during the IND review. |
| | Exclusion Criterion 22: updated to: Diabetic complications, known peripheral vascular disease or clinically significant neuropathy that may increase the risk of amputation. | Because many enrolled patients will be diabetic, and most diabetics experience at least some neuropathy, exclusion was updated to clarify that specifically patients with clinically significant neuropathy that may increase the risk of amputation are excluded. |
| | Exclusion Criterion 23: Updated to: Symptomatic genital or urinary tract infection within 4 weeks prior to randomization or participants with high risk as, determined by the investigator (including concomitant therapy with immunosuppressive potential), to be particularly susceptible to genital or urinary tract infection. | In addition to patients with recent genital or urinary tract infections, those patients likely to be susceptible to |

| Protocol Section | Change | Rationale for change |
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| | | such infections are excluded. |
| | Exclusion Criterion 25: Updated to: Any history of and/or suspected Fournier's gangrene, or participants with high risk as, determined by the investigator (including concomitant therapy with immunosuppressive potential), to be particularly susceptible to Fournier's gangrene. | In addition to patients with history of or suspected Fournier's gangrene infections, those patients likely to be susceptible to such infection are also excluded. |
| | Exclusion Criterion 28: Updated to: Known positivity for Human Immunodeficiency Virus (HIV) infection. HIV antigen/antibody tests will be performed to determine HIV status if allowed and required according to local regulations. | Requested by BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices) and the German Ethics Committee during the Clinical Trial Application (CTA) review. |
| | Exclusion Criterion 33: Removed: Sexually active males must use a condom during intercourse while taking drug and for 5 days after stopping investigational 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 study drug via seminal fluid. | Updated in tropifexor IB edition 10, Release date 10-Dec-2019, Section 7.2.1.4:<br>Based on the FDA guidance on reproductive and developmental toxicities 2011 and after calculation of the safety margins based on potential amount of drug in semen (tropifexor IB Section 4.3.7), there is no requirement for male tropifexor study participants |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | | to use a condom during sexual intercourse and no requirement for contraception in their female partners (FDA 2011).' |
| Section 6.1.3 | Text updated to:<br>Participants (n = 380) will be assigned at Baseline visit to one of the following 4 treatment arms in a ratio of 1.75:1:1:1 in a blinded manner. Placebo capsules/tablets will be given in each treatment arm where necessary to maintain blinding.<br>Arm A: Combination therapy Arm - (N=140): tropifexor 140 µg + licogliflozin 30 mg, once daily.<br>Arm B: Tropifexor monotherapy Arm - (N=80): tropifexor 140 µg (+ placebo matching licogliflozin), once daily.<br>Arm C: Licogliflozin monotherapy Arm - (N=80): licogliflozin 30 mg (+ placebo matching tropifexor),once daily.<br>Arm D: Placebo Arm – (N=80): placebo matching tropifexor + placebo matching licogliflozin once daily. | Text updated to reflect change to study design. |
| Section 6.2.1.1 | Table 6-2: updated to clarify duration of stability of permitted concomitant medications. Revised stability of permitted anti diabetes concomitant therapy to 'Stable dose for at least 3 months prior to baseline' and stability of Vitamin E ≤ 800 IU/day to 'Stable dose for at least 6 months prior to the baseline visit'. Sliding scale insulin permitted. Stability for one month prior to qualifying biopsy has been removed. | Revised stability of permitted anti diabetes concomitant therapy to 'Stable dose for at least 3 months prior to baseline' and stability of Vitamin E ≤ 800 IU/day to 'Stable dose for at least 6 months prior to the baseline visit' was requested by the US Food and Drug Administration (FDA) during the IND review. |
| Section 6.2.2 | Table 6-3: updated to clarify when prohibited medications must be discontinued in participants who take them prior to study participation. | Editorial clarification. |

| Protocol Section | Change | Rationale for change |
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| | Table 6-3: Methotrexate and Alternative Liver Protection medications added to the prohibited medication table | To eliminate confounders of response. |
| Section 6.3.2 | Text moved to introduce the section:<br>The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of treatment arms to randomization numbers. These randomization numbers are linked to the different treatment arms. | Clarification of randomization and IRT |
| [redacted] | | |
| Section 6.6.2 | Text added:<br>Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with Novartis.<br>And:<br>After the emergency break the participant must be discontinued from the study by the investigator. | Additional reason for code break and next steps added as per Novartis template. |
| Section 6.7.2 | Updated text to 'The participant will be dispensed 9 blister packs in a box and 3 bottles in a box for each 4 week period every 4 weeks from baseline through Week 20. At the Week 20, Week 32 and Week 40 visits 2 sets of 4 week supplies of study medication will be distributed (Table 8-1). If the COVID-19 or other pandemic prevents on-site visits the site may arrange delivery of study medication to a participant's home.<br>[redacted] | Added to allow home delivery of study medication if necessary due to the COVID-19 or other pandemic to avoid study medication interruption resulting from participants' inability to obtain study medication from investigative site.<br>[redacted] |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| Section 8 | Added:<br>"The date of each scheduled visit is calculated with the appropriate interval from the date of the baseline/randomization visit, not from the date of the previous visit. If a scheduled visit is late by more than half of the planned interval between it and the next scheduled visit, the visit should be skipped."<br><br>Added:<br>"If the COVID-19 or any other pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsulting) or visits by site staff/home nursing service at the participant´s home depending on local regulations and capabilities, may be considered. In-home visits would be conducted by the site staff (under the responsibility of the investigator), or by a health care provider (HCP) supporting this activity if this is in agreement with the investigator." | Text added to provide additional clarity on visit scheduling and visit windows.<br><br>Added to allow home visits if necessary due to the COVID-19 or other pandemic to avoid study interruption of study assessments resulting from participants' inability to attend study visits at the investigative site. |
| Table 8-1 | Below updated<br><br>• Visit numbers added<br>• Screening visit changed from 8 to 10 weeks<br>• HIV test at screening<br>[redacted] | • Visit numbers added for clarity<br>• Screening period increased to allow sufficient time for turn around of biopsy results<br>• HIV testing Requested by BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices) and |

| Protocol Section | Change | Rationale for change |
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| | | the German Ethics Committee during the Clinical Trial Application (CTA) review.<br>• [redacted] |
| Section 8.1.2 | Statement added: “If the reason for screen failure is an inadequate biopsy sample taken during the screening period, a second liver biopsy cannot be performed for re-screening. If the inadequate liver biopsy sample is historical, the investigator’s clinical judgment and local standard of care will determine if and when the liver biopsy can be repeated for re-screening”. | Requested by BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte - The Federal Institute for Drugs and Medical Devices) and the German Ethics Committee during the Clinical Trial Application (CTA) review. |
| Section 8.2.1 | The second screening visit should only be conducted if participant remains eligible based on the assessments performed at screening visit 1. ALT, AST, total bilirubin and ALP will be tested at screening visits 1 and 2, and must meet the requirements in Section 5.2 at both screening visits to confirm eligibility. | Qualifying ALT, AST, total bilirubin and ALP at both SV1 and SV2 requested by the US Food and Drug Administration (FDA) during the IND review. |
| Section 8.3.1 | Section reorganized to reflect order of assessments performed | Editorial clarification |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| [redacted] | | |
| Section 8.4.1.1 | Text updated to:<br>A complete physical examination will be conducted at screening visit 1, baseline, Weeks 12, 24, and 48 which 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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. At all other visits, a physical examination according to local guidelines, including bilateral foot exams, will be performed. | To clarify at which visits a complete or modified physical examination is required. |
| Section 9.1.1 | Discontinuation of Study Treatment: 'life-threatening events considered to be related to study medication' added as a situation in which study participation might result in a safety risk to the participant.as follows:<br>Any situation in which study participation might result in a safety risk to the participant (including life-threatening events considered to be related to study medication)<br><br>Added text:<br>Participants can discontinue from the study treatment or from the study without withdrawing consent. | Requested by the US Food and Drug Administration (FDA) during the IND review.<br><br>Text added to ensure site staff are clear that withdrawal of consent is not mandatory for, nor synonymous with, discontinuation. |
| Section 10.1.2 | Any AE of pancreatitis (acute, chronic or other), Fournier's gangrene and ketoacidosis will be assessed as serious under "medically significant" even if other seriousness criteria are not met. | AESI pancreatitis, Fournier's gangrene and ketoacidosis are medically significant events. |
| Section 10.1.4 | Updated text: | Clarification of duration of follow up of newborn in |

| Protocol Section | Change | Rationale for change |
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| | 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 at expected delivery date plus 12 months. | case of patient pregnancy. |
| Section 10.2.2 | Text updated to:<br>Once a participant is exposed to study treatment, renal serum and urine laboratory values will be assessed routinely. Renal laboratory triggers and renal events are defined in Table 16-3 in Section 16.3. These laboratory abnormalities should be followed up as indicated in Table 16-3 by the investigator or designated personnel at the trial site. | Details of laboratory values removed to avoid redundancy and risk of inconsistency with Table 16-3. |
| Section 10.2.3 | Adverse Events of Special Interest updated to include dyslipidemia, genital infections, ketoacidosis, and Fournier's gangrene. | Dyslipidemia added as potential risk with FXR agonism, and genital infections, ketoacidosis, and Fournier's gangrene are potential side effects with SGLT2 inhibitors |
| Section 11.1 | Template language related to direct data entry removed | Process not applicable to CLJN452D12201 C |
| Section 12.2 | Demographics and baseline characteristics summary would only be provided for FAS. | Limited difference was expected between SAF and FAS. |
| Section 12.4 | A placebo arm was added to the trial. | The addition of placebo was suggested by Health Authorities and DMC. Furthermore, the placebo response rates of recent studies in NASH are quite different from those of previous studies. |
| | The primary endpoint was changed from the single composite endpoint to two endpoints. | The change was made to align with guidance from |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | | Regulators. These two endpoints are used as primary endpoints in most Phase 3 NASH studies. |
| | The primary test of the study was changed to the comparisons between combination therapy and placebo for the two primary endpoints. | The primary objective of the study is to show the efficacy of the combination therapy compared with placebo. |
| | Comparisons between monotherapies and placebo were added. | To evaluate the efficacy of monotherapies compared with placebo again (after the monotherapy studies).<br><br>Moreover, these comparisons are now possible due to addition of the placebo treatment group. |
| Section 12.4.2 and Section 12.5.1 | P-values would not be provided if formal hypothesis tests were not performed. | This change was implemented to avoid potential confusions or misinterpretation of the results. |
| Section 12.4 | Provided a better summary of the strategies to address intercurrent events and the methods to handle non-intercurrent event missing data. | To clarify the two types of missing data and the strategies/methods to handle them. |
| Section 12.4.1 | The primary endpoints were explained in more detail and were rephrased from sample level (proportion) to participant level (binary). | To make use of the new estimand framework. |
| Section 12.4.2 | The overall Type I error rate was changed from one-sided 0.05 level to two-sided 0.05 level. | To use a more strict alpha level for potential two-sided 0.05 alpha |

| Protocol Section | Change | Rationale for change |
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| | | was suggested by the health authorities. |
| | The hypothesis tests were arranged with hierarchical testing procedure. | To control the overall Type I error rate. |
| | The test order was illustrated by an alpha recycling graph. | To clarify the order of testing. |
| | The null and alternative hypotheses were updated | Comparisons were changed from one-sided to two-sided. |
| Section 12.4.3 | Updated the list of intercurrent events. | To take into account more potential events that have confounding effects to the primary estimands. |
| | Explained the strategies to handle intercurrent events. | To provide a clear plan on how to address intercurrent events. This was suggested in ICH E9 R1 guidelines. |
| Section 12.4.4 | Created a separate subsection for non-intercurrent event missing data. | Suggested by the new estimand framework explained in ICH E9 R1 guidelines |
| | The methods to manage non-intercurrent event missing data were updated. | For clarity purpose. |
| | Multiple imputations would be performed based on fully conditional specification (FCS) with logistic regression instead of discriminant function. | To handle arbitrary missing patterns. |
| Section 12.4.5 | Details of sensitivity analyses removed. | Moved the details of sensitivity analysis from protocol to Statistical Analysis Plan. |

| Protocol Section | Change | Rationale for change |
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| Section 12.5.1 | Replaced the two key secondary endpoints with the original primary composite endpoint | The two previous key secondary endpoints are now the primary endpoints. |
| Section 12.5.1 | The secondary endpoints in Table 12-1 is re-described in the participant level. | To follow the suggestions from ICH E9 R1 guidelines |
| Section 12.5.1 | Added the analyses for ALT, AST, and GGT in Table 12-1. | To align with the secondary objectives described in Table 12-11. |
| Section 12.5.1 | Deleted the description of repeated measurements analysis of covariance (ANCOVA) model beneath Table 12-1. | The analyses for repeated measurements are now described in Table 12-1 |
| Section 12.5.2 | Statement removed:<br>Data from the pre-treatment period and from the period after 30 days after last administration of study treatment will be listed but not summarized.<br><br>Statement added to Section 12.5.2.1:<br>Participants who died any time during the study will be listed with SAEs leading to such deaths.<br><br>Clarification in Section 12.5.2.4:<br>The Fridericia QT correction formula (QTcF) will be used for clinical decisions and for analyses. Notable QTcF values and changes from baseline will be summarized by treatment and scheduled visit, where a notable value is defined as a QTcF ≥450 msec (male) or ≥460 msec (female) and the categories used for the change (increase) in QTcF are: ≤ 30 ms, > 30 to ≤ 60 ms and > 60 ms. | Off treatment data will be managed by listing and or summaries depending on the assessments.<br><br>Updated to clarify the QTcF cutoff in females. |
| Section 12.8 including 12.8.1 and 12.8.2 | New text:<br>Sample size and allocation are determined by three factors:<br>1. Optimizing the power of passing at least one of the combination vs. placebo tests from the two primary endpoints;<br>2. Optimizing the power of passing any monotherapy vs placebo test (given that at least one of the combination vs. placebo tests have succeeded);<br>3. Restricting the size of placebo arm no larger than that of any treatment arm. | Sample size and allocation were re-calculated due to addition of placebo arm, change of primary endpoint(s), revision of hypothesis tests, update of response rate |

| Protocol Section | Change | Rationale for change |
|---|---|---|
| | | assumptions and change in statistical power. |
| Section 15 | Added below references:<br>Bretz, F., Maurer, W., Brannath, W. and Posch, M. (2009). "A graphical approach to sequentially rejective multiple test procedures." Statistics in Medicine 28: 586–604.<br>He YL, Haynes W, Meyers CD, et al (2019) The effects of licogliflozin, a dual SGLT1/2 inhibitor, on body weight in obese patients with or without diabetes. Diabetes Obesity and Metabolism, 21: 1311-21.<br>Rubin DB (1976). Inference and Missing Data. Biometrika, 63:581–92.<br>Rubin DB (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons. | Updated based on revised protocol |
| Section 16 | Table 16-2 updated to reflect triggers and necessary actions by investigators, in context of clinical symptoms, when elevation of liver function tests is observed as compared to baseline. | Updated to be aligned with recommendations received from Health Authorities (including FDA and BfArM) which have been implemented in other Novartis NASH studies. |
| | Table 16-3 updated for completeness to reflect renal laboratory triggers and necessary actions. | To reflect alerts aligned with the patient population and study medication mechanism of action. |
| | Table 16-5 time for collection of 'post previous evening dose' samples updated to 'Recommended<br>18h (+/- 4h)'. | Timing for sample collection is aligned with protocol Section 8.5.2. |

Editorial changes throughout the document for clarity.

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 Informed Consent has been adapted accordingly to reflect the above changes.

No additional risks related to COVID-19 pandemic were identified, and therefore the benefit risk is unchanged.

# Protocol summary

**Table 1-1 Protocol Summary**

| | |
|---|---|
| **Protocol number** | CLJN452D12201C |
| **Full Title** | A randomized, double-blind, parallel-group, multicenter study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy, and each monotherapy, compared with placebo for treatment of adult participants with nonalcoholic steatohepatitis (NASH) and liver fibrosis (ELIVATE) |
| **Brief title** | Study to assess efficacy, safety, and tolerability of oral tropifexor (LJN452) & licogliflozin (LIK066) combination therapy, and each monotherapy, compared with placebo (ELIVATE) |
| **Sponsor** | Novartis Pharma AG |
| **Investigation type** | Drug |
| **Clinical Phase** | Phase IIb |
| **Study type** | Interventional |
| **Purpose** | To compare tropifexor and licogliflozin in combination therapy and each monotherapy, to placebo for efficacy, safety, and tolerability in participants with NASH and liver fibrosis (stage 2 or 3) as per NASH CRN histological score. |
| **Primary Objective(s)** | To evaluate the efficacy of tropifexor + licogliflozin in combination therapy and each monotherapy treatment, as assessed by histologic improvement after 48 weeks compared to placebo in participants with NASH and stage 2 or 3 fibrosis. |
| **Secondary Objectives** | • To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint after 48 weeks of treatment.<br>• To evaluate improvement in fibrosis by at least one stage after 48 weeks of treatment.<br>• To evaluate improvement in fibrosis by at least two stages with no worsening of NASH after 48 weeks of treatment.<br>• To evaluate reduction in body weight from Baseline after 48 weeks of treatment.<br>• To evaluate change in liver fat content after 48 weeks of treatment.<br>• To evaluate the relationship of investigational treatment and markers of hepatic inflammation in NASH (ALT and AST) after 48 weeks of treatment.<br>• To evaluate the relationship of investigational treatment and GGT, a marker of cholestasis and oxidative stress after 48 weeks of treatment.<br>• To evaluate the safety and tolerability of tropifexor (LJN452) in combination with licogliflozin (LIK066), and each monotherapy treatment, compared to placebo, after 48 weeks of treatment |
| **Study design** | This is a randomized, double-blind, parallel-group, multiple-arm study to assess the efficacy, safety and tolerability of tropifexor and licogliflozin |

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| | combination therapy, and each monotherapy compared with placebo, as well as the combination therapy compared to each monotherapy, in participants with NASH and fibrosis. |
| **Rationale** | Tropifexor and licogliflozin each work through a different mechanism of action, thus allowing potential additive or complementary beneficial effects resulting in greater efficacy when used as a combination.<br>Additive or complementary efficacy coupled with acceptable safety and tolerability would support further development of this combination for NASH. |
| **Study population** | Approximately 380 adult male and female participants with NASH and fibrosis stages 2–3 demonstrated on liver biopsy within 6 months prior to randomization. |
| **Key Inclusion criteria** | • Signed informed consent must be obtained prior to participation in the study.<br>• Male and female participants 18 years or older (at the time of the screening visit).<br>• Presence of NASH with fibrosis as confirmed by central reader's evaluation of liver biopsy obtained no more than 6 months before randomization demonstrated by the following:<br>o NASH using NAFLD Activity Score (NAS) >= 4 with at least 1 point each in inflammation and ballooning<br>and<br>o Fibrosis stage 2 or 3 using NASH CRN fibrosis criteria |
| **Key Exclusion criteria** | • Type 1 diabetes mellitus<br>• Uncontrolled type 2 diabetes defined as glycated hemoglobin (HbA1c) ≥ 9.0% at screening<br>• HbA1c < 6.5% at screening in Type 2 diabetics currently treated with insulin or sulfonylureas<br>• Platelet count < LLN (see Central Laboratory Manual)<br>• Clinical evidence of liver impairment as defined by the presence of any of the following abnormalities:<br>o Serum albumin < LLN (see Central Laboratory Manual)<br>o International Normalized Ratio (INR) > ULN (see Central Laboratory Manual)<br>o ALT or AST >5x ULN (in either of the 2 values during screening).<br>o Total bilirubin >ULN (see Central laboratory manual) (in either of the 2 values during screening) (including Gilbert's syndrome)<br>o Alkaline phosphatase > 300 IU/L (in either of the 2 values during screening)<br>o History of esophageal varices, ascites or hepatic encephalopathy<br>o Splenomegaly<br>o MELD score >12 |

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| **Study treatment** | • Eligible participants will be randomized to 3 treatment arms and 1 placebo arm in a ratio of 1.75:1:1:1<br>  • Arm A (N=140): tropifexor 140 µg + licogliflozin 30 mg, once daily<br>  • Arm B (N=80): tropifexor 140 µg (+ placebo matching licogliflozin), once daily<br>  • Arm C (N=80): licogliflozin 30 mg (+ placebo matching tropifexor), once daily<br>  • Arm D (N=80): placebo (placebo matching tropifexor + placebo matching licogliflozin) , once daily |
| **Efficacy assessments** | • Liver biopsy<br>  ○ NASH<br>  ○ fibrosis<br>• MRI (PDFF)<br>• Weight<br>• Liver function tests (LFT)<br>  ○ ALT<br>  ○ AST<br>  ○ GGT |
| **Key safety assessment** | • Adverse events/serious adverse events (AE/SAE)<br>• Adverse events of special interest (AESI)<br>• Laboratory evaluations<br>• Physical examination<br>• Vital signs<br>• Electrocardiogram (ECG) |
| **Other assessments** | [redacted]<br>• NAFLD fibrosis score<br>[redacted]<br>• Pregnancy and assessment of fertility<br>• Height<br>• Waist and hip circumference<br>[redacted] |
| **Data analysis** | The study adopts two primary endpoints: 1. Whether the participant achieves at least one stage improvement in fibrosis without worsening of NASH at Week 48 compared with Baseline; 2. Whether the participant has resolution of NASH and no worsening of fibrosis at Week 48 compared with Baseline. Five pairwise comparisons may be evaluated for each primary endpoint, rendering a total of ten potential comparisons. Family-wise Type I error rate is controlled at two-sided 5% (one-sided 2.5%) level, and is split for the two primary endpoints. Each primary |

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| | endpoint will have its own branch of tests and may pass its alpha to the other branch from its last two tests.<br>The main goal of the study is to demonstrate the combination efficacy of tropifexor + licogliflozin over placebo in participants with NASH and stage 2 or 3 fibrosis, so the two combination therapy vs. placebo tests (one for each primary endpoint) will be performed first. Then, for each primary endpoint, the two monotherapies (LJN452 and LIK066) will be compared with placebo after the combination treatment reveals superiority over placebo with statistical significance. If one of the monotherapy vs. placebo tests succeeds, then it will pass its alpha to the corresponding combination vs. monotherapy test. An alpha recycling graph is made to illustrate the test hierarchy. |
| **Key words** | NASH, Tropifexor, Licogliflozin, LJN452, LIK066. |

# 1 Introduction

## 1.1 Background

### 1.1.1 Non Alcoholic Steatohepatitis (NASH)

Non alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the Western world (Browning et al 2004, Ratziu et al 2010, Szczepaniak et al 2005). The clinical - histologic phenotype of the disease extends from non alcoholic fatty liver to non alcoholic steatohepatitis (NASH). NASH includes not only fat in the liver but also inflammation and hepatocyte injury (ballooning) which over time can lead to increasing fibrosis, cirrhosis and end stage liver disease (Ekstedt et al 2015). 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% (Chalasani et al 2012, Vernon et al 2011). 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 number 2 indication for liver transplantation in the US (Wong et al 2015).

NASH is associated with obesity and Type 2 diabetes mellitus (Hossain et al 2009) and a NASH phenotype can be composed by the combination of several features of the metabolic syndrome (obesity, Type 2 diabetes mellitus, dyslipidemia) along with elevated ALT/AST and fatty infiltration of the liver. Patients with NASH have an increased risk of developing hepatocellular carcinoma (Starley et al 2010). NASH is also associated with an increased risk of cardiovascular mortality and type 2 diabetes mellitus (Targher et al 2005, Targher and Arcaro 2007).

