

Statistical Analysis Plan (SAP)

Protocol Title:	A placebo-controlled, proof-of-concept study to evaluate the safety and efficacy of Lanifibranor alone and in combination with the sodium-glucose transport protein 2 (SGLT2) inhibitor EmpaGliflozin in patiEnts with Non-alcoholic steatohepatitis (NASH) and type 2 diabetes mellitus (T2DM)
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CRF Version No./Date:	2.0/23-May-2023
SAP Version No./Date:	2.0/25-Sep-2024

1.0 Approvals

Sponsor	
Sponsor Name:	Inventiva S.A.
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Biostatistician / Title:	
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(NOTE: Electronic Signatures should only be used if all parties have the ability to eSign)

2.0 Change History

Version/Date	Change Log
0.1/07-Oct-2022	Created as new
0.1/19-Jan-2023	Update and completion following IVA review
0.1/05-May-2023	Updated per IVA review comments
0.2/09-Sep-2023	Updated per IVA review comments
0.3/14-Oct-2023	Updated per IVA review comments
0.4/03-Nov-2023	Updated per IVA review comments Updated according to protocol amendment 5 Included Interim Analysis details
0.5/12-Dec-2023	Updated per IVA review comments
1.0/26-Feb-2024	Updated per IVA review comments
1.0/08-Mar-2024	Updated SAP cosmetically to be eCTD compliance
1.1/14-Jun-2024	Updated per IVA review comments
2.0/17-Jul-2024	Updated per IVA review comments
2.0/25-Sep-2024	Updated SAP cosmetically to be eCTD compliance

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3.0 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Inventiva Protocol 337HNAS21016 (LEGEND).

4.0 Scope

The SAP outlines the following:

- Study Objectives
- Study Design
- Population Sets
- Conventions and Derivations
- Statistical Methods (including Study Estimands) and Analyses

5.0 Introduction

This SAP should be read in conjunction with the clinical study Protocol V6.0 dated 22 February 2024 and case report form (CRF) V2.0 dated 23 May 2023. Any further changes to the Protocol or CRF may necessitate updates to the SAP.

The final approval of the SAP by the sponsor and the ICON statistician will occur prior to study database lock and unblinding of the study treatment codes.

This document is the reference for all the study statistical analyses except pharmacokinetics ones that will be analysed separately, with a specific SAP developed (see Protocol Section 9.4.8).

5.1 Changes from Protocol

The following changes from the protocol have been made in this SAP.

- The on-study period definition was modified from 'beginning at baseline' to 'beginning at screening' to consider the screening visit in analyses.
- The on-treatment period for AEs was modified from ending the earliest of 30 days post last treatment dose or the on-study period last date to 30 days post last treatment dose because this will be the duration whereby patients are considered treated with the study treatment.
- The screened set was included in the SAP for reporting purposes.
- Derived fibrosis markers and [REDACTED] were added for analyses.
- The intercurrent event 'Significant Diet change affecting metabolism' has been added in the Estimand table.
- A data integrity plan was planned to be developed as per protocol, describing how the blinding will be maintained, how integrity of the trial will be protected and to ensure continued adherence to treatment and trial retention for the remaining patients in the trial (among those that are not part of the interim analysis). Since this information are provided in some other documents, this plan was not developed, see [Section 10](#).
- The Supplementary analysis 4 described in [Section 12.5.2.2](#) was removed and the following Supplementary analyses have been renumbered. Indeed, this analysis was based on MAR or MnAR assumptions of the reasons for premature treatment discontinuation. Since only 1 patient prematurely discontinued from the treatment due to a MnAR reason (safety reason=adverse event), this analysis has been judged not useful/needed.

6.0 Study Objectives

6.1 Primary Objective

The primary objective of this study is to assess the effect of lanifibranor alone compared to placebo and the effect of lanifibranor in combination with empagliflozin compared to placebo on Haemoglobin A1C (HbA1c) after a 24-week treatment period.

In line with International Council for Harmonisation (ICH) E9 (R1) addendum, five attributes (treatment, population, endpoint, intercurrent events, and population-level summary) were specified to translate the primary efficacy objective into treatment effects that are to be estimated (estimands), and are described in [Section 12.5.2](#).

The primary estimand is the comparison of lanifibranor alone and lanifibranor plus empagliflozin versus placebo on the change in HbA1c from baseline to end of treatment (Week 24), on the population initiating treatment with lanifibranor or lanifibranor plus empagliflozin, and excluding potential rescue medication and potential significant diet changes affecting metabolism (under the hypothetical strategy where patients would have continued their treatment during 24 weeks without rescue medication or significant diet change).

The following information describe the primary estimand strategy for the analysis of the primary endpoint.

1. The treatment conditions of interest are lanifibranor 800 mg administered daily (blinded), lanifibranor 800 mg administered daily plus empagliflozin (open-label), and are compared with placebo administered daily (blinded).
2. Adults with non-cirrhotic NASH and T2DM are the targeted patient population defined by list of in- and exclusion criteria.
3. The treatment effect is assessed at Week 24 by comparing absolute changes in HbA1c from baseline in each active arm versus placebo.
4. Intercurrent events are handled through a combination of treatment-policy strategy and hypothetical strategy (see [Table 7](#))
5. The population-level summary of the treatment effect will be quantified by comparing at Week 24 the model-adjusted absolute changes in HbA1c from baseline (LSMean), supported by the model-adjusted mean difference (of the absolute changes in HbA1c from baseline) between active arm compared to placebo, obtained through a Mixed Models for Repeated Measures (MMRM) model, adjusted on baseline HbA1c value (detailed below).

6.2 Secondary Objectives

The secondary objectives of this study are to assess the effect of lanifibranor alone compared to placebo and lanifibranor in combination with empagliflozin compared to placebo after a 24-week treatment duration on:

- Liver tests
- Marker of glycaemic control and insulin resistance
- Inflammatory markers
- Lipid parameters
- Body weight and body composition

and to assess the safety and tolerability of lanifibranor alone and in combination with empagliflozin during the 24-week treatment period and the 4-week follow-up period.

[illegible]

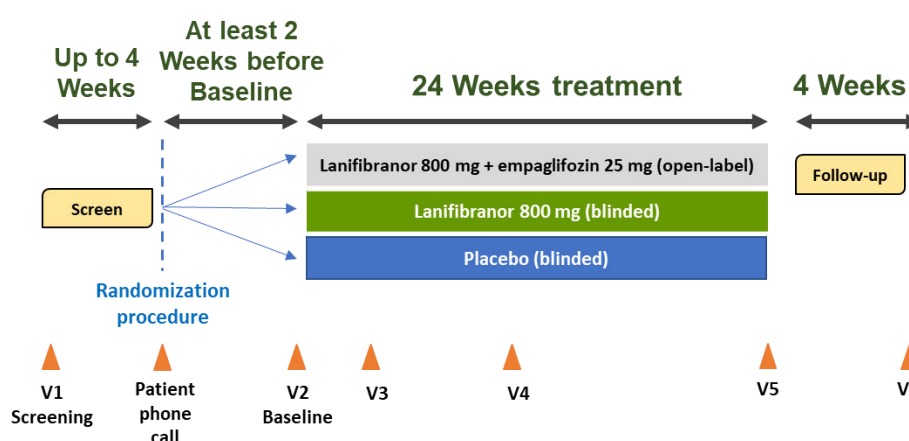
7.0 Study Design

This proof-of-concept study will assess the safety and efficacy of the pan-PPAR agonist lanifibranor alone and in combination with the SGLT2 inhibitor empagliflozin in patients diagnosed with NASH and Type 2 Diabetes Mellitus (T2DM). The study will assess the impact on safety (including body weight changes), metabolic parameters, inflammatory markers, body composition, liver function, and improvement in hepatic steatosis and fibrosis.

The study is designed as a multinational, multicentre, three-arm, randomized, double-blind for lanifibranor and placebo, open-label for the combination lanifibranor plus empagliflozin, placebo-controlled, 24-week treatment study followed by a 4-week post-treatment visit.

The overall study design is shown in [Figure 1](#) below:

Figure 1: Study design



A total of 63 patients are planned to be randomized 1:1:1 to receive:

- Lanifibranor 800 mg QD for 24 weeks or
- Matching placebo QD for 24 weeks or
- Lanifibranor 800 mg QD plus empagliflozin 10 mg QD for 24 weeks.

An interim analysis (IA) will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier.

The objective of this interim analysis will be:

- To obtain preliminary information on observed effects sizes / variability allowing an early insight on the treatment effect on multiple mechanistic endpoints, helping supporting future decision making, both for the LEGEND study and in the overall lanifibranor clinical program
- To stop recruitment should clear trends in study findings be observed thereby minimizing patient exposure with additional patients
- To evaluate early signs on the impact on mechanistic endpoints, to determine whether to continue to perform more complex evaluations on study participants and to aid future decisions

Recruitment will be paused once the first half of the planned patients are randomized. As this is a multicentre trial, some additional patients may have been randomized, and will continue to be followed in the study.

Patients who drop out after randomization but before first study drug administration will be replaced. Patients who drop out after randomization and have already received at least one dose of study drug will not be replaced. Those patients will be considered as early terminations.

The study population consists of adult patients diagnosed with non-cirrhotic NASH and T2DM, with at least 40% being male and 40% being female (see Protocol Section 4 "Study design" for additional information).

A detailed list of procedures performed at each visit is presented in the Protocol (Sections 1.3 and 8).

7.1 Sample Size Considerations

The sample size calculation was done by using SAS® Version 9.4.

The sample size is based on the effect size of lanifibranor versus placebo (first test hierarchical procedure) on the change from baseline in HbA1c at Week 24, assuming an additive effect when empagliflozin is added to lanifibranor (second test hierarchical test).

Based on recent results of the Phase 2 trial NATIVE (NCT03008070), in the sub-population of NASH with T2DM, the mean ($\pm$ standard deviation [SD]) absolute changes in HbA1c from baseline to Week 24 were -0.60 ($\pm$ 0.54)% with lanifibranor 800mg and +0.10 ($\pm$ 0.53)% with placebo, leading to an adjusted mean difference [95% confidence interval (CI)] of -0.69 [-0.95, -0.42]%, obtained from a mixed model for repeated measures (MMRM) model.

Assuming an effect size of lanifibranor versus placebo of 0.60%, an expected SD of the change from baseline of 0.60%, a type I error of 0.05 (2-sided), an allocation ratio of 1:1, the required sample size per group is 21 patients with a power approximately 90%.

The total sample size is 63 patients overall, with 21 patients in each treatment group.

The table below shows the sensitivity of the power to a variety of scenarios of effect size (mean and SD), with 2-sided alpha of 5%.