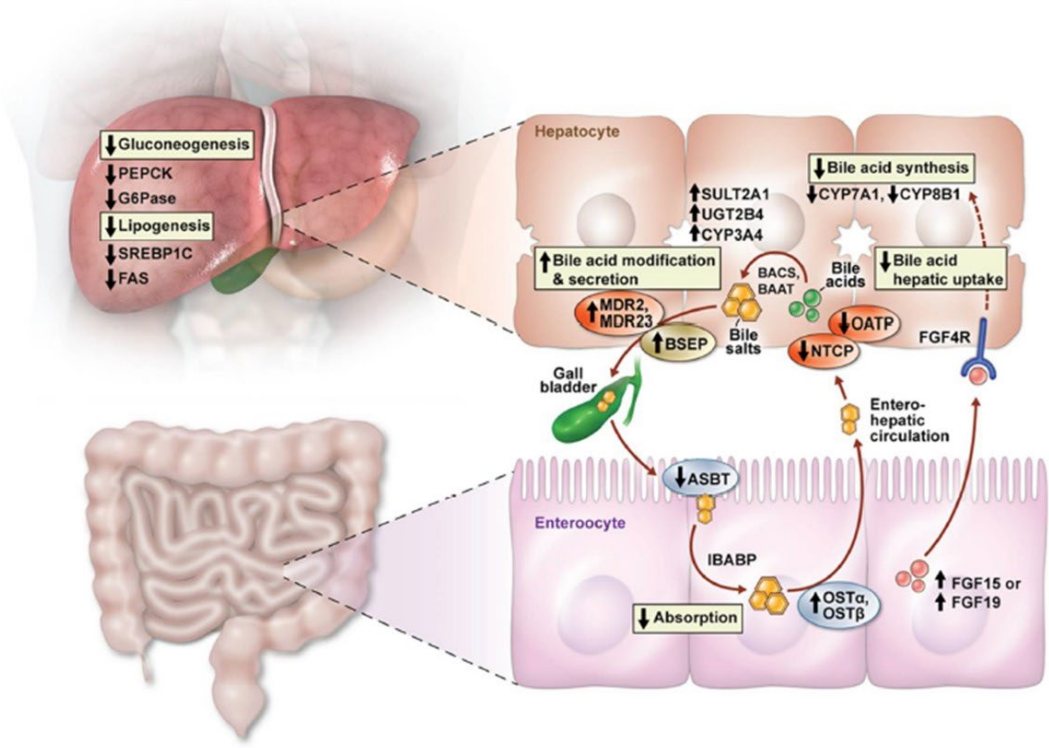
Several studies have been conducted with Vitamin E and thiazolidinediones in patients with NASH, but no long-term benefits have been demonstrated in prospective studies (Sanyal et al 2004). There are a number of agents currently in various stages of testing for the treatment of NASH but no therapy has been approved to date.

Pharmacological activation of the farnesoid X nuclear receptor (FXR) has been proposed as a therapeutic target for NASH (Cariou 2008, Porez et al 2012).

### 1.1.2 Farnesoid X Nuclear Receptor (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 gluconeogenesis and lipogenesis (Figure 1-1) (Pattni et al 2012, Walters et al 2015). In the liver, FXR activation 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 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 2003, Calkin and Tontonoz 2012). 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. (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 phase 2b (FLINT) trial, it was shown that 45% of NASH patients receiving 25 mg OCA once daily for 72 weeks had improved liver histology compared to 21% of NASH patients receiving placebo in the same period (NeuschwanderTetri- et al 2015). In a phase 3 study (REGENERATE), at 72 weeks, treatment with OCA 25 mg improved liver fibrosis (≥1 stage) with no worsening of NASH (p=0.0002) and dose dependent reduction of ALT, AST and GGT was observed, demonstrating consistent efficacy with an overall AE profile similar to previous studies. (Youinossi 2019)

### 1.1.3 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 clinical studies. The investigator's brochure (IB) provides a detailed review of the pre-clinical and clinical information on tropifexor available to date.

As of 05-Aug-2020 (LJN452 investigator's brochure Edition 11), 181 healthy volunteers, and 17 participants with primary bile acid diarrhea in CLJN452X2202 received tropifexor. In

CLJN452X2201, 40 primary biliary cholangitis (PBC) participants were treated with tropifexor at doses ranging from 30 to 150 µg daily. In Parts A and B of the CLJN452A2202 study, 152/198 NASH participants received tropifexor. Analysis of the Part C data of this trial, in which 101/152 participants received tropifexor, is ongoing.

Human safety and tolerability, PK and pharmacodynamic data are available from the First-in-Human study CLJN452X2101. In healthy volunteers the administration of tropifexor once daily for up to 14 days was generally well tolerated. Isolated asymptomatic and reversible elevations in ALT were observed at 100 µg dose and resolved after dose discontinuation. No significant findings in physical exam, vital signs or ECGs have been related to tropifexor; no adverse events related to itch were observed in CLJN452X2101. PK data were consistent with once daily dosing. Human PD data show that after single doses in healthy volunteers, there were dose-dependent increases in FGF19 from 10 to 1000 µg tropifexor. After multiple doses, a maximal mean serum FGF19 was observed at 6 hours after administration of 60 µg tropifexor consistent with likely pharmacological effect.

CLJN452A2202 (FLIGHT-FXR) is an adaptive 3-part Phase 2 study of tropifexor in participants with phenotypic or biopsy-confirmed NASH, 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. In Parts A and B of study CLJN452A2202, one hundred fifty two participants received tropifexor at doses ranging from 10 to 90 µg daily for 12 weeks. [redacted] ALT, hepatic fat fraction by MRI-PDFF, and body weight also improved in a dose dependent manner compared to placebo. Preliminary evaluation indicates that these early changes continued through Week 48 with a clinically meaningful dose response in reducing ALT, a sustained reduction of GGT, Clinically meaningful reduction in Hepatic Fat Fraction, and dose dependent and continued reduction in body weight versus placebo for both 140 µg and 200 µg tropifexor.

Tropifexor was generally well tolerated at all doses without safety signals of concern. Pruritus was reported in the 60 µg, 90 µg, 140 µg, 200 µg, and placebo arms and the frequency was dose dependent. The majority of pruritus events were Grade 1 (mild) in severity. Dose-related increases in LDL-C and decreases in HDL-C were observed by Week 12 with no subsequent worsening. Tropifexor did not affect triglyceride levels.

Based on Data Monitoring Committee (DMC) recommendation and PK/PD modeling, 140 µg and 200 µg daily doses are being tested in Part C (last participant/first treatment on 11 April 2019) to complete the broad dose finding approach in this study. Study duration for Part C is 48 weeks and paired liver biopsies, at Baseline and at Week 48 were performed. The Week 12 analysis of the CLJN452A2202 part C data revealed clear and significant dose response in ALT, PDFF, GGT and body weight reduction which continued through Week 48. The overall rate of adverse events and SAEs was similar across treatment groups, with an increase in pruritus with high dose tropifexor compared to placebo. CLJN452A2202 data were reviewed by the DMC approximately every 6 months, without revealing any significant safety concern to date.

In summary, in clinical studies tropifexor has been well tolerated to date, with doses currently being tested up to 200 µg orally in the ongoing Part C of CLJN452A2202 study.

During the course of this ongoing CLJN452D12201C study tropifexor (and its matching placebo) has been offered in two forms; a) initially as 3 hard gelatin capsules containing 10, 30 and 100 µg tropifexor (or matching placebo) and b) to reduce the pill burden for the participants, as a single hard gelatin capsule containing 140 µg tropifexor (or matching placebo). This change in capsule number is not expected to alter the absorption of tropifexor since the same formulation principle is used for all dose strengths (10, 30, 100 and 140 µg): dry blend in hard gelatin capsule using the same excipients. As a result, and considering the cumulative tropifexor PK data to date including an approximately dose proportional increase in key PK parameters over a wide range of doses and dose strengths (CLJN452X2101). No effect on PK from this change in product form is expected.

### 1.1.4 Licogliflozin

Licogliflozin is a selective and potent inhibitor of the sodium glucose co-transporters (SGLTs) 1 and 2 that decreases absorption of glucose in the gut and reabsorption in the kidney (Chao and Henry 2010). In the normal state, 90% of the filtered glucose is reabsorbed by SGLT2 in the proximal convoluted tubule cells of the kidney, with the remaining 10% reabsorbed by the SGLT1. Inhibition of SGLT2 results in glucosuria, decreased blood glucose and modest weight loss in healthy participants and participants with T2DM (Bays 2013). In addition to expression in the kidney, SGLT1 is also expressed in the small intestine where it is required for glucose and galactose absorption. Thus, inhibition of enteric SGLT1 results in reduction of glucose and galactose absorption (Turk et al 1991) which results in calorie wasting and other potential endocrine-based weight loss mechanisms. Combined SGLT1 and SGLT2 inhibition therefore offers the potential for improved efficacy over SGLT2 selective inhibitors in both lowering blood glucose and body weight.

Licogliflozin was administered to 76 healthy participants in the US, 36 healthy participants in Japan. Single doses of up to 350 mg and repeated doses of up to 300 mg/day for 14 days in healthy participants were generally safe and tolerated. Licogliflozin was also administered to 41 participants with T2DM and 127 obese participants in the US.

In study CLIK066X2101, single and multiple doses of licogliflozin induced glucosuria in healthy volunteers (HVs) and participants with T2DM, and significantly lowered glucose area under the time-concentration curve (AUC) after an oral glucose tolerance test (OGTT) in participants with T2DM. Licogliflozin was found to be tolerated, had in both healthy participants and participants with T2DM.

Treatment of normoglycemic and dysglycemic obese participants with 150 mg qd licogliflozin for 12 weeks in CLIK066X2201 was shown to be safe, and resulted in 5.7% reduction in body weight. Diarrhea was observed as a potential dose-limiting side effect in this study (He et al 2019). These studies are summarized in the LIK066 IB.

Additionally, in the CLIK066B2201 dose finding study in obese or overweight adults in North America and Europe to evaluate weight loss after 24 weeks, 460 participants were randomized to either placebo, QD doses ranging from 2.5 to 150 mg, or BID doses ranging from 2.5 to 50 mg. After 24 weeks of treatment, there was a dose dependent reduction in body weight, with change from baseline of -3.6% in the 50 mg qd group and -4.6% in the 150 mg QD group. In the CLIK066B1201 dose finding study to evaluate weight loss after 12 weeks in Japanese obese participants, 126 participants were randomized to either placebo or doses ranging from 2.5 to

50 mg QD. After 12 weeks, there was a dose dependent reduction in body weight, with change from baseline of -3.41% in the 25 mg group and -3.80% in the 50 mg group.

CLIK066X2204 study tested licogliflozin at doses of 30 and 150 mg for 12 weeks in NASH participants. Results from full study population confirmed that treatment with licogliflozin at 150 mg and 30 mg per day resulted in dose-dependent improvements in markers of liver injury (ALT, AST and GGT) and liver fat content. (LIK066 IB Edition 12) The study clinical report is currently in preparation. Both doses of licogliflozin led to significant placebo adjusted weight loss at the 150 mg and 30 mg doses respectively (LIK066 IB). Licogliflozin treatment also improved glycemic and insulin sensitivity markers; HbA1c and HOMA-IR at both doses. The most common AE was diarrhea, reported by similar number of participants in the placebo and 30 mg groups but at a higher rate in the 150 mg dose group. As in previous studies with licogliflozin, diarrhea was mostly mild in the participants who had it. Only one participant in the 150 mg dose group discontinued treatment as a result of diarrhea.

In summary, in clinical studies, licogliflozin has been well tolerated to date, resulting in improvements in markers of liver injury, hepatic fat, and weight loss with doses tested up to 150 mg orally in the CLIK066X2204 study.

### 1.1.5 Biological rationale for the combination of tropifexor and licogliflozin

Tropifexor and licogliflozin impact distinct targets affecting different nodes of NASH pathophysiology as evidenced by the following data in the tropifexor (LJN452) and licogliflozin (LIK066) Investigator's Brochures:

- Tropifexor activates a nuclear receptor (FXR) that has pleiotropic downstream effects in the liver.
- Licogliflozin inhibits two closely related glucose cotransporters (SGLT1 and 2) in the gut and kidney.
- Both compounds are potent and highly specific for their targets.
- FXR is not associated with changes in SGLT1 or SGLT2 expression or activity, and there is no known downstream intersection of the two pathways.
- Tropifexor specifically increases the enterocyte hormone fibroblast growth factor 19 (FGF19) that has beneficial metabolic and anti-inflammatory effects. No such effect on FGF19 has been described for licogliflozin.

### 1.1.6 Drug interactions

#### 1.1.6.1 Tropifexor

Based upon in vitro investigations as well as a human absorption, distribution, metabolism, and excretion (ADME) study (CLJN452A2101), tropifexor metabolism in humans is catalyzed by multiple uridine 5'-diphosphoglucuronosyltransferases (UGTs), predominantly UGT1A1 and UGT1A3 as well as oxidative metabolism by cytochrome P450 CYP3A4 [DMPK 1809219-01, DMPK R1900333]. Recent clinical data with a UGT1A1 inhibitor indicate no clinically relevant effect of UGT1A1 inhibition on tropifexor pharmacokinetics (PK). Glucuronidation is likely still a relevant clearance pathway for tropifexor but it is typical for inhibition of glucuronidases to have small or negligible clinical effects (Williams et al 2004). Strong CYP3A4 inhibitors and inducers are prohibited in this study. A clinical study (CLJN452A2103) assessing the effect of

strong CYP3A4 inhibitors and inducers on tropifexor PK has been completed after initiation of this trial and confirmed the expected interaction: the strong CYP3A4 inhibitor itraconazole increased the AUC of tropifexor by 47%; the strong CYP3A4 inducer rifampin decreased the AUC of tropifexor by 77-79%.

Tropifexor is not a substrate of any major transporter including organic anion transporting polypeptide OATP1B1, OATP1B3, OATP2B1, organic cation transporter OCT1, P-glycoprotein (P-gp also known as multidrug resistance protein 1), breast cancer resistance protein (BCRP), and multidrug resistance-associated protein 2 (MRP2). Tropifexor at 140 µg QD is not anticipated to act as a perpetrator leading to classical drug-drug interaction (DDI) (i.e. via inhibition of drug metabolism enzymes or drug transporters). While in vitro inhibition of CYP3A4, UGT1A9 and UGT2B7 by tropifexor was observed, due to the low expected Cmax,ss (steady state) (0.01 µM at 140 µg QD) no effect on licogliflozin PK is expected see Section 1.1.6.3.

### 1.1.6.2 Licogliflozin

Based on the human absorption, distribution, metabolism, and excretion (ADME) study and in vitro investigations, licogliflozin is eliminated predominantly via metabolism including direct glucuronidation (UGT1A9, UGT2B4/2B7) and oxidation (mainly by CYP3A4).

Strong CYP3A4 inhibitors and inducers as well as broad UGT inhibitors are prohibited in this study to exclude a potentially relevant effect on licogliflozin PK. Licogliflozin is not an inhibitor of CYP enzymes including CYP3A4 and is also unlikely to induce drug metabolizing enzymes via PXR activation. Licogliflozin inhibits UGT1A1 with IC50 values of 23 µM (total) and 19.7 µM (unbound). No clinically relevant effect on UGT1A1 is expected at 30 mg QD, the dose to be utilized in the proposed combination study with tropifexor, since Cmax,ss is at least 10 fold below IC50. Licogliflozin is a substrate of P-gp, but not of MRP2 and BCRP. Licogliflozin did not inhibit the transporters P-gp, BCRP, MRP2, organic anion transporter 1 (OAT1) and OCT1 and was a poor inhibitor of OATP1B1, OATP1B3, OAT3, OCT2, the multi-anion and toxin extrusion transporter 1 and multi-anion and toxin extrusion transporter 2-K. Overall, licogliflozin has a low potential to act as perpetrator of pharmacokinetic (PK) drug interactions and no effect on tropifexor PK is expected see Section 1.1.6.3.

Due to the very low dose of tropifexor relative to licogliflozin, an impact of licogliflozin on tropifexor solubility could influence its absorption and PK. However, a theoretical assessment of physicochemical properties does not point to an interaction within the gastrointestinal tract, specifically a complex formation is not expected since the two molecules do not bear opposite charges over the intestinal pH range.

### 1.1.6.3 Drug interaction between tropifexor and licogliflozin

The pharmacokinetic drug interaction between tropifexor (140 µg) and licogliflozin (50 mg) was investigated in study CLJN452E12101. (LJN452 IB Edition 11) Preliminary data from this study confirm the absence of a clinically relevant pharmacokinetic drug interaction between these 2 drugs. In the presence of licogliflozin, mean peak plasma concentration (Cmax,ss) of tropifexor decreased by 15% and total exposure (AUCtau,ss) decreased by 13%. In the presence of tropifexor, mean peak plasma concentrations of licogliflozin increased by 8% and total exposure increased by 12%. The small observed changes are within the 0.8-1.25 range and therefore below the effect generally considered a weak drug interaction.

### 1.1.7 Toxicology of tropifexor

Single oral administration of tropifexor did not cause severe acute toxicity.

Tropifexor was also evaluated in oral gavage toxicology studies up to 1 month in mice, 26 weeks in rats, and 39 weeks in dogs.

Below is a summary of the major findings, their adversity and clinical relevance:

- Pharmacological effects (direct and indirect) of clinical relevance:
  - Reversible and non-adverse alterations in serum chemistry parameters were noted at most dose levels in all species, including but not limited to decreases in bile acids, alterations in cholesterol and triglycerides and increases in fibrinogen, blood urea nitrogen (BUN) and alkaline phosphatase (ALP) (intestinal and hepatic isoforms).
- Pharmacological effects (direct and indirect) of limited clinical relevance:
  - In the small and large intestine, reversible clinical signs (abnormal feces and emesis/vomiting) and microscopic findings occurred in rats and dogs at doses ≥0.1 mg/kg/day, becoming dose-limiting at 0.5 mg/kg/day in rats and 0.1 mg/kg/day in dogs. Intestinal effects in animals likely resulted from pharmacological interferences with intestinal bile acid transporters leading to an increase in fecal bile acids, with the dog likely being the most sensitive species due to the higher percentage of intestinal taurocholic acid (a bile acid known to produce mucosal damage).
  - In the liver, hepatocellular hypertrophy occurred in mice at doses ≥0.1 mg/kg/day, rats at doses ≥0.03 mg/kg/day and dogs at doses ≥0.01 mg/kg/day. Hepatocellular hypertrophy was adverse in mice at doses ≥0.3 mg/kg/day and in rats and dogs at doses ≥0.1 mg/kg/day based on the consequential injury to the hepatobiliary tree (hepatocellular necrosis and/or bile duct hyperplasia and/or eosinophilic foci). This change was associated with a minimal hypertrophy/vacuolation of the gall bladder epithelium in male dogs at 0.1 mg/kg. Hepatocellular hypertrophy likely represents an adaptive response to high hepatic concentration of enzyme-inducing drugs (via FXR agonism, indirect nuclear receptor agonism) of limited clinical relevance.
  - In the kidney, vacuolation (at ≥ 100 mg/kg/day, consistent with lipid and likely reflecting pharmacological alteration in the lipid metabolism) and increased mitotic activity (at 1 mg/kg/day) were noted in the proximal convoluted tubules in short term studies in rats. Basophilic tubules were observed at doses ≥ 0.01 mg/kg/day at 13 weeks but not at 26 weeks at similar doses. Reversible increases in creatinine (with or without tubular basophilia) also occurred at doses ≥ 0.1 mg/kg/day. Although adverse to the rat, renal tubular effects are monitorable, reversible and potentially of low clinical relevance given their absence in dogs at higher systemic exposures.
- Pharmacological effects (direct and indirect) of no clinical relevance:
  - Reversible increases in total bilirubin (TBL) (primarily due to indirect/unconjugated bilirubin) occurred in rats at doses ≥ 1 mg/kg/day. Although adverse to rats by their severe magnitude, bilirubin increases are not relevant to humans based on the mode of action (i.e. interferences by high and clinically-irrelevant hepatic concentrations of tropifexor on bilirubin transport/metabolism via UGT-1A inhibition).
  - Reversible increases in calcium and inorganic phosphorus, occasionally accompanied by an increased incidence in renal mineralization, occurred in rats at

doses ≥0.1mg/kg/day. Renal mineralization is considered to reflect a pharmacological (increased Vitamin D receptor activity) exacerbation of a background finding unique to rats.

The no observed adverse effect level (NOAEL) was 0.03 mg/kg/day in both the 26-week rat and the 39-week dog toxicity studies. The systemic exposure at the rat NOAEL was mean AUC0-24h 27.1 ng.hr/mL and at the dog NOAEL was mean AUC0-24h 274 ng.hr/mL. Based on the nature of the non-clinical findings, their monitorability and reversibility and the fact that the dog appears to be the most relevant species for risk assessment, the intended clinical trial design, using the selected dose of 140 µg tropifexor, is not considered to pose an undue risk to participants.

### 1.1.8 Toxicology of licogliflozin

The principal target organs of toxicity identified in oral studies in rats (up to 26 weeks in duration) and/or dogs (up to 39 weeks in duration) were the gastrointestinal (GI) tract, kidney, urinary tract, bone, liver and adrenal gland; effects in these systems were considered related, if indirectly, to inhibition of SGLT1/2. In both species, reduced body weight gain was observed at almost all doses and weight loss occurred at the highest doses evaluated.

Rats tolerated licogliflozin at doses up to 100 mg/kg for 4 weeks, with reversible weight loss and 1 death at the high dose; doses up to 30 mg/kg were tolerated for 26 weeks.

Dogs did not tolerate doses ≥10 mg/kg for prolonged periods (i.e. ≥6 weeks) due to body weight loss, fecal changes and dehydration. The no observed adverse effect level (NOAEL) for licogliflozin was 5 mg/kg/day in the rat and 0.5 mg/kg/day in the dog.

As expected, dose-dependent glucosuria was observed in non-clinical toxicology studies. Renal tubular dilatation was observed in mice (doses ≥ 10 mg/kg/day; 26-week study), rats (doses ≥ 5 mg/kg/day; 13 and 26 week studies) and dogs (doses ≥ 5 mg/kg/day; 13 and 39 week studies) and accompanied by elevations in urinary renal injury biomarkers and urinary microalbumin and protein, which all showed evidence of reversibility following an extended 16-week recovery period. In the highest dose group of rats (100 mg/kg; 4 week study), renal inflammation was observed and was associated with micro-calcifications and elevation in urinary renal injury biomarkers. At higher non-tolerated doses in dogs, licogliflozin administration resulted in ascending pyelonephritis (doses ≥ 10 mg/kg/day but only in 4 week study where urine was collected by catheterization). Increases in urinary calcium, phosphate and magnesium, and decreased serum phosphorus and magnesium were present in both rats and dogs.

Dose-dependent soft stool or diarrhea was observed in both rats and dogs (at doses ≥ 100 mg/kg/day and ≥ 1.5 mg/kg/day, respectively), and cecum hyperplasia was observed in rats. Dose-dependent liver glycogen depletion (dogs) and liver cytoplasmic rarefaction attributed to glycogen accumulation (rats) were observed. Minimal increases (< 2 fold) in transaminase activity were present at high doses in the 4-week rat and dog studies and in the 13-week rat study. Dose-dependent, slight, reversible increases in trabecular bone were observed in rats in repeated dose studies up to 13 week in duration at doses ≥ 5 mg/kg/day, and were associated with increased bone ALP, and decreased serum osteocalcin, vitamin D and parathyroid hormone (PTH). No microscopic bone changes were present in the 26 week oral study in rats,

which examined similar dose levels, and microscopic bone changes were not observed in the dog.

In vitro studies indicate that licogliflozin is not mutagenic or clastogenic. Licogliflozin is considered an aneugen based on in vitro and in vivo data. At the maximal dose for phase 2 studies (150 mg), licogliflozin is not considered likely to pose an aneugenic risk for human participants.

In embryo-fetal development studies conducted in rats and rabbits, no teratogenicity was observed in either species. Fertility was unaffected in studies conducted in rats. Results of a six months carcinogenicity study with licogliflozin in a transgenic mouse model indicates that oral administration of licogliflozin had no effect on survival and showed no evidence of carcinogenic potential.

Based on the nature of the non-clinical findings, their monitorability and reversibility, the intended clinical trial design, using the selected dose of 30 mg licogliflozin, is not considered to pose an undue risk to participants.

### 1.1.9 Toxicology of the combination

Licogliflozin and tropifexor were administered in combination daily via oral gavage to rats for at least 13 weeks to assess the reversibility, persistence, or delayed occurrence of any effects after an 8 week recovery phase (Study 1770788).

Licogliflozin / tropifexor-related clinical observations included mucoid feces and yellow discoloration of the perineal skin and hair coat on Day 2 of the dosing phase for females administered 30/0.1 mg/kg/day licogliflozin / tropifexor. This was transient and, thus, considered tolerated.

Most changes in hematology and serum chemistry were consistent with what was previously observed with either licogliflozin or tropifexor and mostly related to the pharmacology of either compound, with the exception of 2 males administered 30/0.1 mg/kg/day, who had slightly decreased blood pH and slightly elevated ALP.

At the terminal sacrifice, all the microscopic changes were consistent with the ones previously observed with tropifexor and licogliflozin. The primary target organs observed microscopically were the liver, kidney, bone, spleen and gastrointestinal tract and were similar in the combination study compared to the single agent studies. However, there was a slight increase incidence of mucosal hyperplasia in the cecum and colon of animals at 30/0.1 mg/kg/day licogliflozin /tropifexor.

In conclusion, daily oral (gavage) administration of licogliflozin alone or in combination with tropifexor for 13 weeks was tolerated up to 30 mg/kg/day (licogliflozin) and 30/0.1 mg/kg/day (licogliflozin / tropifexor). The potential combination effects seem to be consistent with the pharmacological effect of each of the components.

### 1.1.10 Rationale for testing the combination of tropifexor and licogliflozin

The rationale for evaluating the combination of tropifexor 140 µg and licogliflozin 30 mg daily is based on the following:

1. Each of the drugs used as monotherapy has been shown to have potential benefits in treating NASH based on the data available from non-clinical studies,

preliminary data in NASH participants for both tropifexor and licogliflozin, and a general knowledge about the mechanisms of action of FXR agonists and SGLT1/2 inhibitors. The biologic pathways, not overlapping, are therefore expected to complement each other and address the three main pathologic features of NASH, namely steatosis, inflammation and fibrosis.

2. Based on all preclinical and clinical data for tropifexor and licogliflozin available to date, there are no anticipated safety, tolerability or pharmacokinetic concerns combining these two drugs at the doses tested in this study.
3. The risk to participants in this trial will be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring.

## 1.2 Purpose

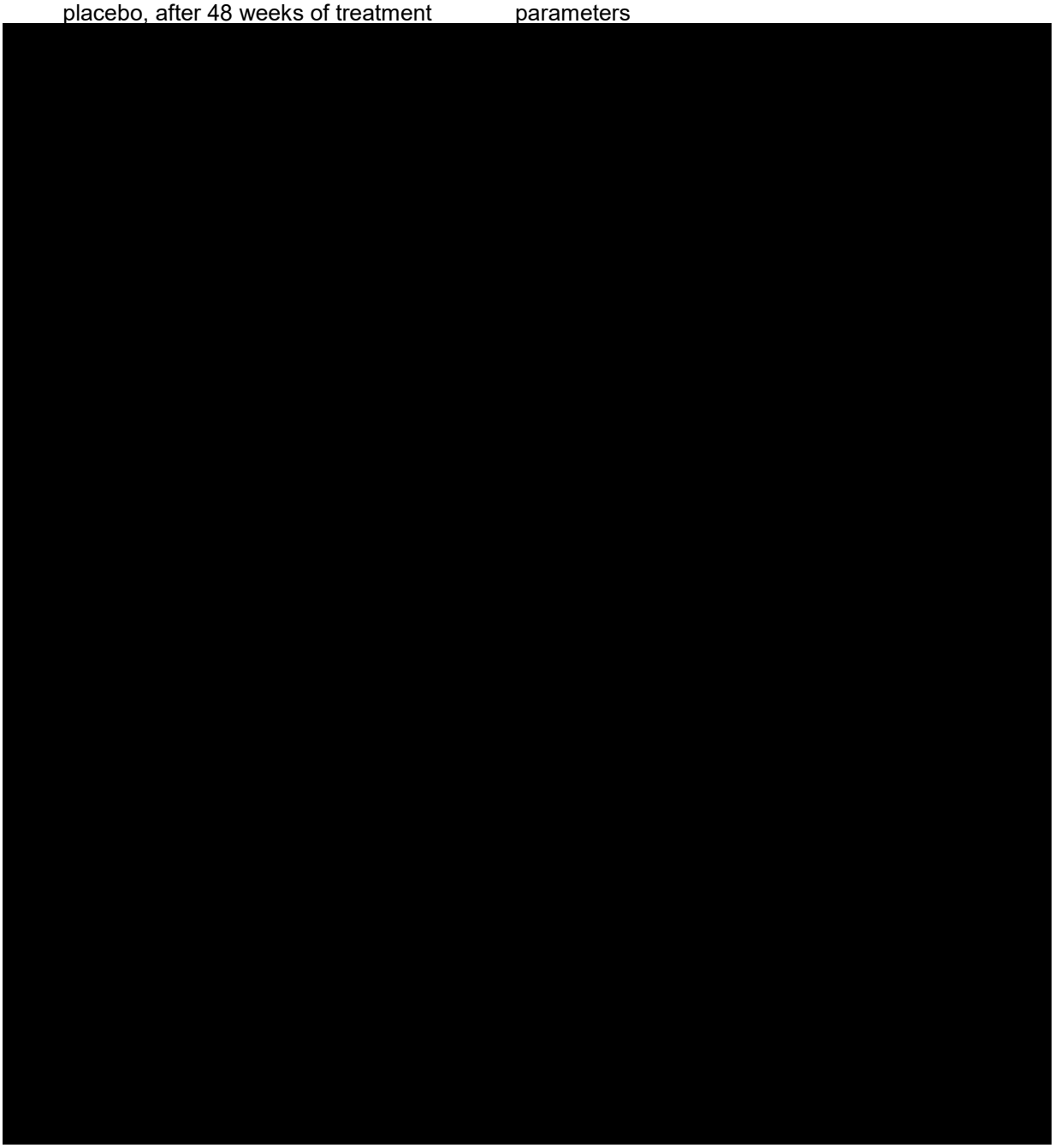
The purpose of this study is to compare tropifexor and licogliflozin in combination therapy and each monotherapy to placebo for efficacy, safety, and tolerability in participants with NASH and liver fibrosis (stage 2 or 3) as per NASH clinical research network (CRN) histological score.

# 2 Objectives, endpoints and estimands

**Table 2-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To evaluate the efficacy of tropifexor + licogliflozin in combination therapy and each monotherapy treatment, as assessed by histologic improvement after 48 weeks compared to placebo in participants with NASH and stage 2 or 3 fibrosis. | • Whether the participant achieves at least one stage of improvement in fibrosis without worsening of NASH at Week 48 compared to Baseline<br>• Whether the participant has resolution of NASH without worsening of fibrosis at Week 48 compared to Baseline |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To evaluate the efficacy of combination therapy and two monotherapies in NASH or fibrosis with a composite endpoint after 48 weeks of treatment. | • **Key secondary endpoint:** Whether the participant achieves resolution of NASH and no worsening of fibrosis OR improvement in fibrosis by at least one stage without worsening of NASH at Week 48 compared with Baseline. |
| • To evaluate improvement in fibrosis by at least one stage after 48 weeks of treatment. | • Whether the participant has at least one stage improvement in fibrosis at Week 48 compared with Baseline |
| • To evaluate improvement in fibrosis by at least two stages with no worsening of NASH after 48 weeks of treatment | • Whether the participant has at least two stage improvement in fibrosis without worsening of NASH at Week 48 compared with Baseline |
| • To evaluate reduction in body weight from Baseline after 48 weeks of treatment | • Whether the participant has 5% or more reduction in body weight at Week 48 compared to Baseline |
| • To evaluate change in liver fat content after 48 weeks of treatment | • Change in liver fat content based on MRI - PDFF (in 40% of participants) over time up to Week 48 compared with Baseline |

| Objective(s) | Endpoint(s) |
|---|---|
| • To evaluate the relationship of investigational treatment and markers of hepatic inflammation in NASH (ALT and AST) after 48 weeks of treatment | • Change in ALT and AST over time up to Week 48 compared with Baseline |
| • To evaluate the relationship of investigational treatment and GGT, a marker of cholestasis and oxidative stress after 48 weeks of treatment | • Change in GGT over time up to Week 48 compared with Baseline |
| • To evaluate the safety and tolerability of tropifexor (LJN452) in combination with licogliflozin (LIK066), and each monotherapy treatment, compared to placebo, after 48 weeks of treatment | • Occurrence of adverse events, serious adverse events, adverse events resulting in discontinuation of study treatment, adverse events of special interest and changes in vital signs and laboratory parameters |



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## 2.1 Primary estimands

The primary question of interest to be answered in the trial using liver histology is:

Does the combination therapy (tropifexor + licogliflozin), administered once per day in participants with NASH and stage 2 or 3 fibrosis over 48 weeks, lead to histologic improvement compared with placebo treatment?

This question gives rise to 2 primary estimands, due to 2 different endpoints of interest.

The first primary estimand has the following attributes with respect to the primary question:

- Treatment: The randomized treatment (the investigational combination therapy <tropifexor 140 µg + licogliflozin 30 mg> or the placebo) taken for 48 weeks, irrespective of administration or dose changes in anti-diabetic and lipid-lowering concomitant medication according to medical need. More details about the treatment are provided in Section 6
- Population: Participants with NASH (using NAFLD Activity Score (NAS) ≥ 4 with at least 1 point each in inflammation and ballooning on the screening histology assessment performed by the central reader) and stage 2 or 3 fibrosis (using NASH CRN fibrosis criteria), as defined by the inclusion and exclusion criteria of the study Section 5.
- Endpoint: Whether the participant achieves at least one stage improvement in fibrosis without worsening of NASH at Week 48 compared with Baseline.
- Summary measure: Odds ratio of the participants achieving at least one stage improvement in fibrosis without worsening of NASH, at Week 48 compared with Baseline, of the two treatments for each pairwise comparison.

The second primary estimand has the subsequent characteristics with respect to the primary question:

- Treatment: The randomized treatment (the investigational combination therapy <tropifexor 140 µg + licogliflozin 30 mg> or the placebo) taken for 48 weeks, irrespective of administration or dose changes in anti-diabetic and lipid-lowering concomitant medication according to medical need.
- Population: Participants with NASH and stage 2 or 3 fibrosis confirmed by biopsy, as defined by the inclusion and exclusion criteria of the study.

- Endpoint: Whether the participant has resolution of NASH and no worsening of fibrosis at Week 48 compared with Baseline.
- Summary measure: Odds ratio of the participants obtaining resolution of NASH and no worsening of fibrosis, at Week 48 compared with Baseline, of the two treatments for each pairwise comparison.

If the answer to the primary question is yes, additional questions may be assessed:

Does the monotherapy (tropifexor OR licogliflozin) alone, taken once per day by participants with NASH and stage 2 or 3 fibrosis over 48 weeks, result in histologic improvement compared with placebo?

If the answer to this question is yes as well, then another question will be evaluated:

Does the combination therapy lead to more histological improvement than monotherapies?

For each primary estimand, the population, endpoint, and summary measure for the additional questions are the same as those for the primary question. Only the treatment will change accordingly. For the first additional question, the treatment of interest would be monotherapy and the control would be placebo, whereas for the second additional question, the treatment of interest would be combination therapy and the control would be monotherapy.

Intercurrent events of primary estimand will be addressed with various strategies (considering that these events occur before the histological assessments at Week 48):

1. Bariatric surgery: participants who have undergone bariatric surgeries during trial participation are considered as non-responders (composite variable strategy).
2. Use of alcohol above protocol permitted amount: the intercurrent events (overuse of alcohol) will be ignored for estimation (treatment policy strategy).
3. Addition or removal of any medication that may have a confounding effect on the endpoints: the treatment effect will be assessed with the intercurrent event ignored (treatment policy strategy); in the supplementary analysis, the treatment effect will be imputed as if the intercurrent event doesn't occur (hypothetical strategy)
4. Premature discontinuation of study treatment due to tolerability, efficacy, adherence, or adverse event: participants who discontinue the treatment after Week 24 will be asked to have their biopsies assessed at Week 48 regardless of the intercurrent event (treatment policy strategy), participants who discontinue the treatment before Week 24 will be considered as non-responders (composite variable strategy), and participants who have no biopsy extracted at Week 48 will be considered as non-responders (composite variable strategy).
5. Death, transplantation and other clinical outcomes: participants will be considered as non-responder (composite endpoint strategy).
6. Acute medical condition not related to the study treatment affecting the liver: participants will have their Week 48 biopsies assessed regardless of the intercurrent events (treatment policy strategy).
7. Acute medical condition related to the study treatment affecting the liver: participants are considered as non-responder (composite endpoint strategy).

# 3 Study design

This is a randomized, double-blind, parallel-group, multiple-arm study to assess the efficacy, safety and tolerability of tropifexor and licogliflozin combination therapy, and each monotherapy compared with placebo as well as the combination therapy compared to each monotherapy, in participants with NASH and fibrosis.

The study consists of 1) a screening period, 2) a treatment period starting from randomization on Day 0 and running to Week 48, and 3) a follow-up period of 4 weeks after the last dose of study treatment. Optional pre-screening should also be considered (Section 8.1.1). The screening period starts from the time of the first assessment after signing of informed consent and continues for up to 10 weeks when all inclusion/exclusion criteria have been evaluated and all Baseline assessments have been performed. The study duration from first dose of study medication is 52 weeks. The total duration of participation may be up to 62 weeks.

Approximately 380 participants with NASH (NAS ≥4) and fibrosis stage 2 or 3 will be randomly assigned to one of the following treatments:

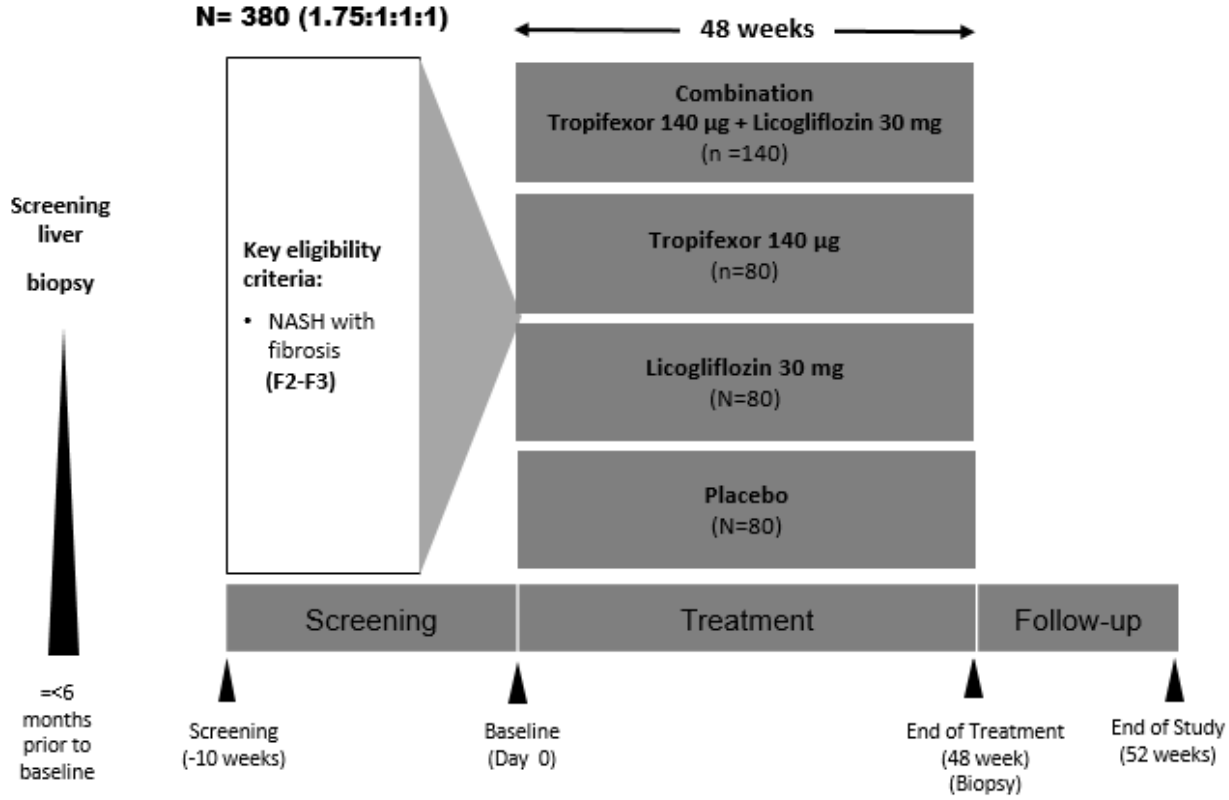
**Arm A**: Combination therapy Arm - (N=140): tropifexor 140 µg + licogliflozin 30 mg, once daily.

**Arm B**: Tropifexor monotherapy Arm - (N=80): tropifexor 140 µg (+ placebo matching licogliflozin), once daily.

**Arm C**: Licogliflozin monotherapy Arm - (N=80): licogliflozin 30 mg (+ placebo matching tropifexor), once daily.

**Arm D**: Placebo Arm – (N=80): placebo matching tropifexor + placebo matching licogliflozin once daily.

**Figure 3-1 Study Design**




# 4 Rationale

## 4.1 Rationale for study design

NASH is a complex disease with the involvement of multiple pathways. Combination therapy with tropifexor (multimodal effect with anti-steatotic, anti-inflammatory and anti-fibrotic properties) and licogliflozin (weight loss through calorie wasting from gut and kidney, better glycemic control, decrease in de novo liver lipogenesis) is expected to result in greater efficacy and higher number of responders than monotherapy. Each drug works through a different mechanism of action, thus allowing potential additive or complementary beneficial effects.

This study is designed as a randomized, double-blind, parallel-group, multi-center, fixed-dose, phase 2 study to assess the efficacy, safety and tolerability of the combination of tropifexor and licogliflozin and each compound as monotherapy compared to placebo as well as the combination therapy compared to each monotherapy, in participants with NASH F2-F3. The primary endpoint is histology-based (whether the participant achieves resolution of NASH and no worsening of fibrosis, OR improvement in fibrosis by at least one stage with no worsening of NASH at Week 48 compared to Baseline). With supportive key secondary histology endpoints and with acceptable safety and tolerability, this study will inform further development of the combination in NASH participants (i.e. this is a Phase 3 enabling study).

## 4.2 Rationale for dose/regimen and duration of treatment

The doses and dosing regimens of licogliflozin and tropifexor are chosen in this study to reflect doses and dosing regimens currently under consideration or evaluation in monotherapy NASH studies. (See Section 6.7.2 for instructions on taking study treatment).

Tropifexor is currently being studied in NASH as monotherapy in study CLJN452A2202. The doses of 10 to 90 µg tropifexor have been tested and were well tolerated in CLJN452A2202 Parts A and B, with an observed dose dependent elevation of FGF19, and reduction in liver fat content, ALT and GGT. CLJN452A2202 Part A biomarker data, suggested that exposures of AUC > 40 ng.hr/mL should be explored. At a dose of 140 µg tropifexor 80% of NASH participants are expected to achieve this threshold and it is therefore chosen as the reference dose for the monotherapy and the combination arms in this study. CLJN452A2202 is ongoing with doses of 140 µg and 200 µg once daily being tested in Part C. The Week 12 analysis of the CLJN452A2202 part C data revealed clear and significant dose response in ALT, PDFF, GGT and body weight reduction. The overall rate of adverse events and SAEs was similar across treatment groups, with an increase in pruritus with tropifexor compared to placebo.

Licogliflozin is currently being tested as 30 mg and 150 mg QD monotherapy in NASH (CLIK066X2204). An interim analysis showed promising reduction of ALT, AST, GGT, body weight, waist circumference, hemoglobin A1c and liver fat. The majority of AEs reported were GI in nature, specifically mild diarrhea. The incidence of diarrhea was similar between the placebo and 30 mg treatment groups. One participants in each treatment group discontinued study medication due to an AE. No SAEs have been reported in participants treated with licogliflozin in this study.

A range of doses from 2.5 to 150 mg licogliflozin have been tested in obese participants (both Japanese and non-Japanese). In obese Japanese participants over 12 weeks of treatment with placebo, 2.5, 10, 25 or 50 mg once daily licogliflozin, 30 mg appeared to be at the plateau of the observed dose-body weight loss curve. However, the rate of diarrhea events increased largely between 25 mg and 50 mg from about 14% to about 39% [CLIK066B1201]. In obese non-Japanese participants over 24 weeks of treatment with placebo, 2.5, 10, 50 or 150 mg once daily licogliflozin, 30 mg appeared to be near the plateau of the observed dose-body weight loss curve, and the incidence of diarrhea increased from about 16% to about 55% in the 10 mg and 50 mg treatment groups, respectively [CLIK066B2201]. Thus 30 mg is expected to have a similar body weight loss while considerably lower diarrhea incidence compared to 50 mg and is therefore preferred. Assuming that data from obese participants are indicative of NASH participants for both body weight loss and diarrhea events, as suggested by the 150 mg dose (with diarrhea events of 18/22 vs 52/77 for NASH vs obese participants), 30 mg is selected for this combination.

In summary, the doses for this study were selected based on the expectation of achieving increased efficacy with the combination therapy, compared to individual monotherapies, while maintaining tolerability and safety of the participants.

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

Currently there is no drug established as standard of care for participants with NASH. Combination of tropifexor and licogliflozin and each of these compounds as monotherapy will

be compared to placebo. Subsequently, the combination treatment will be compared to each of the monotherapies.

A placebo treatment group was added to improve the assay sensitivity and interpretation of the treatment effect given the wide variability observed in histological response in recent studies for those participants receiving standard of care.

## 4.4 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned for this study.

## 4.5 Risks and benefits

When used as monotherapy, tropifexor and licogliflozin have been shown to have potential benefits in treating NASH. Based on the mechanisms of action of FXR agonists and SGLT1/2 inhibitors and the fact that the biologic pathways do not overlap, it is expected that they will complement each other and address the three main pathologic features of NASH, namely steatosis, inflammation and fibrosis.

Appropriate eligibility criteria as well as specific stopping rules, are included in this protocol. Recommended guidelines for supportive management of study drug induced adverse events are provided in Section 10.2.

The risk to participants in this trial is minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, stopping rules and periodic review of safety data by an independent DMC.