Table 1: Power depending on expected effect sizes

Mean difference between the two groups	Standard deviation	Power
0.4	0.5	76%
0.4	0.6	56%
0.5	0.5	89%
0.5	0.6	75%
0.5	0.7	62%
0.6	0.5	97%
0.6	0.6	89% *
0.6	0.7	77%
0.7	0.5	99%
0.7	0.6	96%
0.7	0.7	89%

* Effect size retained for the study

The overall type I error of the study is 0.05 (2-sided). No alpha (type I error) adjustment will be considered for the interim analysis, i.e. still considering 0.05 (2-sided), this study being an exploratory proof-of-concept study. The sample size was not therefore adjusted because of the interim analysis.

7.2 Randomization

The ICON Randomization Development Team generated the randomization schedule according to the Inventiva Protocol V2.0, 25-Jan-2022.

Treatments are allocated in 1:1:1 ratio to lanifibranor 800mg + empagliflozin 10mg (open-label), lanifibranor 800mg (blinded), placebo (blinded).

Randomization is stratified by 2 stratifying factors considered:

- HbA1c at screening ($<7.5\%$, $\geq 7.5\%$)
- Sex (Male, Female)

Details are provided in a dedicated randomization plan Version 2.0, 04-Mar-2022.

8.0 Population Sets

8.1 Screened Set

The screened set includes all patients who signed their informed consent.

8.2 Full Analysis Set

The full analysis set (FAS) includes all randomized patients who received at least one dose of the assigned Investigational Medicinal Product (IMP), regardless of whether they prematurely discontinued randomized treatment or experienced any other intercurrent event, and meeting the targeted patient population of interest consistently with the primary estimand described in [Section 12.5.2](#): Adults with non-cirrhotic NASH and T2DM defined by inclusion criteria No. 4 and 5 met, and exclusion criteria No. 2 and 15 not met.

'Received at least one dose of the assigned IMP' for the combination arm means that at least one dose of the two treatments empagliflozin and lanifibranor are to be received concomitantly, to be considered in the FAS.

Patients will be analysed according to their randomized treatment.

8.3 Interim Analysis Set

The Interim Analysis Set (IAS) consists of approximately the first half of the planned randomized patients from the FAS.

8.4 Per Protocol Set

The per protocol set (PPS) includes all patients in the FAS who do not have any major protocol deviations and who do not prematurely discontinue from treatment.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the Protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Major deviations are considered to have a significant effect on the primary endpoint.

Patients with major protocol deviations will be listed during the blind review and the reason for exclusion will be provided. Protocol deviations will be identified and classified at the blind review meeting.

8.5 Safety Analysis Set

The safety analysis set (SAS) includes all randomized patients who received at least one dose of IMP. Patients in the SAS will be analysed and summarized based on the treatment they actually received.

'Received at least one dose of IMP' for the combination arm means that at least one dose of lanifibranor is to be received, to be considered in the SAS.

8.6 Protocol Deviations

The study specific Protocol Deviation Guidance Document (LEGEND_337HNAS21016 PD Guidance Final V2.0 19 Oct 2023) defines all protocol deviations.

Per ICON processes, protocol deviations data will be entered into system of record Predictive study operations (PSO). The study team and the Sponsor will conduct on-going reviews of the deviation data from PSO and the resulting set of evaluable patients throughout the study, adjusting the deviation criteria as seems appropriate. The evaluable patients set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

8.7 Important Protocol Deviation Identification Listings

The Lead Biostatistician (LST) will develop the required listing shells in conjunction with the programmer and medical director to document the outputs necessary to identify protocol deviations not covered by edit checks, define the analysis sets or agree any non-programmable classifications. It is recommended that the programmed listings are in a separate document in excel format to allow classifications to be added during manual review and the subsequent import or export of updated lists to and from SAS. The DRM listings should be based on the ICON standard shells for blinded data review meetings, the following listings can be considered:

- Protocol deviations identified in the Clinical Trial Management System (with importance flag and coding completed within the system by the Medical Monitoring Associate [MMA]/ Medical Director [MD])
- List of patients violating inclusion, exclusion or selection criteria
- List of patients with missing baseline for the primary efficacy variables/endpoint or missing the primary efficacy variables/endpoint post-baseline
- Listing of potential prohibited medications
- List of patients with no evidence of receiving study IMP (and/or below a set quantity)
- Treatment compliance

9.0 Conventions and Derivations

9.1 Time Points and Visit Windows

The following rules will be used for the by-visit analyses of vital signs, physical examination, electrocardiogram (ECG), laboratory assessments (including primary efficacy endpoint HbA1c and secondary efficacy endpoints: liver tests, markers of glycaemic control and insulin resistance, inflammatory markers, lipid parameters), pregnancy tests, [REDACTED]

Baseline is defined as:

- The last available assessment prior to or on the date of the Baseline visit for all patients

For all populations, assessments will be assigned to visits as follows:

- For non-categorical summaries:
 - Baseline assessment may include visits assigned to screening, for by-visit summaries.
- For categorical summaries as follows:
 - In case of multiple values available, the chronologically first value will be used in each window.
- For both non-categorical or categorical summaries,
 - Scheduled visits will be reclassified, if needed, using expected visit window defined per Table 2.
 - If a visit assessment is missing, then the earliest of any retests/unscheduled visits assigned to this visit and performed within expected visit window (as per Table 2) will be chosen for the analysis.
 - If several assessments are non-missing at a specific timepoint (following re-assignment at per Table 2), then the assessment the closest to the scheduled day of visit will be chosen. If two assessments are concerned, then the one performed at the initial scheduled visit will be chosen.
 - Table 2 will be used for all parameters (Visits, Vital signs, Laboratory parameters, [REDACTED])
 - [REDACTED]
 - Assessments with missing data or marked 'Not Done', 'Not available', 'Unknown', etc. will be treated a missing response.

Table 2: Definition of visit windows for all parameters (Visits, Vital signs, Laboratory parameters, [REDACTED])

Visit	Time point	Scheduled Day of Visit ^a	Expected Visit Window	Window in days
Visit 1 (V1)	Screening		-6 to -2 weeks before Week 0	
-	Randomization		-2 weeks before Week 0 at the latest	
Visit 2 (V2)	Baseline/Week 0	1	*See baseline definition above	
Visit 3 (V3)	Week 4	28	Days 22 to 34	±6 days
Visit 4 (V4)	Week 12	84	Days 70 to 98	±14 days
Visit 5 (V5)	Week 24	168	Days 144 to 189	-24/ +21 days
Visit 6 (V6)	Week 28 ^b	196	Days 190 to 217	-6 / +21days

^a Relative to the date of first dose of study treatment (Day 1)

^b Follow-up for premature discontinuation will not be included in the analyses

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

All data will be listed. However, only data slotted into the Protocol pre-defined visits will be reported in summary tables.

9.2 On-study and on-treatment Periods

The following periods has been defined for the purpose of reporting:

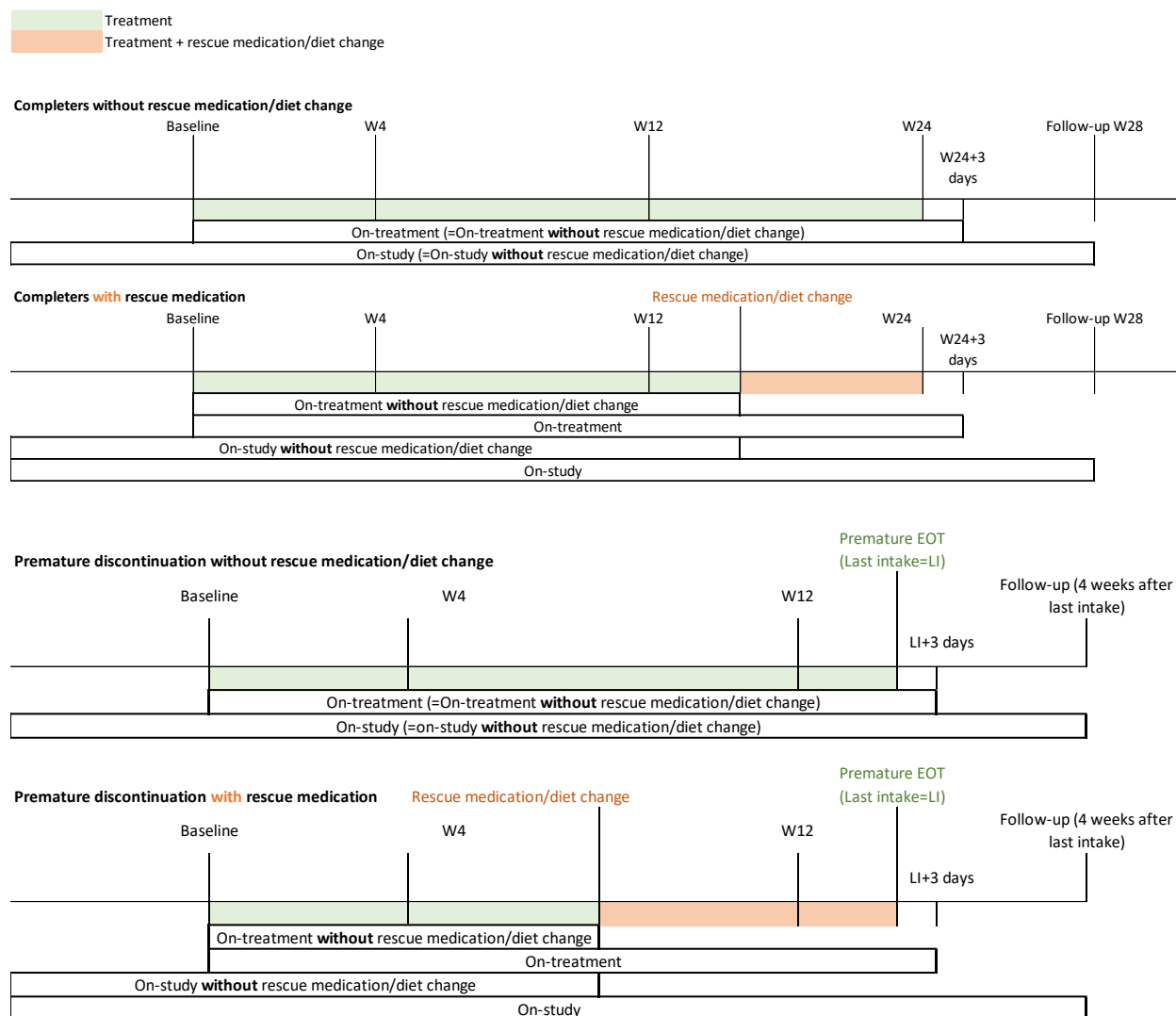
Table 4: Definition of on-study and on-treatment observations periods

Period	Description
On-study	This observation period refers to the time interval during which the patient is assessed throughout the trial. The on-study period is determined as: From the date of screening visit until the latest of: - Follow-up visit date, scheduled to take place 4 weeks after last dose of study treatment - End of study date completed in the EOS form - Withdrawal of consent, - Last contact with the patient (for those who were lost to follow-up), - Death.
On-study without rescue medications and/or significant diet change	This observation period is a subset of on-study observation period, refers to the time interval during which the patient is assessed throughout the trial, before initiating any rescue medications or changing significantly their diet (affecting metabolism). If no Initiation of rescue medication and no significant diet change (affecting metabolism), see 'On-study' definition. If Initiation of rescue medication or significant diet change (affecting metabolism), from the date of screening visit until the earliest of: - Initiation of rescue medication, if any - Significant diet change (affecting metabolism), if any
On-treatment	This observation period refers to the duration whereby patients are considered treated with the study treatment. - For AEs, the on-treatment period is defined as: From the date of first dose of study treatment until the last dose date of study treatment + 30 days, - For all other assessments, the on-treatment period is defined as: From the date of first dose of study treatment until the last dose of study treatment +5 days.
On-treatment without rescue medications and/or significant diet change	This observation period is a subset of on-treatment observation period, where patients are considered treated with study treatment, but have not initiated any rescue medications and have not changed significantly their diet (affecting metabolism). Specifically, it starts at date of first dose of study treatment and the end date is the first of any of the following dates: - The last dose date of study treatment +5 days - Initiation of rescue medication - Date of significant diet change

Data points collected outside an observation period will be treated as missing in the analysis.