Toxicology of the combination is described in Section 1.1.9. All potential risks of each compound are described in the tropifexor and licogliflozin IBs. A brief summary of the benefits and risks of each compound follows:

### 4.5.1 Tropifexor

Based on the mechanism of action of tropifexor as a highly potent and specific agonist of the Farnesoid X Receptor (FXR) and data acquired in nonclinical toxicology studies, the First-in-Human study CLJN452X2101, and the ongoing Phase 2b CLJN452A2202 study, the risk-benefit assessment of tropifexor is as follows:

#### 4.5.1.1 Benefits

Due to its multimodal mechanism of action, tropifexor treatment may have the anticipated benefits on biliary metabolism (reduced synthesis and increased detoxification), lipid distribution (lowering hepatic triglycerides accumulation) as well as anti-inflammatory and anti-fibrotic properties, leading to reduction of hepatic fibrosis and improvement of participant outcomes over longer term treatment. In study CLJN452A2202 in NASH, marked decreases in transaminases and in GGT, liver fat content and body weight were observed in a dose dependent manner, in participants receiving tropifexor compared to placebo.

#### 4.5.1.2 Risks

### Non-clinical

Liver effects: In rats, hepatic effects (hepatocellular vacuolation periportal hepatocellular hypertrophy, and bile duct hyperplasia as well as increases in FXR target gene for alkaline phosphatase expression) occurred at tropifexor doses ≥ 0.03 mg/kg/day in toxicity studies ranging from 2 weeks to 26 weeks in duration. All hepatic effects were either absent or decreased in incidence and severity by the end of the tropifexor-free recovery period indicating that full recovery would likely have been achieved with a longer recovery period. In addition, tropifexor was protective in various rodent models of liver disease/impairment including a model of drug-induced cholangiohepatitis and Alpha-naphthylisothiocyanate (ANIT) induced cholestasis.

### Normal healthy human volunteers

Transient and asymptomatic increases in ALT were observed in healthy volunteers. This ALT increase was rapid in onset and resolved despite continued dosing, indicative of adaptation in humans.

### NASH Participants

Of note, increases in transaminases similar to those observed in healthy volunteers were not seen in NASH participants in CLJN452A2202. Participants with impaired liver function and liver diseases other than NASH are excluded from the ELIVATE study (see exclusion criteria #9 and #10) and liver function tests including transaminases are monitored closely throughout study participation. Guidelines for the evaluation and detection of potential toxicities and for their management and for minimization of risk are discussed in the tropifexor IB and in Appendix 2 of this protocol.

Pruritus and lipid alterations (LDL-C elevation and HDL-C reduction) have been noted in clinical trials with FXR agonists (including tropifexor) and may be dose dependent. Both will be closely monitored in this study (please see the tropifexor IB for details).

Study CLJN452A2103 confirmed that the strong CYP3A4 inhibitor itraconazole increased the AUC of tropifexor by 47% and the strong CYP3A4 inducer rifampin decreased the AUC of tropifexor by 77-79% (Section 1.1.6.1). Therefore strong CYP3A4 inhibitors and inducers are prohibited during study participation (Section 6.2.2)

The Data Monitoring Committee (DMC) will review safety data at regular intervals throughout the study.

## 4.5.2 Licogliflozin

### 4.5.2.1 Benefits

Numerous lines of evidence, including data from a licogliflozin First–in-Human (FIH) clinical study CLIK066X2101, indicate that combining the effects of both SGLT1 and SGLT2 inhibition may offer more effective and safe treatment for obesity and diabetes via numerous mechanisms (Zambrowicz et al 2012). For example, SGLT2 inhibition increases urinary

glucose excretion in both healthy participants and participants with T2DM, and lower glucose levels occur without hypoglycemia due to an insulin independent mechanism of action (Komoroski et al 2009a). Clinical validation of SGLT2 inhibitors as therapeutic targets for T2DM has been firmly demonstrated, and these compounds are now in wide use for T2DM (Wilding et al 2009, Komoroski et al 2009b). Agents such as dapagliflozin and canagliflozin also have additional beneficial effects on blood pressure and body weight (decrease ~2-3% compared to placebo; Scheen and Paquot 2014). In support of the link between obesity and hepatic injury related to excess accumulation of fat in the liver, weight loss leads to improvement in histologic NASH. This suggests that targeting obesity in NASH participants is likely a therapeutic opportunity to limit or reverse liver disease progression (Lassailly et al 2015, Vilar-Gomez et al 2015).

Inhibition of SGLT1 in the gut results in additional numerous weight-lowering mechanisms including calorie wasting from the gut, lower postprandial insulin levels, and an increase in incretin hormone (GLP-1, PYY) release as a consequence of distal, unabsorbed glucose in the gut (Sadry and Drucker 2013). When dosed close to a meal, licogliflozin has more marked efficacy in lowering postprandial glucose, lowering insulin levels, and increasing incretin hormones than when administered 6 hours or more prior to a meal, suggesting that gut luminal exposure to licogliflozin is required for SGLT1 inhibition. The additional benefit of SGLT1 inhibition also carries the risk of diarrhea due to glucose malabsorption. The orally administered, dual SGLT1/2 inhibitor licogliflozin has demonstrated safety, tolerability and efficacy in obesity and diabetes (LIK066 IB, Edition 10).

CLIK066X2204 study tested licogliflozin at doses of 30 and 150 mg for 12 weeks in NASH participants. Results from full study population confirmed that treatment with licogliflozin at 150 mg and 30 mg per day resulted in dose-dependent improvements in markers of liver injury (ALT, AST and GGT) and liver fat content(LIK066 IB edition 12).The clinical study report is currently in preparation. Both doses of licogliflozin led to significant placebo adjusted weight loss at the 150 mg and 30 mg doses respectively. (LIK066 IB). Licogliflozin treatment also improved glycemic and insulin sensitivity markers; HbA1c and HOMA-IR at both doses.

#### 4.5.2.2 Risks

Risks of SGLT1/2 inhibition in human participants may include the development of diarrhea and genital and urinary tract infection (secondary to glucosuria). In study CLIK066X2204, the most common AE was diarrhea, reported by similar number of participants in the placebo and 30 mg groups but at a higher rate in the 150 mg dose group. As in previous studies with licogliflozin, diarrhea was mostly mild in the participants who had it. Only one participant in the 150 mg dose group discontinued treatment as a result of diarrhea (LIK066 IB Edition 12). Other potential risks based on reports with marketed SGLT2 inhibitors include hypoglycemia, Fournier's gangrene (necrotizing fasciitis of the genitalia and perineum), intravascular volume depletion, ketoacidosis, electrolyte disturbance and lower limb (toe) amputation. Appropriate exclusion criteria are applied in this study and guidance is provided to mitigate the risks as per Section 10.2.3. It is recommended that bilateral foot exams be performed at screening to assess the presence of any foot deformity (including amputation), disease, and/or the presence of clinically significant neuropathy that may increase the risk of amputation. Guidelines for the evaluation and detection of potential toxicities, their management and minimization of risk are discussed in detail in the LIK066 IB. The relatively low exposure associated with the dose of

licogliflozin proposed in this study has been tested and is deemed safe in healthy participants, T2DM participants, and obese participants.

### 4.5.3 Study conduct

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

Participants participating in this study might have reductions in hepatic fat and liver fibrosis; it is possible that this is a clinical benefit. For this reason, paired liver biopsies (Screening and Week 48) have been included in this study. Screening biopsies will confirm the diagnosis of NASH (steatosis, lobular inflammation, hepatocyte ballooning) and presence of fibrosis. The primary risks of liver biopsy are pain and bleeding from the site of needle entry into the liver, although the latter occurs in less than one percent of participants. Other possible major complications include the puncture of organs, such as the kidney, lung, colon, or the gallbladder. In order to reduce the risk of bleeding, the coagulation status must be assessed in all participants prior to a biopsy.

There may be participant benefit in the ancillary dietary and exercise counseling accompanying the pharmacologic intervention.

MRI makes use of powerful magnetic fields and radio waves, which are believed to cause no direct adverse consequences when used within approved specifications. No MRI-contrast will be administered in this study. Thus in principle, MRI scans can be repeated in the same participants 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.

## 4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by Local or Regional authorities, i.e,. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and should be permitted/approved by Local or Regional Health authorities and Ethics Committees as appropriate.

# 5 Study Population

The study population will consist of approximately 380 adult male and female participants with histologic evidence of NASH and fibrosis stage 2 or 3 as per NASH CRN histological score; see Inclusion and Exclusion criteria for details.

The study will be conducted in approximately 155 centers worldwide. Since a screening failure rate is expected to be around 70%, approximately 1267 participants may be screened.

The Investigator will ensure that all participants being considered for the study have met the eligibility criteria. No additional criteria should be applied by the investigator so that the study population will be representative of all eligible participants.

Participant selection will be established by checking through all inclusion/exclusion criteria at screening and Baseline. A relevant record of the eligibility criteria must be stored with the source documentation at the study center.

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

## 5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study.
2. Male and female participants 18 years or older (at the time of the screening visit)
3. Presence of NASH with fibrosis confirmed by central reader's evaluation of liver biopsy obtained no more than 6 months before randomization as demonstrated by the following:
    a. NASH using NAFLD Activity Score (NAS) ≥ 4 with at least 1 point each in inflammation and ballooning on the screening histology assessment performed by the central reader

    and

    b. Fibrosis stage 2 or 3 using NASH CRN fibrosis criteria (see Table 8-2 & Table 8-3)
4. Able to communicate well with the investigator, to understand and comply with the requirements of the study

## 5.2 Exclusion criteria

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

1. Taking medications prohibited by the protocol. (see Section 6.2.2, Table 6-3)
2. Pregnant or nursing (lactating) women.
3. Weight at Baseline changed by > 5% since qualifying liver biopsy.
4. History of hypersensitivity to either of the study drugs or their excipients or to drugs of similar chemical classes, or participants with hereditary galactose intolerance, lactase deficiency or glucose-galactose malabsorption.
5. Taking a permitted medication listed in Table 6-2 but who is NOT on a stable dose (within 25% of Baseline dose) from the start of the screening period and
    a. for at least 3 months prior to the Baseline visit for thyroid hormone, oral anti-diabetic medication, insulin, GLP-1 agonists, and estrogen or estrogen containing birth control
    b. for at least 6 months prior to Baseline for Vitamin E
6. Current, or history of, significant alcohol consumption for a period of more than 3 consecutive months within 1 year prior to screening.
    a. Significant alcohol consumption is defined as more than 20 g/day (14 units/week) in females, or more than 30 g/day (21 units/week) in males, on

average. A "unit" of alcohol is equivalent to one (12-ounce; 355 ml) beer, one glass (4-ounce; 120 ml) of wine, or 1 shot (ounce; 30 ml) of hard liquor.

or

b. A score on the alcohol use disorders identification test (AUDIT) questionnaire ≥ 8.

7. Diabetes related:
    a. Type 1 diabetes mellitus.
    b. Uncontrolled type 2 diabetes defined as HbA1c ≥ 9.0% at screening.
    c. HbA1c < 6.5% at screening in Type 2 diabetics currently treated with insulin or sulfonylureas.
8. Platelet count < LLN (see Central laboratory manual).
9. Clinical evidence of liver impairment as defined by the presence of any of the following abnormalities:
    a. Serum albumin < LLN (see Central laboratory manual).
    b. International Normalized Ratio (INR) > ULN (see Central laboratory manual).
    c. ALT or AST > 5× ULN (in either of the 2 values during screening).
    d. Total bilirubin > ULN (see Central laboratory manual) (in either of the 2 values during screening), including Gilbert's syndrome.
    e. Alkaline phosphatase > 300 IU/L (in either of the 2 values during screening).
    f. History of esophageal varices, ascites or hepatic encephalopathy.
    g. Splenomegaly.
    h. MELD score >12.
10. Other forms of chronic liver disease:
    a. Hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg).
    b. Hepatitis C as defined by presence of detectable hepatitis C virus (HCV) RNA.
    c. Autoimmune liver disease.
    d. Primary biliary cholangitis.
    e. Primary sclerosing cholangitis
    f. Wilson's disease.
    g. Alpha-1-antitrypsin (A1AT) deficiency.
    h. Hemochromatosis or iron overload.
    i. Drug-induced liver disease as defined on the basis of typical exposure and history.
    j. Bile duct obstruction.
    k. Suspected or proven liver cancer.
    l. Any other type of liver disease other than NASH.
    m. Hepatitis A as defined by presence of Immunoglobulin M (IgM) antibodies to HAV (IgM anti-HAV).
11. History of liver transplantation or planned liver transplant.
12. History of biliary diversion.

13. History or current diagnosis of ECG abnormalities based on Central ECG report indicating significant risk of safety for participants participating in the study such as:
    a. Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker.
    b. Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pre-treatment screening.
    c. History of familial long QT syndrome or known family history of Torsade de Pointes.
14. Medical history of pancreatitis (acute or chronic).
15. Amylase and/or lipase >3 X ULN.
16. Prior or planned (during study period) bariatric surgery.
17. Calculated eGFR < 60 mL/min/1.73m2 (using the MDRD formula).
18. Hyperkalemia defined as potassium level > 5.2 millimoles per liter (mmol/L)
19. Chronic (> 3 months) use of excessive doses of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) as evaluated by investigator.
20. Ketoacidosis, lactic acidosis, or hyperosmolar coma within six months of randomization.
21. History of lower limb amputation (including toe amputation) unless due to trauma.
22. Diabetic complications, known peripheral vascular disease or clinically significant neuropathy that may increase the risk of amputation.
23. Symptomatic genital or urinary tract infection within 4 weeks prior to randomization or participants with high risk as, determined by the investigator (including concomitant therapy with immunosuppressive potential), to be particularly susceptible to genital or urinary tract infection.
24. Recent history of gastrointestinal disorder associated with chronic diarrhea.
25. Any history of and/or suspected Fournier's gangrene, or participants with high risk as, determined by the investigator (including concomitant therapy with immunosuppressive potential), to be particularly susceptible to Fournier's gangrene.
26. Diabetic foot ulcer within 4 weeks prior to randomization.
27. History of inflammatory bowel disease (ulcerative colitis, Crohn's disease).
28. Known positivity for Human Immunodeficiency Virus (HIV) infection. HIV antigen/antibody tests will be performed to determine HIV status if allowed and required according to local regulations.
29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
30. History or evidence of ongoing drug abuse, within the last 6 months prior to randomization.
31. Use of other investigational drugs within 5 half-lives of randomization, or within 30 days, whichever is longer.

32. Previous exposure to any other investigational or recently (2019 onwards) approved NASH treatment within 6 months prior to qualifying biopsy (participants known to have only received placebo may be included).
33. ~~Sexually active males must use a condom during intercourse while taking drug and for 5 days after stopping investigational 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 study drug via seminal fluid.~~ (With-amendment version 01, this exclusion criterion is no longer applicable).
34. 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)** after stopping of investigational medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    c. Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
    d. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

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

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral 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.

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

35. Any other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study.

Exclusionary laboratory tests can be repeated for eligibility during the screening period if the sample is compromised or otherwise reasonably suspected of being inaccurate.

# 6 Treatment

## 6.1 Study treatment

### 6.1.1 Investigational and control drugs

The 140 µg dose of tropifexor and its matching placebo are each now available as a single hard gelatin capsule. Participating at the time of availability of the single tropifexor/placebo capsule, may continue on the 3-capsule tropifexor (100 µg + 30 µg + 10 µg) or matching placebo regimen described in protocol v01 until the available 3-capsule supply is depleted. After the 3-capsule supply is depleted, participants will take one 140 µg tropifexor or matching placebo capsule daily as described in Table 6-1. See Sections 6.1.3 and Section 6.7.2 for additional information regarding tropifexor dosing utilizing the 3 capsule and single capsule regimens. No change has been made to licogliflozin dosing.

**Table 6-1 Investigational and control drug**

| Investigational/ Control Drug (Name and Strength) | Pharmaceutical Dosage Form | Route of Administration | Presentation Type | Sponsor (global or local) |
|---|---|---|---|---|
| Tropifexor (LJN452) 140 µg | 140 µg hard gelatin capsule | Oral | Double blind | Novartis (global) |
| Placebo Tropifexor (LJN452) 140 µg | Hard gelatin capsule matching to tropifexor (LJN452) 140 µg | Oral | Double blind | Novartis (global) |
| Licogliflozin (LIK066) 30 mg | 10 mg film coated tablets | Oral | Double blind | Novartis (global) |
| Placebo Licogliflozin (LIK066) 30 mg | Film coated tablets matching to licogliflozin (LIK066) 10 mg | Oral | Double blind | Novartis (global) |

### 6.1.2 Additional study treatments

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

An overview of the prohibited medication is given in Table 6-3, and the summary of permitted medication if on stable dose is in Table 6-2.

### 6.1.3 Treatment arms/group

Participants (n = 380) will be assigned at Baseline visit to one of the following 4 treatment arms in a ratio of 1.75:1:1:1 in a blinded manner. Placebo capsules/tablets will be given in each treatment arm where necessary to maintain blinding.

**Arm A**: Combination therapy Arm - (N=140): tropifexor 140 µg + licogliflozin 30 mg, once daily.

**Arm B**: Tropifexor monotherapy Arm - (N=80): tropifexor 140 µg (+ placebo matching licogliflozin), once daily.

**Arm C**: Licogliflozin monotherapy Arm - (N=80): licogliflozin 30 mg (+ placebo matching tropifexor), once daily.

**Arm D**: Placebo Arm – (N=80): placebo matching tropifexor + placebo matching licogliflozin, once daily.

The 140 µg dose of tropifexor and its matching placebo are each now available as a single hard gelatin capsule. Participants participating at the time of availability of the single tropifexor/placebo capsule, may continue on the 3-capsule tropifexor (100 µg + 30 µg + 10 µg) or matching placebo regimen until the available 3- capsule supply is depleted. After the 3-capsule tropifexor or matching placebo supply is depleted, participants will take one 140 µg tropifexor or matching placebo capsule daily. No change is made to licogliflozin dosing. Further details can be found below and in Section 6.7.2.

#### 6.1.3.1 Dosing with 3 capsule (10 + 30 + 100 µg) tropifexor supply

Until 3-capsule tropifexor (100 µg + 30 µg + 10 µg) and matching placebo is replaced by the 140 µg hard gelatin single capsule, in order to maintain the blind, placebo capsules matching tropifexor (LJN452) 10, 30 and 100 µg and placebo tablets matching licogliflozin (LIK066) 10 mg will be given to participants as indicated in Table 6-5, so that all participants will receive 3 capsules and 3 tablets per day. **One capsule from each of the 3 bottles**, and **3 tablets from the blister pack** should be taken close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal, or no more than 30 minutes after consuming the evening meal and at about the same time each day.

#### 6.1.3.2 Dosing with single capsule (140 µg) tropifexor supply

After tropifexor and matching placebo is replaced by the 140 µg hard gelatin single capsule, in order to maintain the blind, placebo capsules matching tropifexor 140 µg and placebo tablets matching licogliflozin (LIK066) 10 mg will be given to participants as indicated in Table 6-6, so that all participants will receive 1 capsule and 3 tablets per day. **One capsule from the bottle**, and **3 tablets from the blister pack** should be taken close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal, or no more than 30 minutes after consuming the evening meal and at about the same time each day.

### 6.1.4 Treatment duration

The planned duration of treatment is 48 weeks. Participants may be discontinued from treatment earlier due to unacceptable tolerability, disease progression and/or at the discretion of the investigator or the participant.

If discontinuation of study treatment occurs, the participant should NOT be considered withdrawn from the study. The participant should return to the clinic as soon as possible, after discontinuation of study drug. In this case, if the participant and study investigator agree, participant may continue in the study without treatment. [redacted] Alternatively, a study treatment discontinuation visit will be conducted.

## 6.2 Other treatment(s)

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

An overview of the prohibited medication is given in Table 6-3, and the summary of permitted medication if on stable dose is in Table 6-2.

### 6.2.1 Concomitant therapy

The investigator must instruct the participant to notify the study site about any new medications he/she takes after the participant is enrolled into the study.

All medications, vaccines, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate case report forms (CRF).

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study. There are no restrictions related to COVID-19 vaccines, and these are allowed throughout study participation as permitted by local regulations.

Drugs to control medically significant lipid abnormalities (which have been confirmed upon repeat testing) can be prescribed according to local standard of care. Participants on medications specified in Table 6-2 can be included if these medications are medically necessary, and the investigator feels the dose will remain stable for the duration of the double-blind treatment period. In addition, doses of oral anti-diabetic medication, insulin, GLP-1 agonists, thyroid hormone, and estrogen or estrogen containing birth control, must be stable for at least 3 months prior to the Baseline visit. Sliding scale insulin therapy is allowed if this approach has been implemented for at least 3 months prior to the Baseline visit. Insulin dose adjustment is permitted during the study if required. Doses of vitamin E $\leq$ 800 IU/day must be stable for at least 6 months prior to the Baseline visit. A stable dose is defined as a dose within 25% of the Baseline dose. New use or dose adjustments > 25% of the Baseline dose of these medications is not allowed after entering the study.

#### 6.2.1.1 Permitted concomitant therapy requiring caution and/or action

**Table 6-2 Medications permitted only if dose is stable (within 25 percent of Baseline dose) and expected to remain stable through the double-blind treatment period**

| Medication | Stable dose start |
|---|---|
| Oral anti-diabetic medications | At least 3 months prior to the Baseline visit |
| Insulin | At least 3 months prior to the Baseline visit |
| GLP-1 agonists such as liraglutide, exenatide, lixisenatide, albiglutide or dulaglutide | At least 3 months prior to the Baseline visit |
| Beta-blockers and thiazide diuretics | At or before Screening Visit 1 |
| Vitamin E < 800 IU/day | At least 6 months prior to the Baseline visit |
| Thyroid hormone | At least 3 months prior to the Baseline visit |
| Phenothiazines | At or before Screening Visit 1 |
| Estrogen or estrogen containing birth control | At least 3 months prior to the Baseline visit |

### 6.2.2 Prohibited medication

Use of the treatments displayed in the below Table 6-3 is NOT allowed after the start of investigational drug, and should be discontinued as soon as screening is considered so that participants medications and conditions are stable and the screening assessments reflect the participant's Baseline condition.

Alcohol consumption is to be strongly discouraged, and if consumed should not exceed 20 g/day (14 units/week) in females and 30 g/day (21 units/week) in males. A "unit" of alcohol is equivalent to 12-ounce, 355 ml beer, 4-ounce, 120 ml glass of wine, or 1 ounce, 30 ml shot of hard liquor.

Use of methotrexate is prohibited as liver fibrosis has been reported with its chronic use.

A study in healthy volunteers was conducted to investigate the effect of UDP glucuronosyltransferase (UGT) inhibition on the pharmacokinetics (PK) of tropifexor by co-administration with the UGT1A1 inhibitor, atazanavir (ATZ) (CLJN452A2110). The inhibition of UGT1A1 by ATZ did not lead to increased exposure of tropifexor, suggesting that inhibition of the UGT1A1 pathway has no clinically relevant impact on tropifexor PK. Therefore, no Drug-Drug Interactions are expected between tropifexor and UGT1A1 inhibitors based on UGT1A1 activity / genotype, and therefore use of these compounds is not prohibited in this study. Non-selective UGT inhibitors are prohibited.

**Table 6-3 Prohibited medications**

| Medication | Timing |
|---|---|
| SGLT2 Inhibitors or combined SGLT1/2 inhibitors<br>Such as: canagliflozin, dapagliflozin, empagliflozin | Stop at least 3 months prior to Baseline |
| Pharmacologically active weight-loss medications<br>Such as: lorcaserin, phentermine/topiramate, bupropion-naltrexone HCL, orlistat) | Stop at least 3 months prior to Baseline |
| Treatment with drugs that have a high incidence of diarrhea<br>Such as: Orlistat, Acarbose. | Stop at or before Screening Visit 1 |
| Treatment with drugs that alter intestinal motility<br>Such as: e.g. erythromycin, metoclopramide, tegaserod, methylnaltrexone, alvimopan, loperamide, diphenoxylate and atropine (Lomotil) and difenoxin and atropine (Motofen)) | Stop at or before Screening Visit 1 |
| Non-selective UGT inhibitors:<br>Such as: diclofenac, probenecid, valproic acid | Stop at or before Baseline |
| Strong CYP3A4 inhibitors:<br>Such as: viekira Pak, indinavir/ritonavir, tipranavir/ritonavir, ritonavir, cobicistat (GS-9350) ,indinavir, ketoconazole, troleandomycin, telaprevir, danoprevir/ritonavir, elvitegravir/ritonavir, saquinavir/ritonavir, lopinavir/ritonavir, itraconazole, voriconazole,mibefradil, LCL161, clarithromycin, posaconazole, telithromycin, grapefruit juice, conivaptan, nefazodone, nelfinavir, saquinavir, idelalisib, boceprevir, darunavir/ritonavir. | Stop at or before Baseline |
| Strong CYP3A4 inducers:<br>Such as: avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort (Hypericum perforatum), rifabutin, phenobarbital, mitotane, enzalutamide. | Stop at or before Baseline |
| Methotrexate | Stop at least 3 months prior to Baseline |
| Vitamin E doses > 800 IU/day | Stop (or reduce dose) at least 6 months prior to Baseline |
| Drugs approved in any market for treatment of NASH | Stop at least 6 months prior to Baseline |
| Alternative Liver Protection medication:<br>Silymarin; Bicyclol; Polyene Phosphatidylcholine (Essentiale); Diammonium Glycyrrhizinate; Reduced glutathione (GSH); S-adenosylmethionine–methionine; Ursodeoxycholic Acid (UDCA) | Stop at or before Screening Visit 1 |

## 6.3 Participant numbering, treatment assignment, randomization

### 6.3.1 Participant numbering

Each participant is uniquely identified in the study by a Participant Number (Participant No.) assigned by Novartis when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial.

The participant number, assigned by Novartis, is composed of a Site Number (Site No.) and a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Once assigned to a participant, the participant number will not be reused.

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

If a participant fails screening and rescreens for the study, THEN the participant must sign a new ICF and be issued a new participant number prior to any screening assessment being conducted for the participant under the new screening participant number. If the participant fails to be treated for any reason, the IRT must be notified within 2 days that the participant was not treated. The reason for not being treated will be entered on the appropriate CRF.

### 6.3.2 Treatment assignment, randomization

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

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

Japanese participants will be assigned to treatment arms with randomization blocking for Japan that is separate from the randomization for all other countries.

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).

This will allow a balanced assignment of participants to each treatment arm.

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

### 6.3.3 Stratification

There will be no stratification for Japanese participants. They will be included in a separate randomization list as described in Section 6.3.2.

To ensure balance of participants among the 4 treatment groups, the following stratum levels will be implemented:

- T2DM yes
- T2DM no

## 6.4 Treatment blinding

This is a double-blind study: participants, 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:

[redacted]

2. Randomization data will be kept strictly confidential until the time of final database lock and will not be accessible by anyone else involved in the study with the exceptions in Table 6-4.
    a. The randomization codes will be disclosed to an independent analysis team to prepare safety and efficacy reports for the DMC. The independent analysts will keep randomization data confidential until data base lock. Data will be shared with the study team under blinded conditions.

[redacted]

3. The identity of the treatments will be concealed by the use of placebo that are each identical in packaging, labeling, schedule of administration, appearance, taste and odor to the respective active treatment. Placebo capsules/tablet will be given in active treatment groups when needed to maintain blinding as described in Section 6.1.3.

A double-dummy design is used because the identity of the study treatment cannot be disguised, as the drug products are visibly different.

Unblinding will only occur in the case of participant emergencies (see Section 6.6.2) and at the conclusion of the study. Unblinding a single participant's treatment at a site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result the participant should be discontinued from the study treatment.

[redacted]

At the time of safety review, the DMC will review unblinded reports created by an independent analysis team. More details will be provided in the DMC charter.

**Table 6-4 Blinding and unblinding plan**

| | **Time or Event** | | | |
|---|---|---|---|---|
| **Role** | **Randomization list generated** | **Treatment allocation & dosing** | **Safety event (single participant unblinded)** | **Safety review** |
| Participants | **B** | **B** | **B** | **B** |
| Site staff | **B** | **B** | **UI** | **B** |
| Novartis CTT | **B** | **B** | **UI** | **B** |
| Global Clinical Supply | **UG** | **B** | **UI** | **B** |
| Randomization Office | **UI** | **UI** | **UI** | **UI** |
| Unblinded Pharmacovigilance sponsor staff | **B** | **UI** | **UI** | **B** |
| Statistician/statistical programmer | **B** | **B** | **UI** | **B** |
| [redacted] | | | | |
| Data Monitoring Committee(DMC) and independent statistician/programmer supporting DMC | **UI** | **UI** | **UI** | **UI** |
| All other sponsor staff not identified above (i.e. trial team, project team, management & decision boards, support functions) | **B** | **B** | **B** | **B** |

Key:

UG: Unblinded at the group level (i.e has access to unblinded group level summary results, but not to the individual participant treatment codes)

UI: Unblinded to individual participant treatment codes

B: Completely blinded

## 6.5 Dose escalation and dose modification

### 6.5.1 Dose escalation guidelines

There is no provision for dose escalation of study medication doses in the protocol

#### 6.5.1.1 Starting dose

Not applicable

### 6.5.2 Definitions of dose limiting toxicities (DLTs)

Not applicable as this is not a dose ranging study.

### 6.5.3 Dose modifications

Temporary interruptions of study medication are permitted. Study medication should be reintroduced under careful monitoring if the investigator feels it is in the best interest of the participant.

For participants who do not tolerate the protocol-specified dosing schedule, dose interruption is recommended in order to allow participants to continue the study treatment, based on investigator's discretion.

These dose interruptions must be recorded on the appropriate CRF.

### 6.5.4 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4 week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists, etc., should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study treatment combination-induced toxicities (i.e. renal, liver) are provided in Section 10.2 and Section 16. All participants must be followed up for adverse events and serious adverse events for 30 days following the last study dose.

## 6.6 Additional treatment guidance

### 6.6.1 Treatment compliance

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed, and to complete the participant diary. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. [redacted]

### 6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant′ s next treatment regimen, and after discussion and agreement with Novartis. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant 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 participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified

participant 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/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name
- participant number

In addition, oral and written information to the participant 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.

After the emergency break the participant must be discontinued from the study by the investigator.

## 6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs Section 6.1.1.

The study drug packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to a certain treatment. Investigator staff will identify the study drug package(s) to dispense to the participant by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the participant, 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 participant's unique participant number.

As per Section 4.6, during a public health emergency as declared by Local or Regional authorities, i.e; pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 8-weeks supply. In this case, regular phone calls or virtual contacts (aligned with the protocol visit schedule in Table 8-1) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site. Where assessment of suitability for continued IMP administration is required (e.g. a protocol required negative urine pregnancy test in WOCBP) the participant will be instructed by site on their requirements to perform these procedures remotely and the communication process with site prior to participant self-administration.

### 6.7.1 Handling of study treatment and additional treatment

#### 6.7.1.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the IB.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) 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 participant 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. Participants will be asked to return all unused study treatment and used/unused packaging at the end of the study or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, 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.

### 6.7.2 Instruction for prescribing and taking study treatment

Participants should be instructed to take the dose of study medication daily, close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal, or no more than 30 minutes after consuming the evening meal and at about the same time each day. Only at Baseline and week 4 visit, the participants should take their doses at the clinic following a meal instead of in the evening.

Once the protocol amendment v02 is approved and after the tropifexor (LJN452) 10, 30 and 100 µg and matching placebo hard gelatin capsule supply is depleted, the participant will receive 9 blister packs in a box (10 mg licogliflozin or matching placebo tablets) and 1 bottle of 140 µg hard gelatin capsules (replacing the 10, 30 and 100 µg tropifexor or matching placebo capsules) for each 4 week period every 4 weeks through Week 20. At the Week 24, Week 32 and Week 40 visits 2 sets of 4 week supplies of study medication will be distributed to accommodate the 8 weekly visit schedule (Table 8-1). The participants will take **3 tablets** from the blister pack and **1 capsule** from the bottle daily as described above.

If the COVID-19 or other pandemic prevents on-site visits the site may arrange delivery of study medication to a participant's home.

#### 6.7.2.1 Overview of treatment - type and number of capsules and tablets taken per day

The 140 µg dose of tropifexor and its matching placebo are each available as a single hard gelatin capsule. Participants on the study at the time of availability of the single tropifexor/placebo capsule, may continue on the 3-capsule tropifexor (100 µg + 30 µg + 10 µg) or matching placebo regimen, as shown in Table 6-5, until the available 3 capsule supply is depleted.

**Table 6-5 Dosing with 3 capsule (10 + 30 + 100 µg) tropifexor supply**

| Treatment Arm | Tropifexor (LJN452) 10µg capsule | Tropifexor (LJN452) 30µg capsule | Tropifexor (LJN452) 100µg capsule | Tropifexor (LJN452) Placebo capsule | Licogliflozin (LIK066) 10mg tablet | Licogliflozin (LIK066) Placebo tablet | Frequency |
|---|---|---|---|---|---|---|---|
| **Arm A** Combo Tropifexor (LJN452) 140 µg & Licogliflozin (LIK066) 30 mg | 1 | 1 | 1 | 0 | 3 | 0 | Daily |
| **Arm B** Mono Tropifexor (LJN452) 140 µg | 1 | 1 | 1 | 0 | 0 | 3 | Daily |
| **Arm C** Mono Licogliflozin (LIK066) 30 mg | 0 | 0 | 0 | 3 | 3 | 0 | Daily |
| **Arm D** Placebo | 0 | 0 | 0 | 3 | 0 | 3 | Daily |

After the 3-capsule supply is depleted, participants will take 1-capsule of 140 µg tropifexor or matching placebo daily as described in Table 6-6. No change is made to licogliflozin dosing.

**Table 6-6 Dosing with single capsule (140 µg) tropifexor supply**

| Treatment Arm | Tropifexor (LJN452) 140µg capsule | Tropifexor (LJN452) Placebo capsule | Licogliflozin (LIK066) 10mg tablet | Licogliflozin (LIK066) Placebo tablet | Frequency |
|---|---|---|---|---|---|
| **Arm A** Combo Tropifexor (LJN452) 140 µg & Licogliflozin (LIK066) 30 mg | 1 | 0 | 3 | 0 | Daily |
| **Arm B** Mono Tropifexor (LJN452) 140 µg | 1 | 0 | 0 | 3 | Daily |
| **Arm C** Mono Licogliflozin (LIK066) 30 mg | 0 | 3 | 3 | 0 | Daily |
| **Arm D** Placebo | 0 | 3 | 0 | 3 | Daily |

IMPORTANT: Please ensure that the date of the change, and the number of capsules (from 3 capsule to 1 capsule) is accurately captured in the eCRF Change in Dosing log for each participant.

Dosing recommendations:

1. Participants should take 3 Tablets from the blister pack (licogliflozin or matching placebo) & 1 or 3 Capsules (tropifexor or matching placebo ) depending on current supply close to the evening meal; either just prior to (within 5 minutes) consuming the evening meal, or no more than 30 minutes after consuming the evening meal, at about the same time each day. Participants directed to take 3 capsules must be reminded that one capsule is to be taken from each of the 3 tropifexor/placebo bottles provided. At Baseline and week 4 the dose will be taken in the morning at the clinic close to a meal instead of in the evening.

[redacted]

4. Participants should be instructed to swallow the capsules and tablets whole and not to chew them.
5. If vomiting or diarrhea occurs during the course of treatment, no re-dosing of the participant is allowed before the next scheduled dose.
6. If a dose is missed and not remembered the same day, it should not be made up on a subsequent day.

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

The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. **It should be emphasized to the participant that the contents of the study medication bottles are not identical; the participant must take one capsule from EACH bottle and 3 tablets from the blister pack each day**. The participant must also be instructed to contact the investigator if for any reason he/she has not taken the study treatment as prescribed.

[redacted]

<u>At site dosing – Baseline and Week 4</u>:

- Participants should take study drug either just prior to (within 5 minutes) consuming the morning meal, or no more than 30 minutes after consuming the morning meal.
- Participants should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, participants should not take the study treatment again before the next scheduled dose.
- No evening dose should be taken on the days of the Baseline and Week 4 visits as the daily dose is taken at the site on those 2 days.

#### 6.7.2.2 Dietary restrictions

No food or alcohol should be consumed for 8 hours before each study visit where blood samples will be collected to ensure these laboratory assessments to be taken in a fasted state.

In case of development of diarrhea, a low carbohydrate meal (i.e. ≤ 50%) close to taking study medication may help to improve the symptom.

To keep the fat intake as constant as possible, participants participating in this study will be instructed to carefully adhere to American Heart Association (AHA) diet or local equivalent if there is a country specific recommended diet, see Section 16.5. Participants will be asked about dietary compliance to the AHA diet (or local equivalent) as outlined in Table 8-1. Participants should also be counseled regarding appropriate exercise as per local standards. Any significant changes to diet or exercise habits should be reported to the investigator.

# 7 Informed consent procedures

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

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council of Harmonization Good Clinical Practice (ICH – E6 GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/ IEC.

Information about common side effects already known about the investigational treatments can be found in the IBs for tropifexor and licogliflozin. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Optional study specific pre-screening consent for pre-screening assessments
- Main study consent, which also includes:
  - [redacted]

- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment.

[redacted]

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements for the duration of the study.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted by site to request her consent to collect pregnancy outcome information.

[redacted]

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

[redacted]

# 8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. The date of each scheduled visit is calculated with the appropriate interval from the date of the Baseline/randomization visit, not from the date of the previous visit. If a scheduled visit is late by more than half of the planned interval between it and the next scheduled visit, the visit should be skipped.

If the COVID-19 or any other pandemic limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsulting) or visits by site staff/home nursing service at the participants home depending on local regulations and capabilities, may be considered. In-home visits would be conducted by the site staff (under the responsibility of the investigator), or by a health care provider (HCP) supporting this activity if this is in agreement with the investigator.

Participants who discontinue from study treatment for any reason (see Section 9.1 for more details) should be scheduled for an end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

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

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

[redacted]

As per Section 4.6, during a public health emergency as declared by Local or Regional authorities, i.e; pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If permitted by a Local Health authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

**Table 8-1 Assessment Schedule**

| Period | Screening | | Treatment | | | | | | | | | | | Unscheduled | EOS/PSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening 1 | Screening 2 | Baseline | W2 | W4 | W8 | W12 | W16 | W20 | W24 | W32 | W40 | W48 | | Follow-Up W52 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - | 14 |
| Days | -70 to -42 | -42 to -1 | 0 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 280 | 336 | - | 364 |
| Weeks | -10 to -6 | -6 to 0 | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 32 | 40 | 48 | 0 | 52 |
| Informed consent | X | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | |
| Inclusion / Exclusion criteria | X | X | X | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | | | |
| Medical history/current medical conditions | X | X | X | | | | | | | | | | | | |
| Protocol solicited medical history | X | X | X | | | | | | | | | | | | |
| Randomization | | | X | | | | | | | | | | | | |
| Contact IRT | X | X | X | | X | X | X | X | X | X | X | X | X | X | X |
| Physical Examination | S | S | S | S | S | S | S | S | S | S | S | S | S | S | S |
| Vital Signs[1] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Body Height | X | | | | | | | | | | | | | | |
| Body Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Period | Screening | | Treatment | | | | | | | | | | | Unscheduled | EOS/PSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening 1 | Screening 2 | Baseline | W2 | W4 | W8 | W12 | W16 | W20 | W24 | W32 | W40 | W48 | | Follow-Up W52 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - | 14 |
| Days | -70 to -42 | -42 to -1 | 0 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 280 | 336 | - | 364 |
| Weeks | -10 to -6 | -6 to 0 | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 32 | 40 | 48 | 0 | 52 |
| Waist circumference | X | X | X | | | | X | | | X | | | X | | X |
| Hip circumference | X | X | X | | | | X | | | X | | | X | | X |
| Prior and ongoing / concomitant medications and non-drug therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Alcohol history / compliance with protocol | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Smoking history | X | | | | | | | | | | | | | | |
| Electrocardiogram (ECG)[2] | X | | | | | | X | | | X | | | X | | |
| [redacted] | | | | | | | | | | | | | | | |
| Liver Biopsy[5] | | X | | | | | | | | | | | X | | |
| Hepatitis serology[6] | X | | | | | | | | | | | | | | |
| HIV antigen/antibody tests | X | | | | | | | | | | | | | | |
| Liver function tests | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Period | Screening | | Treatment | | | | | | | | | | | Unscheduled | EOS/PSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening 1 | Screening 2 | Baseline | W2 | W4 | W8 | W12 | W16 | W20 | W24 | W32 | W40 | W48 | | Follow-Up W52 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - | 14 |
| Days | -70 to -42 | -42 to -1 | 0 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 280 | 336 | - | 364 |
| Weeks | -10 to -6 | -6 to 0 | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 32 | 40 | 48 | 0 | 52 |
| Hematology | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Clinical Chemistry[7] | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Fasting lipid panel | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Coagulation panel[8] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| [redacted] | | | | | | | | | | | | | | | |
| Amylase & lipase[9] | X | | X | X | | | | | | | X | | | | |
| [redacted] | | | | | | | | | | | | | | | |
| Serum BUN,creatinine and eGFR (MDRD) | X | | X | X | X | X | X | X | X | X | X | X | X | | X |
| Urinalysis (central)[10] | X | X | X | X | X | X | X | X | X | X | X | X | X | | X |
| Pregnancy and assessments of fertility | S | S | S | S | S | S | S | S | S | S | S | S | S | S | S |
| Pregnancy Urine dipstick test (local)[11] | S | S | S | | S | S | S | S | S | S | S | S | S | S | S |
| Pregnancy serum test (central lab)[12] | X | X | | | | | | | | X | | | | | |

| Period | Screening | | Treatment | | | | | | | | | | | Unscheduled | EOS/PSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening 1 | Screening 2 | Baseline | W2 | W4 | W8 | W12 | W16 | W20 | W24 | W32 | W40 | W48 | | Follow-Up W52 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - | 14 |
| Days | -70 to -42 | -42 to -1 | 0 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 280 | 336 | - | 364 |
| Weeks | -10 to -6 | -6 to 0 | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 32 | 40 | 48 | 0 | 52 |
| Follicle stimulating hormone (FSH) | X | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | |

| **Period** | **Screening** | | **Treatment** | | | | | | | | | | | **Unscheduled** | **EOS/PSW** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Name** | **Screening 1** | **Screening 2** | **Baseline** | **W2** | **W4** | **W8** | **W12** | **W16** | **W20** | **W24** | **W32** | **W40** | **W48** | | **Follow-Up W52** |
| **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **-** | **14** |
| **Days** | **-70 to -42** | **-42 to -1** | **0** | **14** | **28** | **56** | **84** | **112** | **140** | **168** | **224** | **280** | **336** | **-** | **364** |
| **Weeks** | **-10 to -6** | **-6 to 0** | **0** | **2** | **4** | **8** | **12** | **16** | **20** | **24** | **32** | **40** | **48** | **0** | **52** |
| [redacted] | | | | | | | | | | | | | | | |
| Urine screening for drug abuse | X | | X | | | | | | | | | | | | |
| Drug dispensation | | | S | | S | S | S | S | S | S | S | S | | | |
| Drug administration record | | | X | X | X | X | X | X | X | X | X | X | | | |
| Drug Compliance | | | | X | X | X | X | X | X | X | X | X | | | |
| Participant diary review | | | | S | S | S | S | S | S | S | S | S | S | | S |
| Adverse Events[18] | X | | | | | | | | | | | | | | |
| Serious Adverse Events[19] | X | | | | | | | | | | | | | | |
| Diet Compliance and exercise counseling | | | X | X | X | X | X | X | X | X | X | X | X | | X |
| [redacted] | | | | | | | | | | | | | | | |

| Period | Screening | | Treatment | | | | | | | | | | | Unscheduled | EOS/PSW |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit Name | Screening 1 | Screening 2 | Baseline | W2 | W4 | W8 | W12 | W16 | W20 | W24 | W32 | W40 | W48 | | Follow-Up W52 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | - | 14 |
| Days | -70 to -42 | -42 to -1 | 0 | 14 | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 280 | 336 | - | 364 |
| Weeks | -10 to -6 | -6 to 0 | 0 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 32 | 40 | 48 | 0 | 52 |
| [redacted] | | | | | | | | | | | | | | | |
| Study treatment completion information[21] | | | | | | | | | | | | | X | | |
| Study completion information | | | | | | | | | | | | | | | X |

[X] Assessment to be carried out at respective visit and data for assessment to be recorded in the source, clinical database or received electronically from a vendor
[S] Assessment to be carried out and data for assessment to be recorded in the source documentation at the site only
[1] Vital signs (including blood pressure and pulse measurements)
[2] For any ECGs with safety concerns, two additional ECG must be performed to confirm the safety finding.

[redacted]

[redacted]

[5] Biopsy

a).The liver biopsy can be performed any time during the 10 week screening period, and should only be performed in participants who fulfill Screening visit 1 eligibility criteria refer Section 8.3.1.8 for details.
b) Screening biopsy results confirming eligibility are required prior randomization. Plan for the biopsy visit accordingly. The Screening visit 2 assessment can be performed before the biopsy results are obtained.
c). Read by a central pathologist.
d). Week 48 biopsy optional if participant discontinues before 24 weeks treatment period.

[6] Hepatitis B surface antigen (HBsAg); HCV antibody (Ab) – if detected, reflex to Hepatitis C RNA by PCR; Immunoglobulin M (IgM) Hepatitis A antibodies (IgM anti-HAV) see Section 8.4.2.6.

[7] At screening visit 1 this also includes ferritin, transferrin saturation, iron, and if not historically available also Anti-nuclear antibodies (ANA), Anti-smooth muscle antibodies (ASMA) and Anti-mitochondrial antibodies (AMA), see Section 8.4.2.2

[8] Coagulation parameters including APTT, PT, INR and TT and fibrinogen.

[9.] Amylase & lipase to be analyzed at screening & Baseline and subsequently if pancreatitis is suspected.

[10] Dipstick measurements for color, clarity, specific gravity, pH, bilirubin, nitrite, ketones, protein, glucose, blood, urobilinogen and leukocyte esterase will be performed. If dipstick measurement results are positive (abnormal), microscopy would be assessed.

[11] Women Of Child Bearing potential (WOCBP) must have a urine dipstick pregnancy test every 4 weeks, including at week 28, 36 and 44 (when there are no study visits), up to and including the follow up visit.

[12] After Baseline visit onwards serum sample to be collected for serum pregnancy test only if urine dipstick test is positive – During the study if test is positive, the participant must be discontinued from study drug.

[redacted]

[17] At Baseline and week 4, to be collected at least 1-2 hours post dose at clinic.

[18] Update as necessary

[19] Update as necessary - SAEs must be reported & recorded until 30 days after the participant has stopped study participation; see appropriate protocol Section 10.1.2.

[redacted]

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

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## 8.1 Screening

### 8.1.1 Pre-screening

For participants who do not have a qualifying historical liver biopsy, it is recommended that available ultrasound based elastography (e.g. transient elastography – Fibroscan, Acoustic Radiation Force Impulse (ARFI), 2D-Shear Wave Elastography, where available) be reviewed prior to performing the liver biopsy. Fibroscan may be a useful pre-screening tool prior to liver biopsy.