Baseline data will always be included in an observation period.

The figures below describes these periods.



9.3 Handling of Dropouts, Missing Data and Outliers

Several methods for missing data imputation will be applied, for primary analyses and sensitivity analyses. Those methods are detailed in the corresponding analysis sections.

Of note, for continuous endpoints, MMRMs on observed data at each applicable visit will be used. MMRM is used to handle missingness because outcomes are measured repeatedly over time, and no explicit imputation will be done for missing data. Importantly, it has to be noted that this analysis is not an analysis on observed data only, because the MMRM model in itself, as a Likelihood-based method, is known to be a method of dealing with missing data which performs very well under the missing at random (MAR) assumption. Since a low number of missing data is expected for the primary endpoint in this rather short study, this assumption is deemed to be plausible for the main estimation.

9.4 Handling of Missing or Incomplete Dates

Incomplete dates (partial or missing dates where a full date is permissible) will be presented in the data listings as recorded on the eCRF. However, for calculations (e.g. duration between two dates), dates will be imputed as follows:

Table 5: Imputation Rules for Partial Dates (D: day, M: month, Y: year):

Parameter	Missing	Additional Conditions	Imputation
Start dates	D, M and Y	-	None
	D and M	Same Y as study drug first dose date	Date of study drug first dose date
		Different Y as study drug first dose date but same as screening date	Date of screening date
		Different Y as study drug first dose date and screening date	January 1 st
	D	Same M and Y as study drug first dose date	Date of study drug first dose date
		Different M and/or Y from study drug first dose date	First day of the month
Stop dates	D, M and Y	-	None
	D and M	Same Y as study drug first dose date	Date of study drug first dose date
		Different Y as study drug first dose date	December 31 st
	D	Same M and Y as study drug first dose date	Date of study drug first dose date
		Different M and/or Y from date of study drug first dose date	Last day of the month
Other dates	D, M and Y	-	Corresponding visit date
	D and M	-	July 15 th
	D	-	The 15 th of the month

If after imputation the start date is posterior to the patient's end of study date then the imputed start date should be replaced by the end date.

If the above rules for stop dates result in illogical date with regards to the dates the patient was in the study, then the stop date will be replaced with the patient's end of study date.

9.5 Handling of Outliers

No specific analysis will be done, except individual review of patients in case of outliers using narratives, for safety purpose.

9.6 Derived Variables

9.6.1 General

Durations are calculated as:

$$\text{Start date} - \text{End date} + 1$$

Absolute changes from baseline are calculated as:

$$\text{Value at } V_i - \text{Value at baseline}$$

where i corresponds to a post-baseline time point value.

Relative changes from baseline (in %) are calculated as:

$$100 * \text{Absolute change from baseline} / \text{Value at baseline},$$

if absolute change equal to 0, then relative change from baseline will be equal to 0%.

Fold changes from baseline are calculated as:

$$\text{Value at Vi} / \text{Value at baseline},$$

9.6.2 Disposition

A visit will be considered as performed if the answer to “Was the visit performed?” is ‘Yes’ and/or the corresponding date is filled.

Study duration is defined as the time between baseline and the end of study:

- In months: $(\text{date of end of study} - \text{date of baseline} + 1) / 30.4375$
- In weeks: $(\text{date of end of study} - \text{date of baseline} + 1) * 52/365.25$

Patients will be considered as:

- having prematurely discontinued their treatment if the answer to “Did the patient complete the treatment phase?” is “No” in the “End of Treatment Form”.
- having completed the study if the answer to “Status of the patient at the end of the study” is “Study treatment period completed and follow-up visit performed” in the “Trial Period Disposition” form.

9.6.3 Demographics/Baseline

Patients will be categorized according to their region:

- US if the site is located in the US
- Outside US if the site is located in Europe (France, the Netherlands, Belgium, United Kingdom)

Patients will be categorized according to their age:

- <65 years,
- ≥65 years

Baseline body mass index (BMI) status will be defined as:

- Non-Obese: BMI <30 kg/m²
- Obese: BMI ≥30 kg/m²

BMI class will be defined as:

- Underweight: BMI <18.5 kg/m²
- Normal: $18.5 \leq \text{BMI} < 25$ kg/m²
- Overweight: $25 \leq \text{BMI} < 30$ kg/m²
- Obese class I (moderate): $30 \leq \text{BMI} < 35$ kg/m²
- Obese class II (severe): $35 \leq \text{BMI} < 40$ kg/m²
- Obese class III (morbid): BMI ≥40 kg/m²

A patient will be considered as presenting a metabolic syndrome at baseline when at least 3 of the following criteria are verified (see [Reference 1](#)):

- As reported in the eCRF ‘Disease History - Metabolic Syndrome History’ form:
 - Hypertension
 - Type 2 Diabetes Mellitus (T2DM)
 - High Density Lipoprotein Cholesterol Decreased
 - Hypertriglyceridemia
- And baseline waist circumference ≥94 cm (37 inches) for men, ≥80 cm (31.5 inches) for females

9.6.4 Medications

Antidiabetic medications are grouped into the four following classes;

- Metformin: if CMDECOD in "METFORMIN" "METFORMIN HYDROCHLORIDE;SITAGLIPTIN PHOSPHATE MONOHYDRATE" "JANUMET"
- Sulphonylurea: if World Health Organization (WHO) Drug Anatomical Therapeutic Chemical (ATC) code = A10BB
- DPP4i: if CMDECOD in ("JANUMET" "SITAGLIPTIN" "METFORMIN HYDROCHLORIDE;SITAGLIPTIN PHOSPHATE MONOHYDRATE")
- SGLT2: if CMDECOD in ("EMPAGLIFOZIN" "DAPAGLIFLOZIN")

All patients treated in the lanifibranor 800mg + empagliflozin 10mg group will be assigned SGLT2=Yes (due to Empagliflozin intake).

A patient will be considered as taking at least one antidiabetic treatment if at least one treatment detailed above is received.

Statin treatments will be defined if CMDECOD in "ATORVASTATIN" "ATORVASTATIN CALCIUM" "PRAVASTATIN" "ROSUVASTATIN" "SIMVASTATIN".

9.6.5 Rescue Medications

Rescue medication is defined as use of any new or additional antidiabetic medication, or increase in the dose of background antidiabetic medication above the baseline dose. The dose increase is defined as enlarging the amount of each single dose or by shortening the dosing interval.

As per Protocol Section 6.10.2, the use of rescue medication in case of hyperglycaemia will be permitted during the trial, but only if the criteria below are met:

- Week 1-12: Glucose level >240 mg/dl (>13.3 mmol/l) after an overnight fast, or >400 mg/dl (>22.2 mmol/l) in a randomly performed measurement
- Week 13-24: Glucose level >200 mg/dl (>11.1 mmol/l) after an overnight fast, or >400 g/dl (>22.2 mmol/l) in a randomly performed measurement

Antidiabetic medications defined in [Section 9.6.4](#) as well as insulin and GLP-1 RA may all be given as rescue medication until the end of the trial.

[REDACTED]

[REDACTED]

The following laboratory parameters are considered sensitive to rescue medications (antidiabetic medications):

- Hemoglobin A1C
- Plasma Glucose
- Insulin
- Insulin resistance
- Triglycerides
- GGT
- Adiponectin
- Fructosamine
- Urine Glucose

9.6.6 Significant Diet Change Affecting Metabolism

Significant diet change affecting metabolism is defined as:

- The variable “Did the subject initiate or modify his regular diet since last visit?” is ticked Yes and major deviation reported as “Subject significantly changed [his/her] diet [...] leading to significant HbA1c increase and weight decrease”.

The following laboratory parameters are considered sensitive to significant diet change:

- Haematocrit
- Hemoglobin A1C
- Hemoglobin
- Glucose
- Insulin
- Insulin resistance
- Ketones
- Cholesterol
- HDL Cholesterol
- LDL Cholesterol
- Triglycerides
- Alkaline Phosphatase
- Alanine Aminotransferase
- Aspartate Aminotransferase
- Direct Bilirubin
- Bilirubin
- Gamma Glutamyl Transferase
- Adiponectin
- Fructosamine
- Ferritin
- Haptoglobin
- Unsaturated Iron Binding Capacity
- Iron
- Lactate Dehydrogenase
- Transferrin
- Vitamin B12
- Vitamin B9
- Glucose
- Ketones
- [REDACTED]
- [REDACTED]
- VAT
- SAT
- Diastolic Blood Pressure
- Systolic Blood Pressure
- Weight

9.6.7 Time Between Screening Biopsy And Baseline (Months)

Time between screening biopsy and baseline in months is defined as:

$$(\text{Date of baseline} - \text{date of screening biopsy} + 1) / 30.4375$$

9.6.8 Alcohol Consumption

Alcohol consumption will be derived as follows:

Table 6: Alcohol comparison

Alcohol Type	Alcohol by Volume	Volume		Amount of Alcohol	
		Fluid Ounce	mL	Units ¹	grams
Beer	3.5%	12	350	0.7	9.8
Beer	5%	12	350	1	14
Cider	7%	12	350	1.4	19.6
Distilled spirits or Liquor ²	40%	1.5	45	1	14
Wine	12%	5	150	1	14

¹ Units calculated using the Cleave Books calculator for units of drink, using the US definition of 1 unit of alcohol as 17.7 mL (14.0 g) of pure alcohol (<http://www.cleavebooks.co.uk/scol/ccalcoh3.htm>)

² e.g., gin, rum, vodka, whiskey

Significant alcohol consumption is defined as higher than 30g pure alcohol per day for men and as higher than 20g pure alcohol per day for women.

9.6.9 Treatments

The duration of exposure (treatment duration) in weeks is defined as:

$$(\text{last dose date} - \text{first dose date} + 1) * 52/365.25$$

If last dose date is missing, then date of last known dose administration will be used.

The persistence corresponds to the ratio between the actual number of tablets taken and the expected number of tablets to be received between the study first and last treatment intake.