Prior to screening visit 1 optional study specific pre-screening assessments may be carried out, including Fibroscan and/or local laboratory tests (HbA1c, platelets, INR, total bilirubin, ALT, AST, ALP and serum albumin) to assess participant eligibility for inclusion. Prior to any study specific pre-screening assessments being carried out the pre-screening informed consent form must be signed by the participant.

Only data related to SAEs causally related to pre-screening study procedures blood sampling or Fibroscan will be recorded (Section 10.1.3). All other data related to pre-screening will be recorded only in the source documentation.

If Fibroscan is performed at pre-screening it is not required to be repeated later in the screening period; if the participant is randomized this data will be recorded on the eCRF.

### 8.1.2 Information to be collected on screening failures

All participants who have signed informed consent and subsequently found to be ineligible prior to randomization into the study at Baseline Visit are considered screening failures. If a participant discontinues before entering the treatment period, IRT must be notified within 2 days and the reason for not entering the study will be recorded on the appropriate eCRF. In addition, the following eCRFs should be completed: Visit Date, Informed Consent, Demography, Inclusion/Exclusion Criteria, Participant Re-Screening (if applicable), Protocol Deviation, Disposition, Withdrawal of Consent (if applicable) and SAEs that occurred during the screening period. No other data will be entered into the clinical database for participants who are screen failures (see Section 10.1.3 for SAE reporting details). Data available from third party vendors for screen failed participants will be electronically transferred to the clinical database.

If for any reason the participant is a screen failure, the participant may be rescreened. There is no restriction on the number of times a potential participant may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening. If the reason for screen failure is an inadequate biopsy sample taken during the screening period, a second liver biopsy cannot be performed for re-screening. If the inadequate liver biopsy sample is historical, the investigator's clinical judgment and local standard of care will determine if and when the liver biopsy can be repeated for re-screening. If a participant is a screening failure, but is rescreened and subsequently enrolled, the reason for the original screening failure must be documented in the source documents.

If a participant is rescreened for the study, the participant must sign a new ICF and be issued a new participant number prior to any study related assessment or collecting any data for new screening visit being conducted. For all participants, the investigator/qualified site staff will

record if the participant was rescreened on the rescreening eCRF and any applicable screening numbers the participant was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the Informed Consent eCRF to correspond to the new screening participant number. For rescreening, all screening assessments must be performed as per protocol.

Investigators will have the discretion to record on the medical history eCRF any abnormal test finding that occurred prior to the informed consent signature.

## 8.2 Participant demographics/other Baseline characteristics

Baseline characteristic data to be collected on all participants include (all labs are central) (see also Table 8-1):

12-lead ECG, vital signs, drug testing, hematology, clinical chemistry, urinalysis, physical examination, anthropometric assessments, HIV antigen/antibody tests, Hepatitis A, B or C serology, anti-nuclear antibodies (ANA), anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), iron, ferritin, [redacted] A serum pregnancy test will be performed for women of child-bearing potential, [redacted]

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 [redacted], depending on the assessment as listed in Table 8-1.

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

### 8.2.1 Screening visit 2 – additional assessments

The second screening visit should only be conducted if participant remains eligible based on the assessments performed at screening visit 1. ALT, AST, total bilirubin and ALP will be tested at screening visits 1 and 2, and must meet the requirements in Section 5.2 at both screening visits to confirm eligibility.

The period between screening visit 1 and the anticipated randomization / Baseline visit is a maximum of 10 weeks. If the liver biopsy is performed at screening visit 2, this visit should be done at least three weeks prior to the Baseline visit to allow sufficient time for liver biopsy central reading. The Baseline visit should occur as soon as all eligibility criteria are met.

### 8.2.2 Demographic Information

Participant demographic data to be collected at screening on all participants include: year of birth or age, gender, race, ethnicity, source of referral and child-bearing potential (for females only).

### 8.2.3 Medical History

Any relevant medical history including surgical/medical procedures, protocol solicited medical history, and/or current medical conditions before obtaining informed consent will be recorded in the Medical History eCRF. Significant findings that are observed after the participant has

signed the informed consent form and that meet the definition of an AE must also be recorded in the AE eCRF. 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.

### 8.2.4 Alcohol history and assessments

Any history of alcohol use will be recorded in the eCRF. At screening visit 2 the 10-item questionnaire Alcohol Use Disorders Identification Test (AUDIT) will be used. Further, for all the other visits the 3-item questionnaire, modified AUDIT will be administered to the participants as indicated in Table 8-1.

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

### 8.2.5 Smoking history

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

### 8.2.6 Prior and concomitant medications

Concomitant medications and prior medications taken will be captured at the screening visit, and updated at the Baseline visit. Any change to the ongoing or any new concomitant medication will be recorded in eCRF on an ongoing basis throughout study participation.

### 8.2.7 Treatment exposure and compliance

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

## 8.3 Efficacy

All efficacy assessments should be performed prior to the administration of study treatment.

The recommended order for the efficacy assessments is described below.

### 8.3.1 Efficacy assessments

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

- Weight
- [redacted]
- Blood samples collection for:
  1. Liver function test (LFT)
  - [redacted]

[redacted]

- Liver biopsy

[redacted]

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

#### 8.3.1.1 Weight

Weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes), and waist and hip circumference in centimeters (cm) will be measured as indicated in Table 8-1.

[redacted]

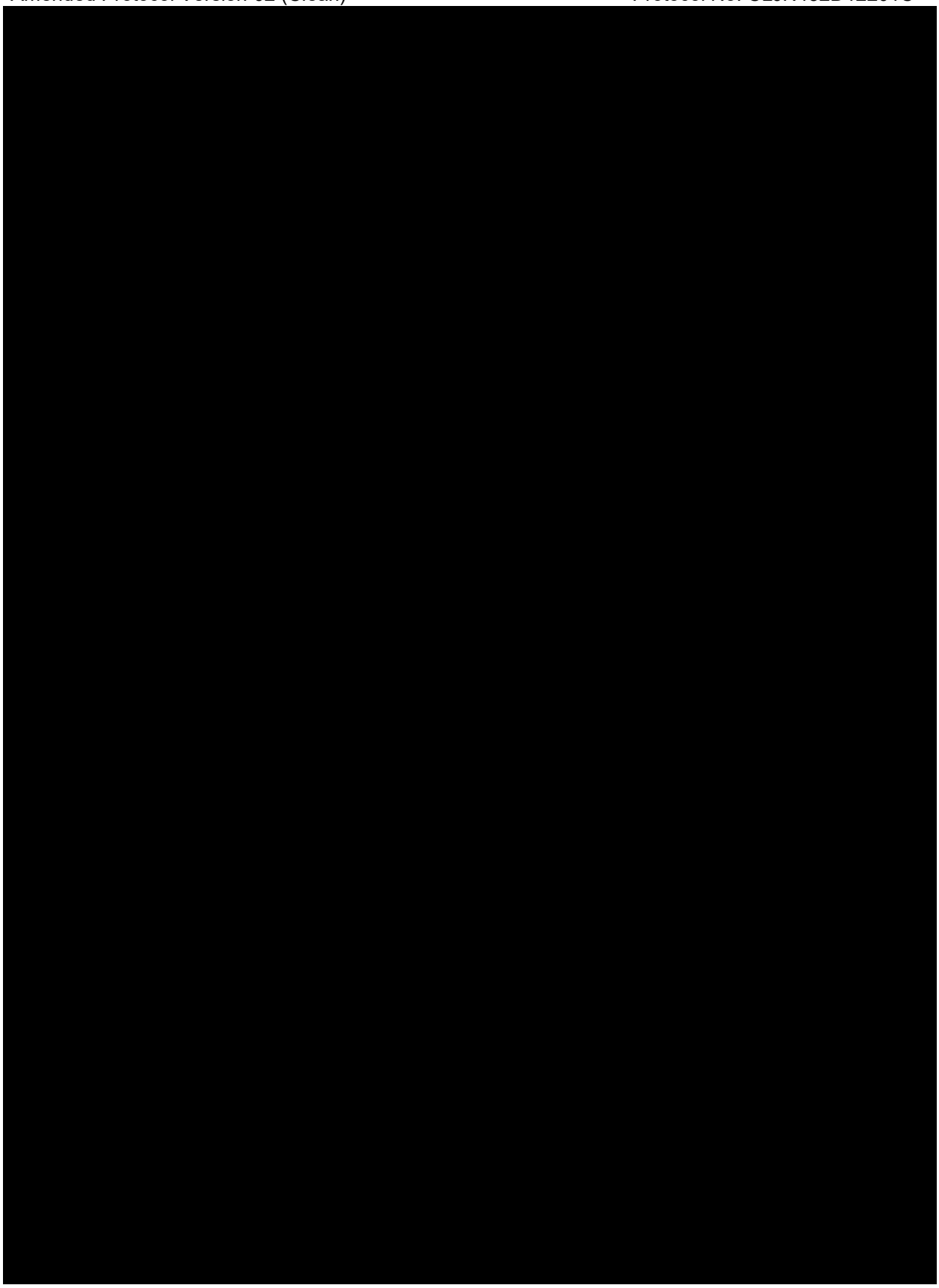
#### 8.3.1.3 Liver function tests

ALT, AST, GGT, total ALP (and isoenzymes if total alkaline phosphatase is >ULN), and 5'nucleotidase (if either GGT or total ALP is > ULN during study participation), TBL, direct and indirect bilirubin and albumin will be assessed as indicated in Table 8-1.

After Baseline visit onwards if the TBL concentration is increased above 1.5 times the upper limit of normal, direct and indirect bilirubin will be quantified.

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

[redacted]



### 8.3.2 Appropriateness of efficacy assessments

The primary and secondary efficacy variables selected for this protocol will detect clinically meaningful changes in liver histology including steatohepatitis and fibrosis, liver fat content, liver enzymes and body weight and indirect markers of NASH. Liver histology assessments determined by the Central Reader's provide the data for the primary endpoint and remain the assessments required by regulatory authorities for diagnosis of NASH and evaluation of treatment effect. Improvement in steatosis as determined by magnetic resonance along with sustained improvement in alanine aminotransferase (ALT) are recommended as valid endpoints of efficacy and are assessments for secondary endpoints in this phase 2 trial (Sanyal et al 2011).

## 8.4 Safety and Tolerability

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

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

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

As per Section 4.6, during a public health emergency as declared by Local or Regional authorities, i.e, pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 2 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

### 8.4.1 Assessments & Specifications

#### 8.4.1.1 Physical examination

A physical examination will be performed on participants according to the schedule defined in Table 8-1.

A complete physical examination will be conducted at screening visit 1, baseline, Weeks 12, 24, and 48 which 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. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. At all other visits, a physical examination according to local guidelines, including bilateral foot exams, will be performed.

Information for all physical examinations must be included in the source documentation at the study site.

Clinically relevant findings that are present prior to signing informed consent form must be recorded on the appropriate CRF that captures medical history screen on the participant eCRF. Significant findings that occur after signing informed consent form which meet the definition of an Adverse Event must be recorded as an adverse event.

#### 8.4.1.2 Vital signs

Clinically notable vital signs are defined in Section 16.1.

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 8-1. After the participant 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 participants. If blood pressure is high (i.e., SBP ≥140 mmHg and/or DBP ≥100 mmHg, or ≥130/80 for participants with diabetes or chronic renal insufficiency), blood pressure measurement will be repeated after a 5 minutes rest and confirmed in the same arm. All measurements should be recorded in source documents and the lowest reading entered in the CRF.

As intravascular volume depletion is a potential risk, if a participant reports symptoms suggesting postural hypotension, erect and supine SBP and DBP should be measured, recorded in source documents and used in guiding AE reporting.

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

#### 8.4.1.3 Anthropometric assessments

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes), and waist and hip circumference in centimeters (cm) will be measured as indicated in Table 8-1.

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

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 participant, but not to the point that the tape is constricting (World Health Organization 2011).

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)]$^2$

### 8.4.2 Laboratory evaluations

Laboratory evaluations will be assessed as indicated in Table 8-1.

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 central laboratory manual.

Clinically notable laboratory findings are defined in Section 16.1.

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 end of study at the latest.

Local lab collection may be used during a public health emergency as declared by Local or Regional authorities, i.e;. pandemic, epidemic or natural disaster that limits or prevents on-site study visits.

If participants cannot visit the site for protocol specified safety lab assessments, an alternative local lab, collection site or relevant clinical facility that are certified for lab diagnostics may be used.

Safety samples (specifically hematology, clinical chemistry and coagulation panels) that can be collected locally will be collected and analyzed in line with the study laboratory manual. Where samples are collected and analyzed at a local laboratory instead of the central laboratory.

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) AE, if central laboratory results are unevaluable, inconclusive or cannot be obtained due to public health emergencies, or when the treating physician cannot wait for central laboratory results for decision making.

The results of the local laboratory will be recorded in the eCRF

#### 8.4.2.1 Hematology

Hematocrit (Hct), Hemoglobin (Hb), mean corpuscular volume (MCV), Red blood cells (RBC), Platelets, White blood cells (WBC), absolute differential WBC count, (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils), RBC Morphology will be measured as indicated in Table 8-1.

#### 8.4.2.2 Clinical Chemistry

Sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN)/urea, [redacted] albumin, ALP, ALT, AST, gamma-glutamyl-transferase (GGT), lactate dehydrogenase (LDH), magnesium, phosphorus, TBL (if > 1.5 x ULN, direct and indirect bilirubin will be quantified), serum creatinine (sCR), uric acid, creatine kinase (CK), total protein, high sensitivity C-reactive protein (hsCRP), haptoglobin; will be measured as indicated in Table 8-1.

At screening visit 1, the following assessments will be included: ferritin, transferrin saturation, total iron, and if not historically available also anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (ASMA), and anti-mitochondrial antibodies (AMA).

Amylase and lipase will be tested at screening and baseline and thereafter if pancreatitis is suspected.

The estimated glomerular filtration rate (eGFR) will be calculated corresponding to each creatinine measurement using the MDRD formula based on the participant's age at the time of measurement, gender and race.

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

Liver function tests: see Section 8.3.1.3

[redacted]

### 8.4.2.3 Coagulation tests

Coagulation parameters including Fibrinogen, Activated Partial Thromboplastin Time (APTT), Prothrombin Time (PT), International Normalized Ratio) (INR) and Thrombin Time (TT) will be assessed as indicated in Table 8-1.

### 8.4.2.4 Fasting lipids profile

Blood samples will be collected for a fasting lipid panel, including total cholesterol, HDL-cholesterol (high-density lipoprotein) and LDL-cholesterol (low-density lipoprotein), VLDL-cholesterol (very low-density lipoprotein), triglycerides, free glycerol, apolipoprotein A1, apolipoprotein B, lipoprotein (a), NMR lipid Subclass Particle Analysis and free fatty acids as per the assessment schedule Table 8-1.

Lipid measurements should be collected after an 8-hour (overnight) fast. Detailed information will be provided in the central laboratory manual.

### 8.4.2.5 Urinalysis

A clean-catch midstream urine sample will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments, as indicated in Table 8-1.

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

Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells).

Urine for calculation of protein to creatinine ratio (PCR) or albumin to creatinine ratio (ACR) can be aliquoted from the clean-catch. (see Table 16-3).

### 8.4.2.6 Hepatitis markers

At screening, the presence of hepatitis C virus (HCV) will be by detection of HCV antibody (Ab). If HCV antibody (Ab) is not detected, participant can continue through the screening process. If HCV antibody (Ab) is detected, reflex test to the polymerase chain reaction (PCR) test for hepatitis C virus RNA will be performed. If HCV RNA is not detected in PCR, participant can continue through the screening process. Presence of HCV RNA is exclusionary.

At Screening, assay for presence of Immunoglobulin M (IgM) Hepatitis A antibodies (IgM anti-HAV) will be performed. Presence of IgM anti-HAV is exclusionary. No further testing is needed.

At Screening, assay for presence of hepatitis B surface antigen (HBsAg) will be performed. Presence of HBsAg is exclusionary. No further testing is needed.

Hepatitis A, B or C serology will be assessed as indicated in Table 8-1 and if deemed appropriate, hepatitis serology will be assessed for liver safety monitoring as indicated in Section 10.2.1.

#### 8.4.2.7 Screening for drug abuse

Urine samples will be collected for a testing for Amphetamines/MDMA Screen, Antidepressants Screen, Barbiturates Screen, Benzodiazepines Screen, Cannabinoids Screen, Cocaine Screen, Opiates Screen, Methadone Screen, Propoxyphene, Phencyclidine (PCP), as per the assessment schedule Table 8-1. Participants will be excluded by exclusion criterion 30 if the treating physician determines the presence of ongoing drug abuse. Participants testing positive (e.g. for prescription medications) are not automatically excluded.

### 8.4.3 Pregnancy and assessments of fertility

#### Pregnancy

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Women of child-bearing potential (WOCBP) are defined as all females physiologically capable of becoming pregnant.

A serum β-hCG test will be performed at the Screening and Baseline Visits for all WOCBP. A positive test at either visit is an exclusion criterion for participating in the study.

From baseline onwards the urine pregnancy dipstick test will be repeated every four weeks up to and including the follow up visit (see Table 8-1) including at weeks 28, 36, and 44, when there are no scheduled site visits. The tests will be performed at the clinical center or at participant's home. In case of home pregnancy test, the women of child-bearing potential will be provided with urine pregnancy test kits. The result will be documented in the participant diary and must be provided to the investigator at next scheduled visit. In case of positive urine pregnancy dipstick test the participant must contact investigator immediately. A positive urine pregnancy test after start of study drug requires its immediate interruption until serum β-hCG is performed and found to be negative. If positive, the participant will enter the post-treatment follow up period. See also Section 10.1.4

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

After Baseline a serum β-hCG test will be performed when there is positive urine pregnancy dipstick test.

Female participants of child-bearing potential, who are or might become sexually active, must be informed of the need to prevent pregnancy during the study and for 5 days after study completion.

The decision on the contraceptive method should be reviewed at least every 3 months to evaluate the individual need and compatibility of the method chosen and the need for additional pregnancy testing.

**Assessments of fertility**

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

Surgical bilateral oophorectomy without a hysterectomy

Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

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

### 8.4.4 Other safety evaluations

#### 8.4.4.1 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 8-1. Determination of eligibility will be based on the ECG report from the central ECG review, not on the ECG machine-generated report.

All ECGs must be performed on the ECG machines provided by vendor assigned for the study by Novartis.

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, HR, PR, QRS, and QT) are to be assessed. Each ECG tracing should be labeled with the study number, participant initials, participant number, date and time, and kept in the source documents at the study site. Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the Novartis before administration of study treatment. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

Local ECG collection may be used during a public health emergency as declared by Local or Regional authorities, i.e, pandemic, epidemic or natural disaster that limits or prevents on-site study visits.

If participants cannot visit the site for protocol specified safety ECG assessments, an alternative local facility, collection site or relevant clinical facility that are certified for ECG collection may be used.

### 8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population and have been used in previous trials in this indication or deemed appropriate based on non-clinical and early clinical experience. Participants are seen frequently during treatment and will be assessed for safety parameters, including AE of special interest for the study medications.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

# 9 Discontinuation and completion

## 9.1 Discontinuation from study treatment and from study

### 9.1.1 Discontinuation from study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- participant/guardian decision
- Pregnancy (see Section 8.4.3 and Section 10.1.4)
- Any situation in which continued study participation might result in a safety risk to the participant (including life-threatening events considered to be related to study medication)
- Following emergency unblinding
- Emergence of the following adverse events:

- For ALT, AST, TBL and/or alkaline phosphatase elevations mandating study treatment discontinuations (see Sections 10.2.1 and Section 16.2 for further instructions and monitoring).
- Any evidence of liver decompensation as defined by ascites, bleeding esophageal varices, hepatic encephalopathy, jaundice.
- Serious COVID-19 infection requiring hospitalization

If the decision of discontinuing the study medication comes from the participant, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment and follow up visits indicated in the assessment schedule (Table 8-1).

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

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

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code see Section 6.6.2.

### 9.1.2 Discontinuation from study

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

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

### 9.1.3 Lost to follow up

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

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

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent/opposition to use data/biological samples occurs only when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)
- No longer wishes to receive study treatment
- 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

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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

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

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

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

If the participant agrees, all efforts should be made to complete a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table.

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

## 9.3 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

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

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

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

For all participants who discontinue treatment early or who complete treatment, a safety follow-up visit (EOS, Week 52) should be conducted 4 weeks after last treatment (EOT, Week 48). The information to be collected at this follow up visit includes concomitant medications, adverse events, and laboratory samples, as detailed on Table 8-1.

All SAEs reported during this time period must be reported as described in Section 10.1.3.

## 9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

This may include reasons related to the

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Practical reasons (including slow enrollment), or
- For regulatory or medical reasons.
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

# 10 Safety monitoring, reporting and committees

## 10.1 Definition of adverse events and reporting requirements

### 10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in clinical investigation participant after providing written informed consent for participation in the study. 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 investigator has the responsibility for managing the safety of individual participant and identifying adverse events

An AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

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

For participants whose NASH status is unknown and who sign the pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 10.1.2 and are reported to be causally related with pre screening procedures (e.g. lab testing). The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with underlying disease. Investigators have the responsibility for managing the safety of individual participant and identifying adverse events. Alert ranges for laboratory and other test abnormalities are defined in Section 16.1.

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

1. The severity grade:
   - 1=mild: usually transient in nature and generally not interfering with normal activities
   - 2=moderate: sufficiently discomforting to interfere with normal activities
   - 3=severe: prevents normal activities

2. Its relationship to the study treatment
   - Yes
   - No

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

3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a serious adverse event (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. 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 interrupted/withdrawn
- concomitant medication or non-drug therapy given
- participant hospitalized/participant's hospitalization prolonged

6. Its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

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

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

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 drugs can be found in the IBs. Summary information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the 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 participant.

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

All adverse events will be collected after ICF is signed and monitored until 30 days after last dose of study treatment.

### 10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of an SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

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

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

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any AE of pancreatitis (acute, chronic or other), Fournier's gangrene and ketoacidosis will be assessed as serious under "medically significant" even if other seriousness criteria are not met.

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

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

### 10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last dose of study treatment must be reported to Novartis safety immediately, without undue delay, under no circumstances later than 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Any SAEs experienced more than 30 days after the last dose of study treatment should only be reported to Novartis safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

SAE reporting requirements in different scenarios are summarized below:

**Table 10-1 SAE reporting requirements in different scenarios**

| Scenario | Reporting requirements |
|---|---|
| Pre-screening participant | SAEs causally related to pre-screening study procedure (e.g. blood sampling or FibroScan) occurring after the participant has provided pre-screening informed consent until the time the participant is deemed not eligible for the study must be reported to Novartis safety using a paper SAE form. |
| Screening participant | SAEs occurring after the participant has provided study informed consent until the time the participant is either deemed a screen failure or is randomized must be reported to Novartis safety, only if they are considered potentially related to study procedure, using the electronic serious adverse event eSAE module of the eCRF. |
| Randomized OR Treated participant | SAEs occurring after the participant has been randomized until 30 days after the last dose of study treatment must be reported to Novartis safety, regardless of suspected causality using the electronic serious adverse event eSAE module of the eCRF. |
| More than 30 days after the last dose of study treatment | SAEs occurring more than 30 days after the last dose of study treatment and for which the investigator suspects a causal relationship to study treatment must be reported to Novartis safety using a paper SAE form. |

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. 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 participant continued or withdrew from study participation. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs during the study period is collected and recorded on the electronic serious adverse event (eSAE) module of the CRF. For SAEs experienced during pre-screening or after the last study visit, a paper SAE Form will be used. 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 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.

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 CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform 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.