Overall percentage persistence is calculated as:

$$100 * \text{actual tablets taken} / \text{expected tablets taken}$$

- Actual tablets taken is defined as:

$$\text{Total number of tablets dispensed} - \text{total number of tablets returned}$$

- Expected tablets taken for the Lanifibranor and Placebo treatments is defined as:

$$2 * (\text{last dose date} - \text{first dose date} + 1)$$

- Expected tablets taken up to Week 24 for the Lanifibranor + Empagliflozin treatment is defined as:

$$3 * (\text{last dose date} - \text{first dose date} + 1)$$

The compliance up to Week 24 corresponds to the ratio between the actual number of tablets taken and the expected number of tablets to be received between the study first treatment intake and Week 24.

Percentage compliance up to Week 24 is calculated as:

$$100 * \text{actual tablets taken up to Week 24} / \text{expected tablets taken up to Week 24}$$

- Actual tablets taken up to Week 24 is defined as:

$$\text{Total number of tablets dispensed up to Week 24} - \text{Total number of tablets returned up to Week 24}$$

- Expected tablets taken up to Week 24 for the Lanifibranor and Placebo treatments is defined as:
 $2 * (\text{date of the Week 24 visit} - \text{first dose date} + 1)$
- Expected tablets taken up to Week 24 for the Lanifibranor + Empagliflozin treatment is defined as:
 $3 * (\text{date of the Week 24 visit} - \text{first dose date} + 1)$

9.6.10 Laboratory

Regarding laboratory parameters that are sensitive to fasting status (i.e. fasting glucose (plasma and urine), insulin resistance (Homeostatic Model Assessment for insulin resistance [HOMA-IR]), insulin, ketones, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, adiponectin, hematocrit), in case of non-fasting value:

- Baseline value:
 - If the Screening value is a fasting one, then the Baseline data will be the Screening value
 - if both are non-fasting values, then the Baseline data will be the Baseline value.

9.6.10.1 Reticulocytes Production Index (RPI)

$RI = \text{Reticulocytes (\%)} * (\text{patient Hematocrit} / \text{normal Hematocrit})$

$RPI = RI / \text{maturation factor} = (\text{patient Hematocrit} / \text{normal Hematocrit}) * (\text{Reticulocytes (\%)} / \text{maturation factor})$

With Normal Hematocrit = 45% and maturation factor:

Hematocrit (%)	Maturation factor
>45*	1.0
36-45	1.0
26-35	1.5
16-25	2.0
<=15	2.5

*For Hematocrit > 45%, maturation factor 1.0 will be used and an extra comment will be printed to flag that the Hematocrit is >45%.

9.6.11 Fibrosis Markers

9.6.11.1 NAFLD Fibrosis Score (NFS)

Non-Alcoholic Fatty Liver Disease (NAFLD) Fibrosis Score (NFS) is calculated according to the formula (See [Reference 2](#)):

$$\text{NFS} = -1.675 + 0.037 * \text{age (year)} + 0.094 * \text{BMI (kg/m}^2\text{)} + 1.13 * \text{impaired fasting glucose/diabetes} \\ + 0.99 * \text{aspartate aminotransferase (AST, U/L) / alanine transaminase (ALT, U/L) ratio} \\ - 0.013 * \text{platelet count (PLT, } \times 10^9/\text{L)} - 0.66 * \text{albumin (g/dL)}$$

where the variable “impaired fasting glucose/diabetes” (yes = 1, no = 0) corresponds to the insulin resistant status defined as:

- Insulin-resistant:
 - Presence of T2DM
 - Absence of T2DM and fasting glucose ≥ 100 mg/dl (5.6 mmol/L)
- Non insulin-resistant: Absence of T2DM and fasting glucose < 100 mg/dl (5.6 mmol/L)

BMI is indeed based on Height and Weight. The height was only collected at baseline. The height at baseline will be used to calculate BMI. The weight at each visit should be used to derive the BMI. BMI should be computed for each visit. For use the NFS calculation, it should be also the BMI computed for visit Screening and Baseline (not the BMI value from CRF).

A variable predicting the fibrosis will be constructed from the NFS:

- NFS ≤ -1.455 : Low probability of F3/F4,
- $-1.455 < \text{NFS} < 0.676$: Indeterminate status
- NFS ≥ 0.676 : High probability of F3/F4

9.6.11.2 FIB-4 Score

FIB-4 score is calculated according to the formula (See [Reference 3](#)):

$$\text{FIB-4} = \text{Age (years)} * \text{AST (U/L)} / \text{PLT (} \times 10^9/\text{L)} * \sqrt{\text{ALT (U/L)}}$$

A variable predicting the fibrosis will be constructed from the FIB-4 score:

- FIB-4 score < 1.45 : Low probability of F3/F4,
- $1.45 \leq \text{FIB-4 score} \leq 3.25$: indeterminate status,
- FIB-4 score > 3.25 : High probability of F3/F4 if score

9.6.11.3 Enhanced Liver Fibrosis (ELF) Score

ELF score is calculated according to the formula (See [Reference 4](#)):

A variable predicting the fibrosis will be constructed from the ELF score:

- ELF score < 4.7 : No to mild fibrosis,
- $4.7 \leq \text{ELF score} < 9.8$: Moderate fibrosis,
- $9.8 \leq \text{ELF score} < 11.3$: Severe fibrosis,
- ELF score ≥ 11.3 : Cirrhosis.

9.6.11.4 MACK-3 Score

MACK-3 Score is calculated using the tool available here (see [Reference 5](#)):

<https://gilles-hunault.leria-info.univ-angers.fr/wstat/mack3-calculator.php?xmp=0>

9.6.12.3 Agile 4 Score

Agile 4 score is calculated according to this formula:

$$Agile\ 4 = \frac{e^{7.50139 - 15.42498 \times \frac{1}{\sqrt{E}} - 0.01378 \times PLT - 1.41149 \times \frac{ALT}{AST} - 0.53281 \times Gender + 0.41741 \times Diabetes\ status}}{1 + e^{7.50139 - 15.42498 \times \frac{1}{\sqrt{E}} - 0.01378 \times PLT - 1.41149 \times \frac{ALT}{AST} - 0.53281 \times Gender + 0.41741 \times Diabetes\ status}}$$

where lower case 'e' is the exponential function, upper case 'E' corresponds to ██████████ PLT ($\times 10^9/L$), ALT (U/L), AST (U/L), diabetes status (presence = 1, absence = 0), gender (female = 1, male = 2), age (years).

9.6.13 Other Markers

9.6.13.1 Aspartate aminotransferase-to-platelet ratio index (APRI)

APRI is calculated according to this formula:

$$APRI = [(AST\ (IU/L) / AST\ upper\ limit / Platelet\ count\ (\times 10^9/L)] \times 100$$

10.0 Interim Analyses

An interim analysis will be conducted once approximately half of the planned patients will be randomized, and have either completed the 24-week treatment period or prematurely discontinued from treatment earlier as of 31-Jan-2024.

No alpha (type I error) adjustment will be considered for the interim analysis, i.e. still considering 0.05 (2-sided), this study being an exploratory proof-of-concept study.

Recruitment will be paused once the first half of the patients are randomized. Once the interim analysis results will be available, recruitment may be re-initiated, or, should clear trends in study findings be observed, recruitment may be stopped thereby minimizing patient exposure with additional patients.

The following stopping criteria may be considered and the recruitment will not be reinitiated after the interim analysis:

- If the primary endpoint is met, i.e. the superiority of lanifibranor 800 mg alone versus placebo on the primary endpoint (Absolute change from baseline in HbA1c at Week 24) is demonstrated in the IAS
- Or if the probability that the final study result will be statistically significant is high, given the data observed thus far and a specific assumption about the pattern of the data to be observed in the remainder of the study, such as assuming the original design effect, or the effect estimated from the current data, or under the null hypothesis, i.e. the conditional power based on observed data at time of IA is $\geq 80\%$

Moreover, as mentioned in protocol Section 7.5, the Sponsor reserve the right to terminate the study should clear trends in study findings be observed.

In that case, recruitment will not be re-initiated. Final analysis will then be performed including the additional patients that may have been randomized but not considered in the first half of the total randomized patients.

Data integrity:

Since the interim analysis (IA) will include only the 32 patients that have already completed their 24-week treatment period at time of 31st Jan 2024, there will be no need to pre-define an unblinded team at Inventiva to review the statistical results of these 32 study-completed patients. However, a sub team dedicated to the quality control and interpretation of statistical results will be defined at Inventiva prior to

releasing/communicating the results externally, and each step will be detailed in the Inventiva communication plan.

At ICON, per SOP, an unblinded team will be dedicated to the database freeze, unblinding and statistical analysis of the 32 patients. The additional patients recruited at time of IA but not part of the IA will be kept blinded for Inventiva and for the blinded team at ICON.

The unblinding process will be described in the unblinding plan. The Data Transfer Specification providing the treatment allocation (from the Interactive Response Technologies tool) will be updated to provide only information from the 32 patients. The laboratory data coming from the central laboratory will also include only information from the 32 patients. The Data Management Plan will detail the data to be included in Data Delivery, including but not limited to the list of patients of the IAS (All randomized and treated patients that will have their W24 or premature end of treatment visit before/on the cut-off date of 31Jan2024).

Therefore, based on these documents and explanations, the blinding of the additional patients recruited at time of IA but not part of the IA will be maintained, the integrity of the trial will be protected and ensuring continued adherence to treatment and trial retention.

Information at time of SAP Version 2.0:

At time of development of this SAP version 2.0, it is to be noted that:

- The interim analysis was conducted on March 2024
- The analysis was based on the SAP V1.0 that was approved and signed before interim unblinding.
- The primary endpoint was met. Therefore, recruitment has been stopped / not been re-initiated.

11.0 Statistical Methods

11.1 Estimands

In line with ICH E9(R1) ([Reference 8](#)) addendum, 5 attributes (treatment, population, endpoint, intercurrent events, and population-level summary) have been specified to translate the primary efficacy objective into treatment effects that are to be estimated (estimands).

Estimands for each confirmatory analysis are described in [Section 12.5](#).

11.2 General Principles

All data processing, summarization and analyses will be performed using Version 9.4 (or later) of the SAS® statistical software package.

Appropriate quality control for most important derived datasets, SAS programs and Tables, Figures and Listings (TFLs) will be performed and detailed in a dedicated programming Quality Control (QC) plan. Appropriate documentation of QC will be developed and maintained throughout the study.

Statistical results will be delivered in several batches:

- The first batch will contain the Top Line Results (TLR)
- The other batches being all other results described in this SAP

The following deliverables will be provided at time of final analysis:

- Two separate documents compiling all TLFs: one for Appendix 14 and one for Appendix 16.2
- SAS programs generating the outputs

11.2.1 Descriptive statistics

Data will be presented in summary tables overall and by treatment group, assessment and visit (where applicable).

The number of missing will be presented if it is greater than zero for at least one treatment group.

Population statistics will be displayed as N in each table and figure summary.

Unless specified otherwise, data will be displayed using the following treatment group labels, in the order presented:

- Lanifibranor
- Lanifibranor + Empagliflozin
- Placebo

Descriptive summary statistics for **continuous variables** will include the number of available observation (n), mean, SD, median, quartiles 1 and 3, minimum and maximum.

The 95% two-sided confidence interval (CI) will be calculated when appropriate using the standard method (standard normal distribution).

The minimum and maximum will be displayed to the same precision as the associated collected value, mean, median and quartiles with one more decimal place; and SD and CIs with two more decimal places (with a maximum of 3 decimals).

Descriptive summary statistics for **categorical variables** will include frequency counts and percentages [n (%)]. For analysis of medical history, medications or adverse events, the denominator for percentage calculations will be the number of patients in the analysis population (N). Otherwise, the denominator for percentage calculations will be the number of patients with non-missing data in the analysis population. Where a frequency count of 0 is observed, the accompanying percentage will be blank.

The 95% two-sided CIs will be calculated when appropriate using the exact (Clopper-Pearson) method.

Percentages will be displayed with one decimal, and CIs with two decimals.

11.2.2 Poolability of investigative Sites

Data from all investigative sites will be pooled based on the assumption of clinical compatibility, where all sites use a common study protocol, data collection/validation is the same across all sites.

To explore homogeneity of treatment effect across centres/geographical regions, an analysis by geographic region (US, Outside US) (see [Section 12.5.2.3](#)) will be performed if there is at least 20% of patients in each region.

If the geographical regions are found to be significantly heterogeneous with respect to the primary endpoint, additional analyses will be conducted to assess differences between regions in baseline and procedural variables that might explain differences in primary outcome.

11.2.3 Treatment groups comparison

For statistical tests, the type I error risk of these will be set at 5% (2-sided) without adjustments for multiplicity testing, unless for the primary analysis (see [Section 12.5.1](#)).

Other than p-values of primary analysis that will be confirmatory, p-values will be exploratory two-sided with associated 95% CIs.

P-values will be displayed to three decimal places. Any p-value less than 0.001 will be presented as <0.001, even if it would normally round up to 0.001.

11.2.3.1 Continuous variables

Comparison of treatment groups for continuous variables will be performed using:

- For single post-baseline measurement: an Analysis of Covariance (ANCOVA) using the SAS MIXED procedure with the treatment group and baseline value and the 2 stratifying factors (unless otherwise specified) as covariates

Or

- For repeated post-baseline measurements: a Mixed Model for Repeated Measures (MMRM) when specified using the SAS MIXED procedure with:
 - The change (absolute or relative) from baseline as endpoint (MODEL statement of the MIXED procedure)
 - The treatment group, time, interaction (treatment group * time) as fixed effects and baseline value and the 2 stratifying factors (unless otherwise specified) as covariate (MODEL statement of the MIXED procedure). Treatment group, time and stratifying factors being considered as categorical variables
 - A time repeated measure (REPEATED statement of the MIXED procedure) within each subject (SUBJECT = subject as option of the REPEATED statement). Unless otherwise specified, an autoregressive covariance matrix of order 1 with unequal variance [ARH(1)] will be used as option of the REPEATED statement.

It is assumed that the variance at each time point is not the same and tends to increase due to an increase over time of withdrawals and treatment responders. It is also assumed that two consecutive measures are correlated (r) and the correlation decreases with the time interval between visits. This structure is more flexible than AR(1) because variances can be unequal but is consuming less degrees of freedom than the fully unstructured variance covariance matrix (UN).
 - The Kenward-Roger approximation to estimate denominator degrees of freedom and adjust standard errors (ddfm=kr option in MODEL statement)

In order to explore the validity of the model (and more accurately the assumption regarding independence, normality and constant variance of residuals), the following graphs will be provided: Q-Q plot of the residuals, distribution of residuals with its corresponding normal density estimate and scatterplot of residuals vs. predicted values.

To evaluate the treatment effect (each active arm vs. placebo) at Week 24, the following contrasts of interest will be used:

- Lanifibranor vs. Placebo: -1 for Placebo, 1 for Lanifibranor and 0 for Lanifibranor + Empagliflozin
- Lanifibranor + Empagliflozin vs. Placebo: -1 for Placebo, 0 for Lanifibranor and 1 for Lanifibranor + Empagliflozin.

The least squares mean (LSMean) will be displayed with one more decimal place than the associated collected value, and SE and CIs with two more decimal places.

11.2.3.2 Categorical variables

Comparisons of treatment groups for categorical variables will be performed using the FREQ procedure with Cochran-Mantel-Haenszel (CMH) test option, adjusted for the 2 stratifying factors, separately between each active arm and placebo.

The primary handling of result heterogeneity across strata will be performed through the Breslow-Day test. If the homogeneity hypothesis is rejected, then the estimate of the difference in percentage points between each active arm and placebo along with the 95% CI will be provided within each stratum, as well as the p-value of the association test between treatment and categorical variable (Chi² test or Fisher's exact test). A significant interaction between stratum and treatment (Breslow Day test) means that the treatment effect has not the same magnitude in both class of the stratum. In the absence of qualitative interaction there will be no further adjustment of the type one error for multiplicity of testing.

If two or more strata contain small cell counts (<5) that render the stratified CMH test inappropriate, comparisons of treatment groups will be performed using a logistic regression with treatment group indicator and the 2 stratifying factors in the model.

The risk difference will be displayed with one more decimal place than the associated collected value, and CIs with two more decimal places.

11.2.4 Listings

All data collected and derived, will be presented in listings by treatment group, country, patient, assessment and visit (where applicable), unless otherwise specified.

Dates will be displayed as YYYY-MM-DD.

12.0 Statistical Analyses

12.1 Patient Disposition and Data Sets Analysed

Tabulation of the number and percentage of patients in the following categories will be summarized overall and by country:

- Screened
- Non-randomized
- Randomized
- SAS
- FAS
- FAS with no rescue medication taken during the 24-week period
- PPS

The reasons of non-randomization will also be presented: screen failures, adverse event (AE), Sponsor request, lost to follow-up, withdrawal by subject, withdrawal of consent, other.

Tabulation of the number and percentage of SAS, FAS and PPS patients will be provided overall and by treatment group. The reasons of non-inclusion in each analysis set will also be presented.

The denominator for percentages of Not-randomized and Randomized patients will be the number of Screened patients, the one for SAS, FAS and PPS will be the number of Randomized patients.

The distribution of visits performed will be summarized.

The study duration in months and weeks will be summarized.

The number and percentage of patients who completed the treatment and who discontinued the treatment prematurely, including the primary reasons for premature discontinuation of treatment will be presented.

Treatment duration (weeks) will also be summarized.

The end of study status (Study treatment period completed/prematurely discontinued +/- follow-up visit performed/not performed).

Patient disposition will also be listed.

12.2 Protocol Deviations

All protocol deviations, including those leading to exclusion from the PPS will be listed and summarized by treatment group.

12.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics (including pregnancy results) will be listed and summarized by treatment group and overall for the FAS, PPS and Safety Set (if different from FAS).

12.3.1 Demographics

Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Baseline height (cm)

The total counts and percentages of patients will be presented for the categorical variables of:

- Age group (<65, ≥65 years)
- Sex (Male, Female)
- HbA1c (<7.5%, ≥7.5%)

Both stratified and actual values of stratifying factors will be presented in case of any mis-stratification. If none, the footnote “All patients were correctly stratified” will be added to the corresponding table.

- Region (US, Outside US)
- Country (US, France, The Netherlands, Belgium, UK)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino). The modality Unknown will be considered as missing.
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, White). The modality Unknown will be considered as missing.

No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements, such as vital signs, will be summarized by treatment group with the post-baseline measurements.

12.3.2 Metabolic Syndrome

The total counts and percentages of patients will be presented for the categorical variables of (see [Section 9.6](#)):

- Presence of metabolic syndrome at baseline (Yes, No)
- Number of criteria met in the metabolic syndrome definition at baseline (0, 1, 2, 3, 4, 5), refer to [Section 9.6.3](#) for criteria.
- Each one of the 5 criteria met (No, Yes)

12.3.3 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 24.1 (or a later version if updated during the study) for System Organ Class (SOC) and Preferred Term (PT) and summarized by treatment group and overall.

The total counts and percentages of patients will be presented for the categorical variable of Diagnosis of NASH (based on a historical liver biopsy or based on LiverMultiScan® assessment).

If based on a historical liver biopsy: standard descriptive statistics will be presented for the continuous variable of time between screening biopsy and baseline (months).

Medical history will be listed.

12.3.4 Prior and Concomitant Medications

Medications received prior to or concomitantly with study treatment will be coded using the World Health Organization (WHO) Drug dictionary version March 2020 (or a later version if updated during the study), for ATC Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken with a stop date prior to the first dose date of study treatment.
- Concomitant medications are those with a start date on or after the first dose date of study treatment, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment, or ongoing.

If a medication cannot be classified as “prior” or “concomitant” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be summarized separately for FAS and PPS, by treatment group and overall.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC level 2), chemical subgroup (ATC level 4), and generic term.

The total counts and percentages of patients will be presented for the categorical variables of:

- Antidiabetic treatment at baseline (Yes, No)
- Metformin at baseline (Yes, No)
- Sulphonylurea at baseline (Yes, No)
- DPP4i at baseline (Yes, No)
- SGLT2 at baseline (Yes, No)
- Statins at baseline (Yes, No)
- Initiation of a rescue medication during the on-treatment period (Yes, No)

The time to initiation of a rescue medication (weeks) will be summarized on patients who took at least one rescue medication.

Definitions are given in [Section 9.6](#).

Prior and concomitant medications will be listed together.

12.3.5 Alcohol Consumption

The following parameters will be summarized descriptively by treatment group at each time point:

- Alcohol consumption since last visit (Yes, No)
- Binge drinking during the last year before entering the study (only at baseline) (Yes, No)

12.4 Measurements of Study Treatment Compliance

The following parameters will be summarized by treatment group and overall for the FAS:

Standard descriptive statistics will be presented for the continuous variables of:

- Overall percentage persistence (%)
- If Week 24 visit performed, percentage compliance up to Week 24 (%)

The total counts and percentages of patients will be presented for the categorical variables of:

- Overall percentage persistence (<50%, ≥50% to <80%, ≥80% to ≤120%, >120%)
- If Week 24 visit performed, percentage compliance up to Week 24 (<50%, ≥50% to <80%, ≥80% to ≤120%, >120%)

Each treatment persistence/compliance parameter will be listed.