### 10.1.4 Pregnancy reporting

#### Pregnancies

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

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. After consent is provided, 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 at expected delivery date plus 12 months.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome.

Any SAE experienced during 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.

If participants cannot visit the site to have serum pregnancy tests during a public health emergency as declared by Local or Regional authorities, i.e; pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used.

Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

### 10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to safety only if associated with an SAE. Misuse or abuse will be collected and reported in the

safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

**Table 10-2 Guidance for capturing the study treatment errors including misuse/abuse**

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

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

## 10.2 Additional Safety Monitoring

### 10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drugs, a standardized process for identification, monitoring and evaluation of liver events has to 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 AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Elevations in ALT and AST during study conduct must be reviewed in the context of participant's baseline value, prior to study medication initiation. Participants with baseline values of ALT or AST > 5× ULN are excluded.

Participants who develop elevations in liver-related laboratory parameters and/or clinical symptoms suggestive of liver disease should be managed according to Table 16-2. If ALP, ALT, AST, or bilirubin elevations reach the specified thresholds outlined in Table 16-2, the participant must return to the study site for re-evaluation within 48 to 72 hours after the laboratory results becoming available, at which time central confirmatory laboratory testing will be performed. This includes ALP, ALT, AST, total and direct bilirubin and INR. [redacted] If prompt evaluation is not possible within 48 to 72 hours following receipt of abnormal laboratory results, study drug should be interrupted immediately (date of last study drug dose must be recorded in the eCRF) and the participant must return to the study site as soon as possible for re-evaluation. The sponsor should be notified of laboratory abnormalities and any clinical symptoms within 48 hours of available laboratory results and/or assessment of clinical symptoms.

If the elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption or discontinuation (as described in Table 16-2) if deemed appropriate and close monitoring, causality and clinical evaluation should be performed as below;

- Repeating the liver tests to confirm elevation as described in Table 16-2
- Discontinuation of the investigational drug if appropriate. Note that discontinuation is mandatory in the case of decompensated cirrhosis as defined by ascites, bleeding esophageal varices, hepatic encephalopathy, jaundice or any other liver decompensation related symptom
- Hospitalization of the participant if appropriate
- An investigation of the liver event which needs to be followed until resolution
- Obtain a more detailed history of symptoms and prior or concomitant diseases
- Obtain a history of concomitant drug use (including nonprescription or over-the-counter medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Rule out acute viral hepatitis types A, B, C, D, E and alcoholic hepatitis; hypoxic/ischemic hepatopathy; autoimmune hepatitis and biliary tract disease and other liver diseases.
- Obtain a history of exposure to environmental chemical agents

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

Participants who permanently discontinue study drug due to potential liver toxicity must be followed for close monitoring until abnormalities stabilize to baseline levels or baseline grade of abnormality and the participant is asymptomatic. All follow-up information, and the procedures performed must be recorded on the appropriate CRFs.

### 10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, renal serum and urine laboratory values will be assessed routinely. Renal laboratory triggers and renal events are defined in Table 16-3 in Section 16.3. These laboratory abnormalities should be followed up as indicated in Table 16-3 by the investigator or designated personnel at the trial site.

### 10.2.3 Adverse events of special interest

#### 10.2.3.1 Pruritus

Pruritus is a common adverse event for the FXR-agonist class of drugs. Events will be captured during the study. Pruritus should be managed according to normal standard of care. If a participant experiences pruritus, an interruption in dosing of study medication can be considered. Although not specific to NASH, guidance for pruritus management can be found in the guidelines of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) for the management of cholestatic pruritus. (Lindor KD, Gershwin ME, Poupon R et al 2009, J Hepatol 2009). Protocol rules outlined in Section 6.2 for Other Treatments must be followed.

#### 10.2.3.2 Dyslipidemia

Management of dyslipidemia is critical in participants with NASH. Increases in LDL-C and decreases in HDL-C are observed with experimental treatments for NASH including the FXR-agonist class of drugs, such as tropifexor. The participant's cardiovascular risk should be assessed by the investigator. Lipids are monitored by regular laboratory testing during the study. Dyslipidemia should be aggressively managed to achieve appropriate target levels, as recommended by local/ regional guidelines. Interventions, such as diet, exercise, and especially early introduction of lipid-lowering agents (e.g. statins) should be considered. Doses of lipid lowering agents should be adjusted as required to reach appropriate lipid levels.

Laboratory abnormalities related to lipids should be reported as an adverse event only if the criteria in Section 10.1 are met. Cardiovascular events would be closely monitored and captured during the study.

#### 10.2.3.3 Diarrhea

Osmotic diarrhea has been observed in participants treated with licogliflozin (inhibition of absorption of glucose and fructose in the gut). Events will be closely monitored and captured during the study. Participants with gastrointestinal disorders associated with chronic diarrhea are not included in the study. If a participant experiences diarrhea, an adjustment of the diet, or interruption or discontinuation in dosing of study medication can be considered. Events of diarrhea should be recorded in the participant diary and on the AE eCRF.

#### 10.2.3.4 Genital infections

In clinical studies with licogliflozin, a small number of participants experienced non-serious, mild genital infections (mainly mycotic) with AEs including balanitis and vulvovaginal infections. This is observed due to dose dependent glucosuria as a consequence of SGLT2 inhibition. All genital infections reported in licogliflozin clinical trials were non-serious with the overall frequency similar to published reports for marketed SGLT2 inhibitors (dapagliflozin, canagliflozin).

Participants with symptomatic genital infection in the 4 weeks before randomization should be excluded. The possibility of genital infections (mainly mycotic like thrush) is described in the clinical study informed consent forms. Participants will be instructed to pay attention to genital hygiene and have appropriate hydration and be warned that severe genital infection may require urgent medical attention (see Section 10.2.3.8, Fournier's gangrene).

#### 10.2.3.5 Hypoglycemia

Participants with T2DM treated with antidiabetic medications (especially insulin and sulfonylureas) are at risk of hypoglycemia. Licogliflozin is effective in reducing glucose level and may lead to hypoglycemia in participants receiving other antidiabetic medications (especially insulin and insulin secretagogue). Diabetic participants must continue their routine self-monitoring of glucose levels and be educated regarding hypoglycemic symptoms (dizziness, lightheadedness; palpitations, heart racing/pounding, shaking, sweating, hunger, blurred vision, impairment of motor function, confusion), explanation of possible triggers (strenuous exercise, delayed meals, changes in meal composition, illness, periods of prolonged fasting) and treatment by the physician managing the participant's diabetes.

During the course of the study, if a participant experiences clinically symptomatic hypoglycemia, an immediate medical evaluation should be conducted. Glucose levels will be measured. If a confirmed glucose level is <56 mg/dL by repeated measurement, background anti-diabetic medication may require dose adjustment, or study treatment may be interrupted and the participant treated according to standard of care for hypoglycemia.

Events consistent with or suspected to be hypoglycemia, should be recorded in the participant diary and on the AE eCRF.

Furthermore, this study outlines inclusion and exclusion criteria to minimize this risk and exclude participants at risk of this adverse event (please refer to Section 5 for details).

#### 10.2.3.6 Pancreatitis

In the 2012 update to the diagnosis Atlanta classification of acute pancreatitis, 2 of the following 3 features are required for diagnosis: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back), (2) serum lipase (or amylase) activity at least 3 times greater than the upper limit of normal (ULN), and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography, magnetic resonance imaging or transabdominal ultrasonography. (Banks et al 2012) Therefore, in the event of AE of significant abdominal pain or other suggestive features, consider whether the participant may have pancreatitis; amylase and lipase should be checked and the need for diagnostic imaging considered. If pancreatitis is confirmed by this definition, the event must be reported as an SAE even if hospitalization is not required. All tests and procedures related to the diagnosis and treatment of the event should be recorded in the appropriate eCRFs. The acute episode should be managed as in normal clinical practice. Study medication may be interrupted during investigation of the event. If pancreatitis is confirmed, licogliflozin and other potentially suspect medicinal products should be discontinued.

#### 10.2.3.7 Ketoacidosis

Euglycemic ketoacidosis is a rare adverse event reported with SGLT-2 inhibitor class of drugs. Participants are advised to maintain hydration and avoid excessive alcohol consumption. Participants should seek medical attention immediately in case they develop any of the following symptoms: vomiting, dehydration, labored breathing, unusual fruity smell in breath, tachycardia, confusion or disorientation and/or coma. Please note that blood glucose levels may be normal in this condition. Laboratory investigations for ketones, electrolytes and anion gap must be performed immediately. The participant must be hospitalized and managed for ketoacidosis as in normal clinical practice. Study medication should be interrupted and precipitating factors must be identified. Participants are advised to interrupt study medication in situations which can predispose ketoacidosis such as during prolonged fasting due to illness or surgery. If ketoacidosis is confirmed, the event must be reported as an SAE. All tests and procedures related to the diagnosis and treatment of the event should be recorded in the appropriate eCRFs.

#### 10.2.3.8 Fournier's Gangrene

Fournier's gangrene is a rare adverse event reported with SGLT-2 inhibitor class of drugs. Participants are advised to pay attention to genital hygiene. Participants developing fever with pain or swelling in genital or anal region or any other signs/symptoms of infection of genitalia

or perineum must seek medical advice immediately. Prompt treatment (including antibiotics and consideration of surgical debridement) should be instituted. Study medication should be discontinued. If the diagnosis of Fournier's gangrene is confirmed, the event must be reported as an SAE. All tests and procedures related to the diagnosis and treatment of the event should be recorded in the appropriate eCRFs.

## 10.3 Committees

### 10.3.1 Data Monitoring Committee

This study will include an external Data Monitoring Committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. 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, metabolic disorders or general medicine. The main tasks of the committee for this study will be to review emerging safety data and primary efficacy data and provide recommendations to the sponsor concerning safety.

The 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 participants develop similar SAEs, or otherwise if found necessary by the sponsor, the DMC chairman will be alerted. Further details regarding relevant data and actions will be specified in the separate DMC charter.

# 11 Data Collection and Database management

## 11.1 Data collection

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

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

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

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

## 11.2 Database management and quality control

Novartis personnel or designated contract research organization (CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating

the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis or a designated CRO at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

## 11.3 Site monitoring

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

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

# 12 Data analysis and statistical methods

A final analysis will be conducted after all participants finish the end of study or premature study discontinuation visit. No interim analysis for earlier statistical inference is planned for the study. Analyses for DMC review will be outlined in a separate DMC charter.

Unless if specified differently, descriptive analysis for categorical data will be summarized as frequencies and percentages and continuous data will be summarized with the mean, standard deviation, median, minimum, and maximum.

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

## 12.1 Analysis sets

Following analysis populations will be defined for the statistical analysis:

Screened analysis set (SCR) comprises of all participants who signed the informed consent.

Randomized Analysis set (RAN) comprises of all participants who received a randomization number, regardless of whether participants received study medication.

Full Analysis Set (FAS) comprises of all participants to whom study treatment has been assigned by randomization. Participants who were mis-randomized (not qualified for randomization but randomized inadvertently) and did not receive investigational medication, however, are excluded from the FAS. Efficacy analysis will be conducted on FAS. Following the intent-to-treat (ITT) principle, participants are analyzed according to the treatment they have been assigned during the randomization procedure regardless of actual treatment received and the true stratum the participant belongs to if a participant is assigned to wrong stratum during randomization.

Safety Analysis Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

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

The number and percentage of participants 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 participants. The frequency (%) of participants with protocol deviations and criteria leading to their exclusion from each analysis set will be presented for randomized set.

## 12.2 Participant demographics and other baseline characteristics

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

Categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline, including NASH specific co-morbidities, will be summarized separately by system organ class and preferred term and by treatment group.

## 12.3 Treatments

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

The duration of exposure (days) to investigational treatment, the dose intensity (computed as the ratio of actual cumulative dose received and actual duration of exposure) and the relative dose intensity (computed as the ratio of dose intensity and planned dose intensity) will be summarized for the safety set. The proportion of participants with dose reduction will also be presented by treatment groups.

Proportion of participants non-compliance with the planned study treatment, which is defined as relative dose intensity >1.25 or <0.75, will be summarized descriptively for the double-blind treatment period.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by treatment group according to the World Health Organization (WHO), Anatomical Therapeutic Chemical (ATC) classification system.

## 12.4 Analysis of the primary endpoint(s)/estimand(s)

The two primary endpoints to be analyzed are:

1. Whether the participant has at least one stage improvement in fibrosis without worsening of NASH at Week 48 compared with baseline;

2. Whether the participant achieves resolution of NASH and no worsening of fibrosis at Week 48 compared with baseline.

Five pairwise comparisons may be evaluated for each primary endpoint, rendering a total of ten potential comparisons. Family-wise Type I error rate is controlled at two-sided 5% (one-sided 2.5%) level, and is split for the two primary endpoints. Each primary endpoint will have its own branch of tests and may pass its alpha to the other branch from its last two tests.

The main objective of the study is to demonstrate the combination efficacy of tropifexor + licogliflozin over placebo in participants with NASH and stage 2 or 3 fibrosis, so the two combination therapy vs. placebo tests (one for each primary endpoint) will be performed first. Then, for each primary endpoint, the two monotherapies (LJN452 and LIK066) will be compared with placebo after the combination treatment reveals superiority over placebo with

significant evidence. If one of the monotherapy vs. placebo tests succeeds, then it will pass its alpha to the corresponding combination vs. monotherapy test. An alpha recycling graph is presented in Section 12.4.2 to illustrate the test hierarchy.

The following estimand framework is adopted to meet the objective.

1. Population: Participants with NASH (using NAFLD Activity Score (NAS) ≥ 4 with at least 1 point each in inflammation and ballooning on the screening histology assessment performed by the central reader) and stage 2 or 3 fibrosis (using NASH CRN fibrosis criteria), as defined by the inclusion and exclusion criteria of the study Section 5.
2. Treatment of interest: the combination therapy (tropifexor 140 µg + licogliflozin 30 mg, once daily) is the treatment of interest in the comparisons of combination vs. placebo, combination vs. tropifexor, and combination vs. licogliflozin, whereas the monotherapy (tropifexor 140 µg once per day or licogliflozin 30 mg once per day) is the treatment of interest in the comparisons of tropifexor vs. placebo and licogliflozin vs. placebo.
3. Variables of interest: histological response defined as:
   a. Whether the participant achieves improvement in fibrosis by at least one stage without worsening of NASH at week 48 compared with baseline.
   b. Whether the participant has resolution of NASH (absence of ballooning with no or minimal inflammation by histology) and no worsening of fibrosis at week 48 compared with baseline.
4. Summary measure: Odds ratio of participants achieving histological response at Week 48 for the following comparisons for each primary endpoint: combination vs. placebo, monotherapies vs. placebo, and combination vs. monotherapies.
5. Intercurrent events include
   - Early discontinuation of study treatment before week 48 visit.
   - Non-histologic clinical event suggesting treatment failures (e.g bariatric surgery, liver transplant and death due to disease).
   - Study treatment incompliance defined as relative dose intensity >1.25 or <0.75.
   - More than four weeks of cumulative exposure to any prohibited medications Section 6.2.2, alcohol usage more than what is permitted in the protocol, initiation of other T2DM or lipid lowering medication (e.g. GLP-1 modulator, statins), initiation of other treatment being evaluated or approved for NASH, or new concomitant interventions for weight control before the assessment for primary endpoint. The identification of relevant medications will be based on ATC3 and/or ATC5 codes, which will be included in analysis data set specifications. The list of concomitant interventions with significant effect for general weight loss will be determined based on blinded review of the study data.

For the intercurrent events related to the primary estimand, various strategies (such as treatment policy and composite variable) defined in ICH E9 (R1) will be utilized for the analyses. For instance, participants who discontinue the treatment after Week 24 will be asked to have their biopsies assessed at Week 48 regardless of the intercurrent event (treatment policy strategy), participants who discontinue the treatment before Week 24 will be considered as non-responders (composite variable strategy), and participants who have no biopsies extracted at Week 48 will be considered as non-responders (composite variable strategy).

For non-intercurrent event missing data, certain multiple imputation methods will be applied to estimate the endpoints.

### 12.4.1 Definition of primary endpoint(s)/estimand(s)

Section 2.1 describes the primary estimands that contain the primary endpoints. This section defines the primary endpoints in detail.

**The study uses two primary endpoints.**

**The first primary endpoint is**: Whether (yes or no) the participant achieves improvement in fibrosis by at least one stage without worsening of NASH at week 48 compared with baseline.

One stage fibrosis improvement is defined as the decrease by one point on the NASH CRN fibrosis score, i.e. "from 3 to 2" or "from 2 to 1" (considering that the randomized participants either has stage 2 or stage 3 fibrosis at baseline). Worsening of NASH is determined if any of three components of the NAS score (Steatosis, Lobular inflammation or Hepatocyte ballooning) at Week 48 is greater than that at baseline (FDA definition).

**The second primary endpoint is**: Whether (yes or no) the participant has resolution of NASH and no worsening of fibrosis at week 48 compared with baseline.

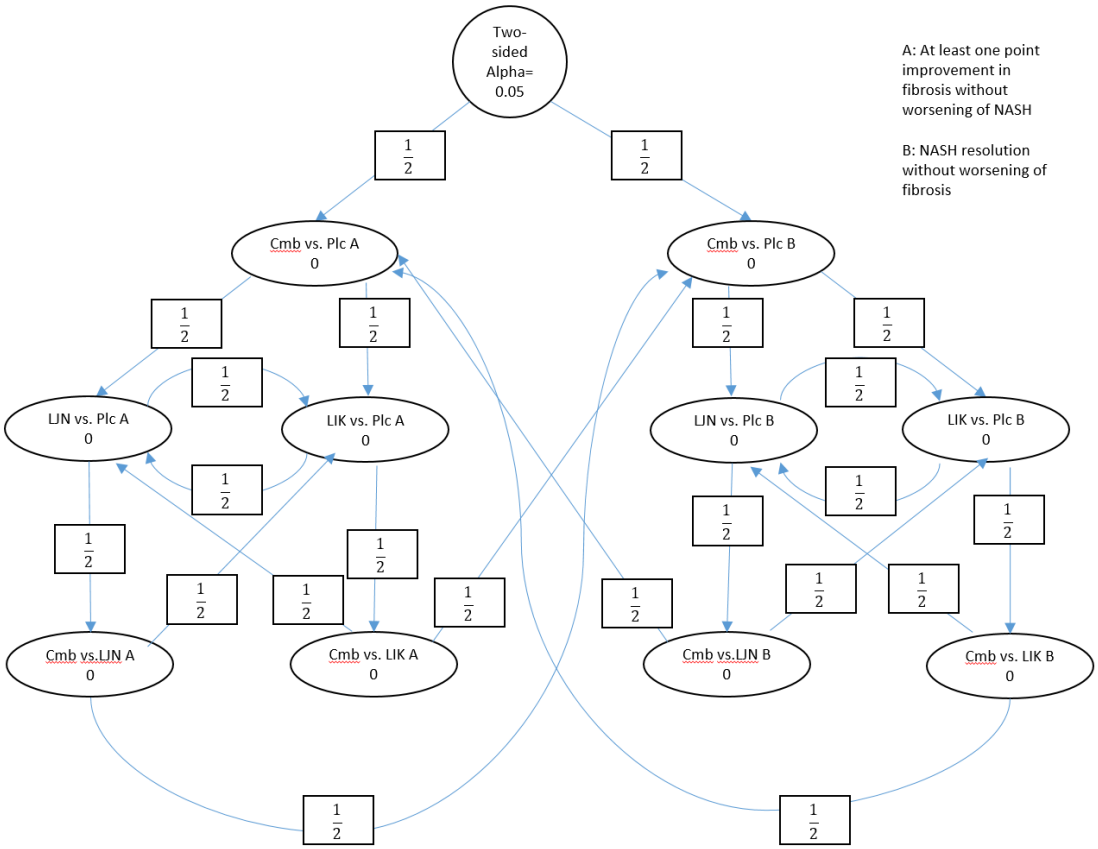
Resolution of NASH is satisfied if the NAS score for lobular inflammation $\leq 1$ AND the NAS score for Hepatocyte ballooning = 0, regardless of the value for steatosis (FDA definition). Worsening of fibrosis is defined as an increase in the NASH CRN fibrosis score from baseline to Week 48, i.e. "from 2 to 3", "from 2 to 4", or "from 3 to 4".

The two binary primary endpoints will be summarized as odds ratios for pairwise comparisons between treatments.

### 12.4.2 Statistical model, hypothesis, and method of analysis

The main goal of the study is to reveal the efficacy of the combination therapy (tropifexor + licogliflozin) compared with placebo in the two primary endpoints, so the two tests of combination therapy vs. placebo (one for each endpoint) will be conducted first. The study will be considered successful if at least one of these two tests passes with statistical significance. An overall two-sided 5% (one-sided 2.5%) alpha is adopted to the study and is splitted evenly to the two primary endpoints. In addition to the comparison between combination therapy and placebo, another four pairwise comparisons may be evaluated for each primary endpoint, rendering a total of ten ([1+4]*2=10) potential comparisons. Each primary endpoint will have its own branch of tests and may pass its alpha to the other branch from its last two tests. Under each branch, the two monotherapies (LJN452 and LIK066) will be compared with placebo after the combination treatment shows superiority over placebo with significant evidence. If one of the monotherapy vs. placebo tests succeeds, then it will pass its alpha to the corresponding combination vs. monotherapy test. An alpha recycling graph (Bretz et al 2009) is presented in Figure 12-1 below to illustrate the test relationship.

**Figure 12-1 An alpha recycling graph**




Within each primary endpoint branch, five comparisons may be evaluated in the following levels:

- Combination vs. placebo
- Tropifexor (LJN452) vs. placebo; licogliflozin (LIK066) vs. placebo
- Combination vs. tropifexor (LJN452);
- Combination vs. licogliflozin (LIK066);

Since there are two primary endpoints, a total of ten comparisons may be tested.

The comparisons are based on the four arms of the study: one combination therapy arm, two monotherapy arms and one placebo arm. The proportions of histological responders in these four arms are assumed following binomial distributions $(n, p)$. The sampling distribution of the difference $\hat{p}_{m\_i} - \hat{p}_{m\_j}$ will be asymptotically normal with mean $p_{m\_i} - p_{m\_j}$ and variance $\frac{p_{m\_i}(1-p_{m\_i})}{n_{m\_i}} + \frac{p_{m\_j}(1-p_{m\_j})}{n_{m\_j}}$, where $m$ is the index of the primary endpoint ($m = A$ if the

endpoint is "at least one stage improvement in fibrosis without worsening of NASH". $m = B$ if the endpoint is "NASH resolution without worsening of fibrosis".), and $i$ & $j$ are the indices of the two treatments in the comparison. For example, in the first level tests, $i$ represents the combination treatment and $j$ denotes the placebo. The information of proportion difference is later used for sample size calculation.

Some additional notations:

$p_A = (p_{A\_Cmb}, p_{A\_LIK}, p_{A\_LJN}, p_{A\_Plc})$~ True (population-wise) response rates of combination, licogliflozin, tropifexor and placebo with respect to at least one stage improvement in fibrosis without worsening of NASH at Week 48.

$p_B = (p_{B\_Cmb}, p_{B\_LIK}, p_{B\_LJN}, p_{B\_Plc})$~ True (population-wise) response rates of combination, licogliflozin, tropifexor and placebo with respect to NASH resolution without worsening of fibrosis at Week 48.

$n_A = (n_{A\_Cmb}, n_{A\_LIK}, n_{A\_LJN}, n_{A\_Plc})$~ Numbers of participants in the combination, licogliflozin, tropifexor and placebo arms to be analyzed for primary endpoint A.