12.5 Efficacy Analyses

12.5.1 Hypotheses, Testing Strategy and Multiplicity

The following confirmatory one-sided hypotheses will be tested as:

- Superiority of lanifibranor 800mg alone versus placebo on change from baseline in HbA1c at Week 24

$$H_{Lani,0}: \mu \geq 0\% \text{ against } H_{Lani,1}: \mu < 0\%$$

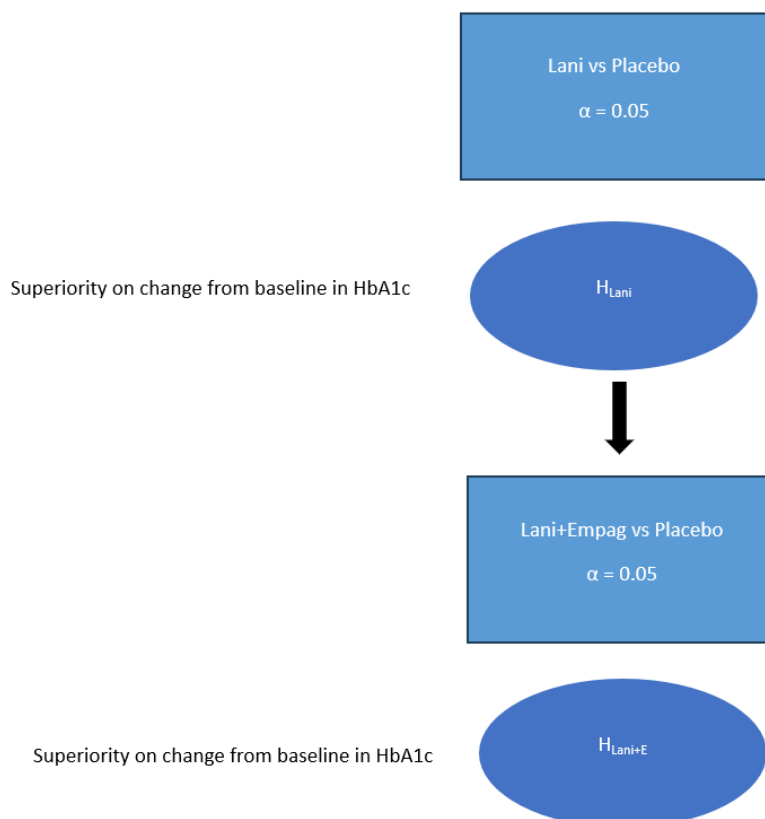
- Superiority of lanifibranor 800mg plus empagliflozin versus placebo on change from baseline in HbA1c at Week 24

$$H_{Lani+E,0}: \mu \geq 0\% \text{ against } H_{Lani+E,1}: \mu < 0\%$$

where μ is the mean treatment difference in HbA1c from baseline $\mu = \text{active treatment} - \text{placebo}$.

Operationally the hypotheses will be evaluated by two-sided tests at the 5% significance level.

The confirmatory hypotheses will be tested using a hierarchical fixed testing procedure. Lanifibranor alone will be compared to placebo at the 2-sided $\alpha=0.05$ level (H_{Lani}), and should this test pass, the lanifibranor plus empagliflozin combination will be compared to placebo at the same $\alpha=0.05$ level (H_{Lani+E}).



12.5.2 Primary Efficacy Endpoint

The primary endpoint 'Absolute change in HbA1c from baseline at Week 24 (%)' will be calculated for each patient as: HbA1c value at Week 24 - HbA1c value at Baseline, see Baseline definition in [Section 9.1](#).

The [Table 7](#) below provides the estimand attributes for the primary analysis of the primary endpoint.

12.5.2.1 Primary Analysis

Analysis period

The on-study without rescue medications period will be considered, see [Section 9.2](#).

For patients who prematurely discontinued from the treatment, value to be considered at Week 24 will be:

- the values collected at time of the follow-up visit performed after the end of treatment, if not collected post-rescue medication
- missing otherwise.

Of note, the value collected at time of premature discontinuation will be re-allocated in a pre-specified protocol visit, as per [Section 9.1](#).

For patients who completed the study, no missing data will be replaced.

Descriptive analyses

HbA1c raw data, absolute and relative changes in HbA1c from baseline will be summarized at baseline (HbA1c raw data only) and at each post-treatment, where values at Week 24 visit will include imputed data (see above). Line plots of each treatment group means with whiskers extending to the upper and lower bounds of the 95% CI over time will be displayed from baseline to Week 28, at each measured visit for raw data, absolute and relative changes from baseline.

Evaluation of treatment effect using MMRM

To assess the superiority of each active arm versus placebo on absolute change in HbA1c from baseline, the primary analysis for the primary estimand will be a MMRM.

The model will include all post-baseline HbA1c measurements collected at scheduled visits as dependent variables, excluding HbA1c measurements collected post-rescue medication.

The independent effects included in the model will be treatment group, time, treatment group*time interaction as fixed effects, baseline HbA1c and sex as covariates and patient effect as a random effect.

Treatment effect will be quantified by providing the LSMean treatment estimates of the three arms, treatment differences (lanifibranor 800mg - placebo, and lanifibranor 800mg+empagliflozin – placebo), SE, and 95% CI. Corresponding 2-sided p-value comparing each active arm to placebo will be given at Week 24.

In the MMRM model, an autoregressive covariance matrix of order 1 with unequal variance [ARH(1)] will be considered. It is assumed that the variance at each time point is not the same and tends to increase due to an increase over time of withdrawals and treatment responders. It is also assumed that two consecutive measures are correlated (r) and the correlation decreases with the time interval between visits. This structure is more flexible than AR(1) because variances can be unequal but is consuming less degrees of freedom than the fully unstructured variance covariance matrix (UN). If the ARH(1) covariance matrix does not converge, AR(1) will be used, then UN.

The following SAS code will be used on datasets containing only protocol pre-defined visits [input_data] and using the imputed value [HbA1c_Aval]:

```
proc mixed data=[input_data] method=reml; * The input dataset included post-treatment
visits data, W28 will be used if W24 is
missing;
class [trtgrp] aday cohortn usubjid Sex;
model HbA1c_Aval = [trtgrp] aday [trtgrp]*aday HbA1c_Base Sex / ddfm=KR residual;
repeated aday / patient=usubjid type=arh(1); * ar(1) or UN in supplementary;
lsmeans [trtgrp] / pdiff cl alpha=[alpha];
ods output lsmeans=LSM diffs=Diff;
run;
```

Missing Data Considerations at Week 24

The MMRM is a well-established method that accounts for the uncertainty pertaining to missing data. This analysis assumes that the missing data mechanism is MAR. Since a low number of missing data is expected for the main endpoint in this rather short study, this assumption is deemed to be plausible for the main estimation.

Indeed, the proportion of missing data is expected to be low based on the NATIVE Phase 2 trial (NCT03008070), and missing data will mainly be due to withdrawal from trial (without follow-up visit performed) or lost to follow-up, or initiation of rescue medication.

Under this assumption MAR, the statistical behaviour of the missing data (given the observed responses and model fixed effects and covariates) is assumed to be the same as the observed data, i.e. the method provides an unbiased estimate of the treatment effect that would have been observed if all patients had continued on-treatment for the full study duration.

The supplementary analyses (see [Table 8](#)) will evaluate the sensitivity of the results due to the impact of missing data.

The number of missing HbA1c data at Week 24 and the reason for missingness will be reviewed during the trial.

Table 7: Approach for the primary endpoint, intercurrent events and estimands (primary analysis)

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	Missing data imputation	1. Statistical model 2. Summary measures 3. Period
Primary	Adults with non-cirrhotic NASH and T2DM defined by list of in- and exclusion criteria	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	Treatment policy The data collected at the follow-up visit (4 weeks after the intercurrent event) will be considered as per study design*.	Effect of the initially randomized treatments regardless of treatment discontinuation	For patients who prematurely discontinued, Missing data at Week 24 replaced by the data collected at the follow-up visit, missing otherwise	1. MMRM model used to handle missingness under MAR assumption. 2. At Week 24: - Model-adjusted absolute changes in HbA1c from baseline (least squares mean), - Model-adjusted mean difference (of the absolute changes in HbA1c from baseline) between active arm compared to placebo, obtained through an MMRM model, adjusted on baseline HbA1c value and sex, autoregressive covariance matrix of order 1 with unequal variance (ARH(1)) 3. On-study without rescue medications and/or significant diet change affecting metabolism
		Intake of a rescue medication**	Hypothetical strategy**** The data at Week 24 (after the intercurrent event) will not be considered, even if collected, and set to missing.	Effect of the initially randomized treatments had all patients remained on their randomized treatment throughout the study, i.e., effect assuming patients did not initiate rescue medication	Missing data at Week 24 not replaced (no explicit imputation)	
		Significantly diet change affecting metabolism***	Hypothetical strategy**** The data at Week 24 (after the intercurrent event) will not be considered, even if collected, and set to missing.	Effect of the initially randomized treatments had all patients remained on their randomized treatment throughout the study, i.e., effect assuming patients did not change significantly their diet (affecting metabolism)	Missing data at Week 24 not replaced (no explicit imputation)	
		Low compliance to treatment	Treatment policy The data at Week 24 (after the intercurrent event) will be used.	Effect of the initially randomized treatments regardless of adherence to randomized treatment	Missing data at Week 24 not replaced (no explicit imputation)	

* As per study design, the patient will be asked to come for a follow-up safety visit 4 weeks after the premature treatment discontinuation, and will then be withdrawn from the study.

** See [Section 9.6.5](#)

*** See [Section 9.6.6](#)

**** The hypothetical estimand assesses the glycaemic benefit a future patient is expected to achieve if initiating treatment with lanifibranor or lanifibranor+empagliflozin excluding potential rescue medication(s) and/or significant diet change. Accordingly, only data collected prior to initiation of rescue medication or prior to significant diet change will be used to draw inference. This will avoid confounding from rescue medication and/or significant diet change.

The constructed estimand assesses the expected glycaemic benefit in a future population that results from patients initiating treatment with lanifibranor or lanifibranor+empagliflozin excluding potential rescue medication(s) and/or significant diet change.

12.5.2.2 Sensitivity Analyses

To explore the robustness of the primary analysis, sensitivity analyses will be performed for the primary estimand. Each supplementary analysis only modifies one aspect of the primary analysis at a time, in line with the addendum ICH E9(R1) recommendations (see [Table 8](#)).

1. Supplementary 1: sensitivity analysis for the primary analysis, the statistical methodology change is the replacement of heterogeneous autoregressive 1st order [ARH(1)] with a variance covariance structure either AR(1) or UN.
The same analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed
2. Supplementary 2 will consider to use data collected after the intercurrent events (intake of rescue medication or significant diet change) up to Week 24.
The same descriptive analyses and analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed, but on the on-study period (rather than on-study without rescue medication or significant diet change).
This estimand assesses the expected glycaemic benefit in a future population that results from patients initiating treatment with lanifibranor or lanifibranor+empagliflozin including potential rescue medication(s) and/or significant diet change.
3. Supplementary 3 will set any data after the intercurrent event (premature treatment discontinuation) to missing at Week 24. Any data collected post treatment discontinuation and/or post rescue medication and/or significant diet change will be considered as missing.
The same descriptive analyses and analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed, but on the on-treatment period without rescue medication or significant diet change (rather than on-study without rescue medication or significant diet change).
This estimand assesses the glycaemic benefit a future patient is expected to achieve if initiating and continuing treatment with lanifibranor or lanifibranor+empagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication or significant diet change will be used to draw inference.
4. Supplementary 4 will use actual treatment arm rather than randomized arm.
The same descriptive analyses and analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed.
5. Supplementary 5 will add more baseline characteristics as covariates, such as Sex, Age group, Baseline BMI status, Presence of metabolic syndrome at baseline, cT1, and MRI-PDFF to the model.
The same analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed.
6. Supplementary 6 is same as primary except completers will be used instead of FAS.
The same descriptive analyses and analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed
7. Supplementary 7 is same as primary except PPS will be used instead of FAS.
The same descriptive analyses and analyses of treatment effect as detailed in [Section 12.5.2.1](#) will be performed

Table 8: Approach for the primary endpoints, intercurrent events and estimands (supplementary analyses)

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	Missing data imputation	1. Statistical model 2. Summary measures 3. Period
Supplementary 1 (Statistical methodology changed)	As primary	As primary	As primary	-	As primary	1. As primary 2. Using AR(1) or unstructured variance covariance matrix (UN) rather than ARH(1) 3. On-study without rescue medications
Supplementary 2 (Estimand strategy changed: treatment-policy for rescue medications)	As primary	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	As primary	As primary	As primary	1. As primary 2. As primary 3. On-study
		Intake of a rescue medication	Treatment policy The data at Week 24 (after the intercurrent event) will be used.	Effect of the initially randomized treatments regardless of initiation of rescue medication	No imputation, the data at Week 24 will be used.	
		Significant diet change affecting metabolism	Treatment policy The data at Week 24 (after the intercurrent event) will be used.	Effect of the initially randomized treatments regardless of significant diet change affecting metabolism	No imputation, the data at Week 24 will be used.	
		Low compliance to treatment	As primary	As primary	As primary	
This estimand assesses the expected glycaemic benefit in a future population that results from patients initiating treatment with lanifibranor or lanifibranor+empagliflozin including potential rescue medication(s). This estimand is based on FAS using the on-study period (see Table 4).						

Table 8: Approach for the primary endpoints, intercurrent events and estimands (supplementary analyses)

Analysis	Population	Intercurrent events	Estimand strategy	Measures of intervention effect	Missing data imputation	1. Statistical model 2. Summary measures 3. Period
Supplementary 3 (Estimand strategy changed: hypothetical strategy for premature discontinuation)	As primary	Premature treatment discontinuation: - Due to safety reason - Not due to safety reason	Hypothetical strategy The data at Week 24 (after the intercurrent event) will be set to missing.	As primary	Missing data at Week 24 not replaced (no explicit imputation)	1. As primary 2. As primary 3. On-treatment without rescue medications
		Intake of a rescue medication	As primary	As primary	As primary	
		Significant diet change affecting metabolism	As primary	As primary	As primary	
		Low compliance to treatment	As primary	As primary	As primary	
The hypothetical estimand assesses the glycaemic benefit a future patient is expected to achieve if initiating and continuing treatment with lanifibranor or lanifibranor+empagliflozin. Accordingly, only data collected prior to discontinuation of trial product or initiation of rescue medication will be used to draw inference. This estimand is based on FAS using the on-treatment without rescue medication period.						
Supplementary 4 (Treatment arm changed)	As primary	As primary	As primary	As primary		As primary, but using actual treatment received rather than randomized treatment
Supplementary 5 (Covariates added)	As primary	As primary	As primary	As primary		As primary, but adding some baseline characteristics as covariate. (see Section 12.5.2.2)
Supplementary 6 (Completers)	Completers	As primary	As primary	As primary		As primary
Supplementary 7 (Per protocol)	Per protocol population	As primary	As primary	As primary		As primary
Completers are defined as all patients who completed the 24-week treatment period, ie who do not prematurely discontinue from the treatment.						

12.5.2.3 Sub-group Analyses

Exploratory analyses of the primary endpoint will be performed for the following sub-groups:

- Stratified HbA1c at screening ($<7.5\%$, $\geq 7.5\%$)
- Actual HbA1c at screening ($<7.5\%$, $\geq 7.5\%$), if any discrepancy
- Sex (Male, Female)
- Age group (<65 years, ≥ 65 years)
- Baseline BMI status (Obese, Non-obese)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White)

Similar analyses as those described for primary analysis (refer to [Section 12.5.2.1](#)) will be performed by each subgroup.

The parameters quantifying the treatment effect and 95% CI for each comparison (lanifibranor versus placebo, and lanifibranor+empagliflozin vs placebo) and p-values will also be presented for each subgroup on forest plots.

12.5.3 Secondary Analyses

The analyses will be done on the FAS population described in [Section 8.2](#).

No multiplicity adjustment when testing for treatment effect on secondary/exploratory endpoints will be done. P-values will be considered exploratory.

All secondary efficacy data will be listed. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings. Baseline value will also be flagged.

12.5.3.1 Liver Tests

The on-treatment period without significant diet change (see [Section 9.2](#)) will be considered for all liver tests parameters, except GGT where the on-treatment period without rescue medications or significant diet change will be considered.

Main analysis

- **Descriptive analysis**

ALT, AST, GGT, ALP, total and direct bilirubin will be described over time using descriptive statistics by treatment group, in terms of:

- Raw values
- Absolute and relative changes from baseline

The 95% CI of the mean will also be provided.

The 2 time points prior to first intake (screening and baseline [last available data before treatment, see [Section 9.1](#)]) will be presented.

Those analyses will also be presented by sex and treatment group for parameters with lower limit of normal [LLN] or upper limit of normal [ULN] that depend on sex.

Line plots of means (raw values and changes) with whiskers extending to the upper and lower bounds of the 95% CI over time will be displayed from screening to Week 28 for all continuous parameters by treatment group (and by treatment group and sex for parameters with lower limit of normal [LLN] or upper limit of normal [ULN] that depend on sex: ALT, AST, GGT, ALP).

• **Evaluation of treatment effect (each dose versus placebo)**

MMRM will be performed as detailed in [Section 11.2.3](#), considering only on-treatment without rescue medications or significant diet change period.

12.5.3.2 Glycaemic control

The following table describes for each **continuous** parameter the type of analyses to be done.

The on-treatment period without rescue medications or significant diet change (see [Section 9.2](#)) will be considered, these parameters being sensitive to rescue medications and significant diet change (see [Section 9.6.5](#)).

Table 9: Glycaemic control parameters' analyses

Parameter	Main analyses (see Section 12.5.3.1 describing the methodology)	Sensitivity analyses	Subgroup analyses
HbA1c	Descriptive analysis Treatment effect (each active versus placebo): see Section 12.5.2	see Section 12.5.2	see Section 12.5.2
HOMA-IR	Descriptive analysis Treatment effect (each active versus placebo)	None	None
Insulin	Descriptive analysis Treatment effect (each active versus placebo)	None	None
Glucose	Descriptive analysis Treatment effect (each active versus placebo)	None	None
Fructosamine	Descriptive analysis Treatment effect (each active versus placebo)	None	None
Adiponectin	Descriptive analysis + Fold Treatment effect (each active versus placebo)	None	By sex
Ketones	Descriptive analysis Treatment effect (each active versus placebo)	None	None

Evaluation of treatment effect will also be assessed on the following categorical variables at Week 24, overall and then by sex, using CMH as detailed in [Section 11.2.3](#).

- HbA1c <7% and no new antidiabetic treatment or increase in dosages of antidiabetic treatments (binary endpoint)
- HbA1c <6.5% and no new antidiabetic treatment or increase in dosages of antidiabetic treatments (binary endpoint)
- HbA1c absolute decrease $\geq 1\%$ and no new antidiabetic treatment or increase in dosages of antidiabetic treatments (binary endpoint)
- HbA1c absolute decrease $\geq 0.5\%$ and no new antidiabetic treatment or increase in dosages of antidiabetic treatments (binary endpoint)
- HOMA index (HOMA <3, ≥ 3).

12.5.3.3 Inflammatory markers

The on-treatment period (see [Section 9.2](#)) will be considered.

Table 10: Inflammatory markers' analyses

Parameter	Main analyses (see Section 12.5.3.1 describing the methodology)	Subgroup analyses
hsCRP	Descriptive analysis Treatment effect (each active versus placebo): see Section 12.5.2	None
IL-6	Descriptive analysis Treatment effect (each active versus placebo)	None
IL-1 β	Descriptive analysis Treatment effect (each active versus placebo)	None

12.5.3.4 Lipid parameters

The on-treatment period without significant diet change (see [Section 9.2](#)) will be considered, except triglycerides where the on-treatment period without rescue medications or significant diet change will be considered.

Table 11: Lipid parameters' analyses

Parameter	Main analyses (see Section 12.5.3.1 describing the methodology)	Subgroup analyses
Total cholesterol	Descriptive analysis Treatment effect (each active versus placebo): see Section 12.5.2	By sex
LDL	Descriptive analysis Treatment effect (each active versus placebo)	By sex
HDL	Descriptive analysis Treatment effect (each active versus placebo)	By sex
Triglycerides	Descriptive analysis Treatment effect (each active versus placebo)	By sex

12.5.3.5 Body weight and body composition

The on-treatment period without significant diet change (see [Section 9.2](#)) will be considered for body weight.

The on-study values without significant diet change (see [section 9.2](#)) will be considered for all other data related to body composition (VAT, SAT, Spleen and liver volumes...).

Table 12: Body weight and body composition analyses

Parameter	Main analyses (see Section 12.5.3.1 describing the methodology)	Subgroup analyses
Body weight	Descriptive analysis Treatment effect (each active versus placebo): see Section 12.5.2	By Sex
L3 visceral adipose tissue [L3 VAT] Cross-sectional area of VAT measured in the axial plane at the third lumbar vertebra (L3) in cm ² .	Descriptive analysis Treatment effect (each active versus placebo)	By Sex
L3 subcutaneous adipose tissue [L3 SAT] Cross-sectional area of SAT measured in the axial plane at the third lumbar vertebra (L3) in cm ² .	Descriptive analysis Treatment effect (each active versus placebo)	By Sex
L3 VAT/SAT ratio, derived as [L3 VAT]/ [L3 SAT]	Descriptive analysis Treatment effect (each active versus placebo)	By Sex
L3 Back Muscle Percentage intramuscular fat (%). Percentage of intramuscular fat within the back muscles measured in the axial plane at the third lumbar vertebra (L3)	Descriptive analysis Treatment effect (each active versus placebo)	By Sex
Thigh SAT Cross-sectional area of SAT in the thigh measured in the axial plane 200mm below the femoral head in mm ² , derived as the mean of left and right thigh SAT	Descriptive analysis Treatment effect (each active versus placebo)	By Sex
Thigh medial SAT Cross-sectional area of SAT, medial to the femur [REDACTED] [REDACTED] [REDACTED]	[REDACTED] effect (each active versus placebo)	By Sex
Thigh Muscle Fat Infiltration (MFI) MFI measured as a percentage in the axial plane 20cm below the femoral head.	Descriptive analysis Treatment effect (each active versus placebo)	By Sex

[illegible]

- [REDACTED]
- [REDACTED]
- (b) (7)(C), [REDACTED], [REDACTED] [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

■ [REDACTED]

[REDACTED] [REDACTED] [REDACTED]

■ [REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]		
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

12.6 Safety Analyses

12.6.1 Extent of Study Drug Exposure

Duration of exposure (see [Section 9.6](#)) will be summarized using descriptive statistics for each treatment group, and overall for FAS, PPS and SAS.