$n_B = (n_{B\_Cmb}, n_{B\_LIK}, n_{B\_LJN}, n_{B\_Plc})$~ Numbers of participants in the combination, licogliflozin, tropifexor and placebo arms to be analyzed for primary endpoint B.

$\hat{p}_A = (\hat{p}_{A\_Cmb}, \hat{p}_{A\_LIK}, \hat{p}_{A\_LJN}, \hat{p}_{A\_Plc})$~ Observed response rates of the combination, licogliflozin, tropifexor and placebo arms with respect to at least one stage improvement in fibrosis without worsening of NASH at Week 48.

$\hat{p}_B = (\hat{p}_{B\_Cmb}, \hat{p}_{B\_LIK}, \hat{p}_{B\_LJN}, \hat{p}_{B\_Plc})$~ Observed response rates of the combination, licogliflozin, tropifexor and placebo arms with respect to NASH resolution without worsening of fibrosis at Week 48.

The null and alternative hypotheses of the ten comparison tests can be represented in the following form of odds ratio:

$$H_{m\_k\_0}: \frac{p_{m\_i}(1-p_{m\_i})}{p_{m\_j}(1-p_{m\_j})} = 1 \text{ vs. } H_{m\_k\_1}: \frac{p_{m\_i}(1-p_{m\_i})}{p_{m\_j}(1-p_{m\_j})} \neq 1 ,$$

where $m$, $k$, and $i\&j$ are the indices of the endpoint, the test, and the compared populations, respectively. For instance, if the endpoint to be analyzed is "whether the participant achieves improvement in fibrosis by at least one stage without worsening of NASH at week 48 compared with baseline", then $m = A$ and the five relevant comparisons are:

Combination vs. placebo (test 1, $k = 1, i = Cmb, j = Plc$)

Tropifexor (LJN452) vs. placebo (test 2,$k = 2, i = LJN, j = Plc$); licogliflozin (LIK066) vs. placebo (test3, $k = 3, i = LIK, j = Plc$)

Combination vs. tropifexor (LJN452) (test 4, $k = 4, i = Cmb, j = LJN$); combination vs. licogliflozin (LIK066) (test 5, $k = 5, i = Cmb, j = LIK$)

There are ten potential tests to be performed for the two primary endpoints (five for each primary endpoint), and it is important to control the overall Type I error rate for these tests. The alpha recycling graph presented in Figure 12-1 shows how alpha transfers among them. If the data fails to reject the null hypothesis of a test, then the alpha of that test will not be passed to others. This restriction ensures the control of overall Type I error rate. Again, for the primary

endpoints, the overall alpha is set at two-sided 5%. A logistic regression model with the logit of probability for histological response as the dependent variable, treatment groups as the main effect, baseline fibrosis stage and T2DM (No/Yes) as explanatory variables, and the baseline BMI as a covariate will be utilized to test the hypotheses at each step. While this model will be the typical logistic regression in most cases, it should be set as the Firth logistic regression if some arm (such as the placebo) has a low response rate, as the Firth method returns less biased results for data with rare events. The null hypothesis of *k*th test, if executed, will be rejected if the p-value for the coefficient of treatment effect in the *k*th comparison is less than or equals to its corresponding alpha. If no alpha is passed to a specific comparison, then its corresponding test will not be performed and p-value will not be calculated. More statistical specifications of the model will be described in the statistical analysis plan (SAP).

The number and percentages of histological responders at week 48 in FAS will be summarized by treatment groups. The difference between the treatment of interest and the alternative treatment will be presented along with 95% confidence interval calculated based on the normal approximation for distribution of the difference between two binomial random variables.

### 12.4.3 Handling of remaining intercurrent events of primary estimand

Intercurrent events of primary estimand will be addressed with various strategies (given that these events occur before the histological assessments at Week 48):

1. Bariatric surgery: participants who have undergone bariatric surgeries during trial participation are considered as non-responders (composite variable strategy).
2. Use of alcohol above protocol permitted amount: the intercurrent events (overuse of alcohol) will be ignored for estimation (treatment policy strategy).
3. Addition or removal of any medication that may have a confounding effect on the endpoints: the treatment effect will be assessed with the intercurrent event ignored (treatment policy strategy). The treatment policy strategy may not be ideal if the confounding medications highly affect the endpoints. Consequently, a supplementary analysis will be conducted where the treatment effect is imputed as if the intercurrent event doesn't occur (hypothetical strategy)
4. Premature discontinuation of study treatment due to tolerability, efficacy, adherence, or adverse event: participants who discontinue the treatment after Week 24 will be asked to have their biopsies assessed at Week 48 regardless of the intercurrent event (treatment policy strategy), participants who discontinue the treatment before Week 24 will be considered as non-responders (composite variable strategy), and participants who have no biopsy extracted at Week 48 will be considered as non-responders (composite variable strategy).
5. Death, transplantation and other clinical outcomes: participants will be considered as non-responder (composite endpoint strategy).
6. Acute medical condition not related to the study treatment affecting the liver: participants will have their Week 48 biopsies assessed regardless of the intercurrent events (treatment policy strategy).
7. Acute medical condition related to the study treatment affecting the liver: participants are considered as non-responder (composite endpoint strategy).

### 12.4.4 Handling of missing values not related to intercurrent events

While not possible to confirm missing completely at random (MCAR), the histological response status from the early termination visit after at least 24 weeks of study treatment will be used for the primary analysis in case of missing primary endpoint at week 48. Participants otherwise with primary endpoint missing or any primary endpoint after intercurrent events will have the values imputed using multiple imputation (MI) methods (Rubin 1976, Rubin 1987) under a missing at random (MAR) assumption.

For multiple imputation: an arbitrary missing pattern will be assumed and a fully conditional specification (FCS) method with logistic regression will be applied. The logistic model will be used to analyze the multiple imputed datasets, and pooled results will be obtained based on Rubin's combination rules. More implementation details of the multiple imputation (MI) will be specified in the SAP.

The proportion of participants with missing primary endpoints at week 48 will be compared among the combination therapy, monotherapies and the placebo.

### 12.4.5 Sensitivity analyses for primary endpoint(s)/estimand(s)

Any sensitivity analysis of the primary efficacy estimands will be described in the SAP.

## 12.5 Analysis of secondary endpoints

Summary tables of descriptive statistics will be presented by treatment group, and by scheduled visit where applicable, for secondary endpoints. Counts and percentages will be presented for categorical variables and the arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile will be presented for continuous variables.

### 12.5.1 Efficacy [redacted] endpoint(s)

Secondary efficacy endpoints will be analyzed in the FAS and planned analyses are outlined in Table 12-1 below:

**Table 12-1 Planned Analyses**

| Endpoints | Analysis |
|---|---|
| Key secondary endpoint: whether the participant achieves resolution of NASH and no worsening of fibrosis OR Improvement in fibrosis by at least one stage without worsening of NASH at Week 48 compared with baseline. | Same statistical methods as for one branch of the primary analysis with overall Type I error rate controlled at two sided 0.05 level. |
| Whether (yes or no) the participant has at least one stage improvement in fibrosis at week 48 compared with baseline | Same statistical methods as for the key secondary endpoint analysis with neither hypothesis tests nor p-values. |
| Whether (yes or no) the participant has at least two stage improvement in fibrosis stage and no worsening of NASH at week 48 compared with baseline | Same statistical methods as for the primary analysis with neither hypothesis tests nor p-values. |
| Change in liver fat content based on MRI - PDFF (in 40% of participants) over time up to Week 48 compared with baseline | Descriptive statistics, adjusted mean and mean differences of treatment of interest vs. alternative treatment with 95% CI by scheduled visits based on repeated measurement analysis of covariance (ANCOVA) model will be presented. |
| Whether (yes or no) the participant has 5% or more reduction in body weight at Week 48 compared to baseline | Number and percentage of participants with 5% or more reduction in body weight. Difference in percentages between treatment of interest and alternative treatment along with 95% CI calculated based asymptotic normal distribution of difference in proportions will be presented. CMH test stratified with baseline T2DM status will be performed to estimate odds ratio (95% CI) between treatment of interest and alternative treatment. |
| Change in ALT and AST over time up to Week 48 compared with Baseline | The mixed model of repeated measurement will be fitted to changes from baseline in these endpoints over time. The point estimate and the associated 95% CI of the change from each treatment at each visit will be presented. |
| Change in GGT over time up to Week 48 compared with Baseline | The mixed model of repeated measurement will be fitted to changes from baseline in GGT over time. The point estimate and the associated 95% CI of the change from each treatment at each visit will be presented. |

### 12.5.2 Safety endpoints

For all safety analyses, the safety set will be used and will be presented by actual investigational treatment as participant first received after randomization.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). The on-treatment period lasts from the date of first administration of study treatment to 30 days after the date of the last actual administration of any study treatment.

A separate summary for death including on treatment and post treatment deaths will be provided.

#### 12.5.2.1 Adverse Events

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

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Separate summaries will be provided for study medication related adverse events, serious adverse events, other significant adverse events and adverse events leading to study drug discontinuation.

Participants who died any time during the study will be listed with SAEs leading to such deaths.

#### 12.5.2.2 Clinical laboratory evaluation

Summary statistics for standard laboratory test results will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Number (percent) of participants with post-treatment changes in lab parameters related to hepatotoxicity (ALP, ALT, AST, or bilirubin elevations as outlined in Section 10.2.1 and Table 16-2) will also be summarized.

#### 12.5.2.3 Vital signs

The change from baseline in vital sign parameters, including Anthropometric measurements, will be summarized at scheduled post-baseline visits by treatment group. Change from baseline will only be summarized for participants with both baseline and post-baseline values.

Participants with clinically notable vital signs as defined in Section 16.1 will be listed.

#### 12.5.2.4 ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted centrally.

Number of participants changing in normal or abnormal ECG will be summarized by treatment and scheduled visit.

The Fridericia QT correction formula (QTcF) will be used for clinical decisions and for analyses. Notable QTcF values and changes from baseline will be summarized by treatment and scheduled visit, where a notable value is defined as a QTcF ≥450 msec (male) or ≥460 msec (female) and the categories used for the change (increase) in QTcF are: ≤ 30 ms, > 30 to ≤ 60 ms and > 60 ms.

[redacted]

## 12.7 Interim analyses

No interim analysis is planned for the study. Analysis needed for safety review by DMC will be defined in a separate DMC charter.

## 12.8 Sample size calculation

Sample size and allocation are determined by three factors:

1. Optimizing the power of passing at least one of the combination vs. placebo tests from the two primary endpoints;
2. Optimizing the power of passing any monotherapy vs placebo test (given that at least one of the combination vs. placebo tests have succeeded);
3. Restricting the size of placebo arm no larger than that of any treatment arm.

### 12.8.1 Primary endpoint(s)

Assumptions about true histological response rates for various treatments and placebo are made for sample size calculation. Published studies so far (Table 12-2) suggest unignorable placebo effect ranging from 8% to 18% for different populations and endpoints, but unpublished studies indicate some even higher placebo rates. For each primary endpoint, the response rates of the two monotherapies are assumed to be similar to each other and higher than that of placebo, and the response rate of the combination therapy is deemed to be the highest.

**Table 12-2 Placebo effects on histological responses**

| Histological Response definition | Time point | Histological study | NASH population with Fibrosis stages | Placebo response rate |
|---|---|---|---|---|
| Fibrosis improvement of 1 stage and no worsening in NASH | Month 18 | REGENERATE (2019) Obeticholic acid | F1 + F2 + F3 | 10.6% |
| | | | F2 + F3 | 11.9% |
| | Week 52 | CENTAUR (2018) Cenicriviroc | F1 + F2 + F3 | 10.4% |
| | Week 52 | ARREST (2018) Aramchol | F1 + F2 + F3 | 17.5% |
| | Week 48 | STELLAR3 (2019) Selonsertib | F3 | 13.2% |
| | Week 48 | STELLAR4 (2019) Selonsertib | F4 | 12.8% |
| NASH resolution with no worsening in Fibrosis | Month 18 | REGENERATE (2019) Obeticholic acid | F1 + F2 + F3 | 8% |
| | | | F2 + F3 | 7.9% |
| | Week 52 | GOLDEN (2016) Elafibranor | F0+F1+F2+F3 | 9% |

**Table 12-3 Response rate setting used for sample size and power calculation**

| Treatment / Primary Endpoint | True Response Rate | | | |
|---|---|---|---|---|
| | Combination | LJN452 | LIK066 | Placebo |
| At least one stage improvement in fibrosis without worsening of NASH | 35% | 30% | 30% | 20% |
| NASH resolution without worsening of fibrosis | 25% | 20% | 20% | 10% |

Table 12-3 shows the assumed response rates of treatments and placebo under the two primary endpoints. Since both endpoints involve fibrosis and NASH, it is reasonable to expect these endpoints associated with each other. The participant level correlation of the two endpoints is set at +0.5 to be conservative in evaluating sample size and power.

Sample size is first determined by reaching 80% power for passing the combination therapy vs. placebo test on at least one of the primary endpoints under equal allocations of the four arms. Table 12-4 displays the powers under various sample sizes. From the table, it is clear to see that a sample size of 380 can obtain 80% power for the tests of interest.

**Table 12-4 Powers of different sample sizes under equal allocation**

| Sample Size | | | | | Power | | |
|---|---|---|---|---|---|---|---|
| Total | LJN452 | LIK066 | Combo | Placebo | Cmb vs. Plc on Endpoint A | Cmb vs. Plc on Endpoint B | Cmb vs. Plc on at least one of Endpoint A and B |
| 200 | 50 | 50 | 50 | 50 | 0.31 | 0.42 | 0.52 |
| 220 | 55 | 55 | 55 | 55 | 0.33 | 0.45 | 0.56 |
| 240 | 60 | 60 | 60 | 60 | 0.37 | 0.49 | 0.60 |
| 260 | 65 | 65 | 65 | 65 | 0.39 | 0.53 | 0.63 |
| 280 | 70 | 70 | 70 | 70 | 0.41 | 0.57 | 0.67 |
| 300 | 75 | 75 | 75 | 75 | 0.45 | 0.60 | 0.70 |
| 320 | 80 | 80 | 80 | 80 | 0.47 | 0.62 | 0.72 |
| 340 | 85 | 85 | 85 | 85 | 0.50 | 0.65 | 0.75 |
| 360 | 90 | 90 | 90 | 90 | 0.51 | 0.68 | 0.77 |
| 380 | 95 | 95 | 95 | 95 | 0.55 | 0.72 | 0.80 |
| 400 | 100 | 100 | 100 | 100 | 0.57 | 0.73 | 0.82 |

After total sample size is fixed, allocation of the four arms is assessed based on three factors:

1. Increasing the power of passing at least one of the combination vs. placebo tests from the two primary endpoints;
2. Slightly decreasing the power of passing any monotherapy vs placebo test (given that at least one of the combination vs. placebo tests have succeeded);
3. Constraining the size of placebo arm no larger than that of any treatment arm.

**Table 12-5 Powers of passing at least one of the combination vs. placebo tests under various allocations of 380 participants**

| Sample Size | | | | Power |
|---|---|---|---|---|
| LJN452 | LIK066 | Combo | Placebo | Cmb vs. Plc on at least one of Endpoint A and B |
| 34 | 34 | 278 | 34 | 0.72 |
| 49 | 49 | 233 | 49 | 0.80 |
| 65 | 65 | 185 | 65 | 0.84 |
| 80 | 80 | 140 | 80 | 0.85 |
| 95 | 95 | 95 | 95 | 0.80 |
| 110 | 110 | 50 | 110 | 0.62 |

According to Table 12-5, allocation of 80 (LJN452), 80 (LIK066), 140 (Combo), and 80 (placebo) provides good power for passing at least one of the combination therapy vs. placebo tests from the two primary endpoints.

Power calculations were performed with simulations (n=100000) implemented in R 3.5.3, where the primary analysis in each simulated study was performed using z-tests of difference in proportions without continuity correction for simplicity.

The missing Week 48 biopsy rate of the study is anticipated to be around 20%. The missing response data due to intercurrent events will be addressed with intercurrent event strategies specified in ICH E9, whereas those not related to intercurrent events will be substituted with certain multiple imputation methods. Sample size adjustment is not needed because the treatment response rates are already assumed with conservative values.

### 12.8.2 Secondary endpoint(s)

The tests of the key secondary endpoint are not used for sample size calculation. These tests are similar to the five tests of each primary endpoint and will be performed after the tests of primary endpoints succeed.

# 13 Ethical considerations and administrative procedures

## 13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Council for Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

## 13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 13.3 Publication of study protocol and results

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

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

### 13.4 Quality Control and Quality Assurance

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

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

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

## 14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

### 14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of participants included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

# 15 References

References are available upon request

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# 16 Appendices

## 16.1 Appendix 1: Clinically notable laboratory values and vital signs

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 16.2 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 $\geq$ 450 msec for males or $\geq$ 460 msec for females, all such ECGs will be flagged by the Central CRO and require assessment for clinical relevance and continuance of the participant by the Investigator.

For vital signs, please see Table 16-1 for notable abnormalities.

**Table 16-1 Vital signs**

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

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

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

Table 16-2 describes detailed thresholds and actions needed when elevations of liver parameters is observed or symptoms / adverse events indicative of liver toxicity appear. These symptoms could include jaundice, clinical evidence of liver decompensation, histology findings suggestive of drug induced liver injury or development of benign or malignant liver neoplasms.

For transaminases (ALT, AST), GGT, ALP, DBL and TBL, the baseline value will be calculated as the mean of the assessments before first administration of the study drug, which are those taken at the Screening and Baseline visits.

For normal reference ranges for AST, ALT, GGT, TBL and ALP, please refer to the values provided by the Central Laboratory.

**Table 16-2 Management of Participants with Confirmed ALP, ALT, AST, or Bilirubin Elevations With or Without Liver Related Clinical Symptoms**

| Baseline | Treatment-Emergent (Confirmed[a]) | Liver-Related Clinical Symptoms[b] | Action taken | |
|---|---|---|---|---|
| | | | Monitoring[c] | Study Drug |
| **ALT and/or AST** | | | | |
| Baseline ALT and/or AST < 2 × ULN | ALT and/or AST > 3 × ULN but ≤ 5 × baseline | None | Laboratory monitoring and causality evaluation | Continue dosing |
| | | Present | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| | ALT and/or AST > 3 × ULN but ≤ 5 × baseline AND total bilirubin > 2 × ULN (in Gilbert's syndrome, see footnote[f]) | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| | ALT and/or AST > 3 × ULN and > 5 × baseline | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Permanently discontinue |

| Baseline | Treatment-Emergent (Confirmed[a]) | Liver-Related Clinical Symptoms[b] | Action taken | |
|---|---|---|---|---|
| | | | Monitoring[c] | Study Drug |
| Baseline ALT and/or AST ≥ 2 × ULN | ALT and/or AST > 2 × baseline but ≤ 3 × baseline | None | Laboratory monitoring and causality evaluation | Continue dosing |
| | | Present | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| | ALT and/or AST > 2 × baseline but ≤ 3 × baseline AND total bilirubin > 2 × ULN[f] | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| | ALT and/or AST > 3 × baseline | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Permanently discontinue |
| Baseline normal or elevated ALT and/or AST values | ALT and/or AST<br>> 3 × ULN and > 2 × baseline AND either<br>total bilirubin > 2 × baseline OR INR increase by >0.3 to a value >1.5 | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring, as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| **ALP** | | | | |
| Baseline ALP ≤ ULN | ALP > 1.5 × ULN<br>(not due to known bone pathology) | None | Laboratory monitoring and causality evaluation[c] | Continue dosing |
| | | Present | Comprehensive clinical evaluation and laboratory monitoring, as | Interrupt dosing[e] |

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

| Baseline | Treatment-Emergent (Confirmed[a]) | Liver-Related Clinical Symptoms[b] | Action taken | |
|---|---|---|---|---|
| | | | Monitoring[c] | Study Drug |
| Baseline normal or elevated direct bilirubin | Direct bilirubin > 1.5 mg/dL | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring[c], as well as causality evaluation[d], [redacted] | Interrupt dosing[e] |
| **ALT, AST, ALP and Total Bilirubin** | | | | |
| Baseline normal | Normal or elevated values | Present | Comprehensive clinical evaluation and laboratory monitoring[c], as well as causality evaluation[d], [redacted] | Continue or Interrupt dosing as appropriate[g] |
| | Potential DILI cases defined as ALT or AST > 3 × ULN and TBL > 2 × ULN | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring[c], as well as causality evaluation[d], [redacted] (Refer Section 10.2.1 for required investigations) | Interrupt dosing[e] |
| Baseline elevated | Potential DILI cases defined as [AST or ALT > 2 x baseline] OR [AST or ALT >7 × ULN] whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN] | With or without liver-related clinical symptoms | Comprehensive clinical evaluation and laboratory monitoring[c], as well as causality evaluation[d], [redacted] (Refer Section 10.2.1 for required investigations) | Interrupt dosing[e] |

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

[a] The required confirmatory measurement should be obtained within 48 to 72 hours after the laboratory results become available. If prompt evaluation is not possible, study drug should be interrupted immediately (date of last study drug dose must be recorded in the eCRF).
[b] Combination of clinical symptoms of abdominal pain, worsening or new fatigue, anorexia, nausea, rash, vomiting, diarrhea, fever, pruritus, and/or eosinophilia (> 5%).
[c] Frequent hepatic laboratory testing and clinical assessments, including a thorough causality evaluation, should be performed every other week at minimum, in consultation with the sponsor,

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

until resolution of clinical symptoms and/or stabilization of liver biochemistries to baseline levels or baseline grade of abnormality. Also, see Section 10.2 for suggested investigations particularly for Potential Hy's law.

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

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

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

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

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

**Table 16-3 Specific Renal Alert Criteria and Actions**

| **Serum Event** | |
|---|---|
| Serum creatinine increase 25 – 49% compared to baseline | Confirm 25% increase after 24-48h<br>Follow up within 2-5 days |
| Acute Kidney Injury: Serum creatinine increase ≥ 50% compared to baseline | Follow up within 24-48h if possible<br>Consider study treatment interruption<br>Consider participants hospitalization /specialized treatment |
| GFR is <60 ml x min1 x 1.73 m2 | Follow up within 24-48h if possible<br>Consider study treatment interruption |
| GFR is <30 ml x min1 x 1.73 m2 | Follow up within 24-48h if possible<br>Consider study treatment interruption |
| Urine Event | |
| Albumin- or Protein-creatinine ratio increase ≥ 2-fold (2 x baseline)<br>Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol;<br>Protein-creatinine ratio (PCR ) ≥ 1g/g or ≥ 100mg/mmol | Confirm value after 24-48h<br>Perform urine microscopy<br>Consider study treatment interruption / or discontinuation |
| New onset dipstick proteinuria (≥ 3+) | Confirm assessment within 24-48 hours<br>Consider causes and possible interventions<br>Assess serum albumin & serum total protein<br>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected |
| New onset dipstick hematuria (≥ 3+), (after excluding menstruation, urinary infection, extreme exercise, or trauma) | Confirm assessment within 24-48 hours<br>Urine sediment microscopy<br>Perform serum creatinine, ACR |
| For all renal events: | |
| Document contributing factors in the eCRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed<br>Monitor participant regularly (frequency at investigator's discretion) until either:<br>Event resolution:<br>• sCr within 10% of baseline<br>• protein-creatinine ratio within 50% of baseline,<br>• albumin-creatinine ratio within 50% of baseline.<br>Event stabilization:<br>• sCr level with ± 10% variability over last 6 months<br>• protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months<br>• albumin-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months. | |

[redacted]

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

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

American Heart Association (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.