The following parameters will be summarized in a table using descriptive statistics by treatment group in the safety set of patients:

- Treatment prematurely discontinued during study (Yes, No)
- Treatment duration (weeks)
- Overall persistence (%)
- Overall compliance up to Week 24 (%)

Duration of exposure will be listed.

12.6.2 Adverse Events

All safety analyses will be performed on the SAS. Safety assessments will be reported descriptively, using the on-treatment period.

Adverse events (AEs) will be coded using the MedDRA dictionary version 24.1 (or a later version if updated during the study), and classified as either non-treatment-emergent AEs (pre-treatment AEs, post-treatment emergent AEs [PTEAEs]) or treatment emergent AEs (TEAEs) as follows:

- Non-treatment-emergent AEs (nTEAEs), i.e. pre-treatment AEs are events that start prior to the date and time of first dose of study treatment.
- PTEAE are events that start more than 30 days after stop of study treatment.
- TEAEs are events with start date and time on or after the date and time of first dose of study treatment and up to 30 days after date and time of last dose of study treatment, and events with start date and time prior to the date and time of first dose of study treatment whose severity worsens on or after the date and time of first dose of study treatment.

The relationship between an AE and treatment is assessed as 'Not related' and 'Related'.

The number and percentage of patients reporting each nTEAE will be summarized (patients with more than one nTEAE of each category will be counted only once) as well as the corresponding absolute counts for each treatment group and overall, by SOC (sorted alphabetically) and PT (sorted by descending overall total). The same will be done with PTEAEs

An overview table will summarize the number and percentage of patients with at least one of the following AEs, as well as the absolute counts of number of TEAEs, by treatment group, overall and by sex:

- Any AE;
- Any nTEAE
- Any PTEAE
- Any TEAE
- Any TEAE by severity (Mild, Moderate, Severe);
- Any AESI
- Treatment-related TEAEs;
- TEAEs leading to treatment discontinuation;
- Treatment related TEAEs leading to discontinuation;
- TEAEs leading to treatment interruption
- Serious TEAEs (SAEs) (including major adverse cardiac events [MACE]: non-fatal myocardial infarction, non-fatal stroke, cardiovascular death, hospitalization for acute coronary syndrome);
- Treatment-related SAEs;

- SAEs leading to death;
- Treatment-related SAEs leading to death;
- SAEs leading to treatment discontinuation;

The number and percentage of patients reporting each TEAE and the absolute count of TEAEs will be summarized by SOC and PT. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending frequency overall total. The following summaries will be produced:

- TEAEs by SOC and PT;
- Treatment-related TEAEs, by SOC and PT

In the above summaries, patients with more than one AE within a particular SOC are counted only once for that SOC. Similarly, patients with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

No statistical comparisons of AEs between treatment groups will be performed.

The occurrence of AEs by treatment group will be displayed graphically. The AEs will be sorted by relative risk and the corresponding 95% CIs will be displayed in the graph as well.

Relative risk is calculated as:

Probability of events experienced in treated group / probability of events experienced in non-treated group

For all analyses of safety data, in addition to the previous raw cumulative incidence proportions, the exposure adjusted incidence rates will be provided in the results, calculated as:

Number of patients experiencing the AE / Total exposure-years among patients in the respective treatment group at risk of an initial occurrence of the event.

Total exposure-years is calculated as the sum of all patients' time until initial occurrence of AE or end of follow-up without an event in years.

The exposure-years for each adverse event will also be displayed.

All AE data will be listed by treatment group and start date. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of SAEs, AEs leading to discontinuation of study treatment and AEs resulting in death will be produced.

12.6.3 Adverse Events of special Interest (AESI)

The number and percentage of patients reporting each AESI and the absolute count of events will be summarized using the AESI label, sorted by descending frequency in overall total.

These events are:

- Anaemia
- Heart Failure
- Aminotransferases Elevation
- Bone Fracture
- Peripheral Oedema
- Cholelithiasis
- Hypoglycaemia
- Ovulation Resumption

12.6.4 Hypoglycaemia

Glucose distribution will also be presented by treatment group, CTCAE grade and IHSG criteria, using the worse glucose value reported during the study (post first intake).

CTCAE Criteria:

- Grade 1: < LLN - 55 mg/dL (< LLN - 3.0 mmol/L)
- Grade 2: <55 - 40 mg/dL (<3.0 - 2.2 mmol/L)
- Grade 3: <40 - 30 mg/dL (<2.2 - 1.7 mmol/L)
- Grade 4: <30 mg/d (<1.7 mmol/L); life-threatening consequences; seizures
- Grade 5: Death

IHSG Criteria:

- Level 1: ≤ 3.9 mmol/L (70 mg/dL)
- Level 2: ≤ 3.0 mmol/L (54 mg/dL)
- Level 3: Severe hypoglycaemia, as defined by the ADA, denotes severe cognitive impairment requiring external assistance for recovery

12.6.5 Physical Examinations

Physical examination results for each body system (Normal/Abnormal) and details of abnormalities will be listed for each patient.

12.6.6 Vital Signs

The following vital signs parameters will be described over time from baseline to Week 28 using descriptive statistics by treatment group, in terms of raw values, absolute and relative changes from baseline (the 95% CI of the mean will also be provided) for continuous variables, total counts and percentages of patients for categorical variables:

- Systolic blood pressure (SBP) (mmHg);
- Diastolic blood pressure (DBP) (mmHg);
- Pulse rate (bpm);
- BMI (kg/m^2);
- BMI (Obese, Non-obese, see [Section 9.6.3](#))
- BMI class (Underweight, Normal, Overweight, Obese class I, II and III, see [Section 9.6.3](#))
- Waist circumference (cm);

(body weight is already presented in [Section 12.5.3.5](#))

The on-treatment period without significant diet change (see [Section 9.2](#)) will be considered.

Line plots of means (raw values and changes) with whiskers extending to the upper and lower bounds of the 95% CI over time will be presented from baseline to Week 28 for all continuous parameters by treatment group.

All vital signs data will be listed and baseline value will be flagged.

12.6.7 ECGs

For all patients, a single ECG will be performed at Screening and Week 24 (EOT). Additional ECG can be performed at other time points (Week 4, Week 12 or Week 28).

The following analysis summaries will be presented and listed for raw values, absolute and relative changes from baseline for continuous variables, total counts and percentages of patients for categorical variables, by treatment group using the worst value reported during the study (post first intake).

- QT duration corrected according to Fridericia formula (QTcF) (ms)
- QTcF >450 ms (Yes, No)
- QTcF >480 ms (Yes, No)
- QTcF >500 ms (Yes, No)

- Absolute change from baseline in QTcF (ms)
- Absolute change from baseline ≥ 60 ms (Yes, No)
- Absolute change from baseline ≥ 30 ms (Yes, No)
- Heart rate (HR) (beats/min)
- HR in categories < 40 beats/min (Yes, No)
- HR in categories > 120 beats/min (Yes, No)
- Relative change in HR from baseline $> 25\%$ (Yes, No)
- Status over time (based on the central reader evaluation):
 - Normal or Abnormal NCS - Normal or Abnormal NCS
 - Normal or Abnormal NCS - Abnormal CS
 - Abnormal CS – Normal or Abnormal NCS
 - Abnormal CS - Abnormal CS

The on-treatment period (see [Section 9.2](#)) will be considered.

Each parameter will be described at each study visit using descriptive statistics by treatment group and by sex.

Line plots of means (raw values and changes) with whiskers extending to the upper and lower bounds of the 95% CI over time will be presented from baseline to Week 28, for QTcF and HR by treatment group and by sex.

12.6.8 Laboratory Data

Clinical laboratory data to be summarized include all laboratory parameters that are not already presented as part of Efficacy Analyses (see [Section 12.5](#)). The Protocol Table 4 presents the laboratory parameters to be evaluated in the study.

All laboratory data will be reported in International System of Units (SI) units.

The following clinical laboratory parameters will be described over time from baseline to Week 28 using descriptive statistics by treatment group, in terms of raw values, absolute and relative changes from baseline (the 95% CI of the mean will also be provided) for continuous variables, total counts and percentages of patients for categorical variables:

- SARS-Cov2
- Serology (HBsAg, anti-HCV, HIV1 & 2 antibodies)
- Haematology (Complete blood count: leukocytes (WBC) plus differential count (neutrophils, eosinophils, basophils, lymphocytes, monocytes), reticulocytes, platelets, erythrocytes, Hb, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), Mean corpuscular haemoglobin concentration (MCHC))
- Serum chemistry (Electrolytes (Na, K, Ca, Ph, Bicar), CPK, pancreatic lipase, pancreatic amylase)
- Renal function (Serum creatinine, urea, albumin, eGFR)
- Coagulation (INR, aPTT)
- Cardiac test (NT-proBNP)
- Serum iron biomarkers (Iron, ferritin, transferrin, iron binding capacity, vitamin B12, folate, LDH, haptoglobin)
- Pregnancy test (β -hCG [serum test at screening, urine test at all other visits])
- Urinalysis (pH-value, glucose, protein, blood, nitrite, bilirubin, urobilinogen and leukocytes, blood, ketones)

The on-treatment period (see [Section 9.2](#)) will be considered for all laboratory parameters, except Hemoglobin, Haematocrit, Serum iron biomarkers and Urine Blood Ketones where the on-treatment period without significant diet change will be considered and urine glucose where the on-treatment period without rescue medications or significant diet change will be considered.

In addition, the number and percentage of clinical laboratory status (Normal, Abnormal) will be summarized at each time point by treatment group.

The above analyses will also be presented by sex and treatment group for parameters with LLN or ULN that depend on sex: Hemoglobin, Platelets, Haematocrit, MCV, Reticulocytes, Leukocytes, Ferritin, CPK.

Line plots of means (raw values and changes) with whiskers extending to the upper and lower bounds of the 95% CI over time will be displayed from baseline to Week 28 for all continuous laboratory parameters by treatment group (and by treatment group and sex for parameters with LLN or ULN that depend on sex: Hemoglobin, Platelets, Haematocrit, MCV, Reticulocytes, Leukocytes, Ferritin, CPK).

All laboratory data will be listed. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings. Baseline value will also be flagged.

12.6.8.1 AESI-related laboratory parameters:

Frequency tables of clinical laboratory data related to AESI will be provided:

- related to anaemia:
 - at least one post-treatment haemoglobin < LLN
 - at least one post-treatment haemoglobin < LLN and assessed as clinically significant
 - at least one haemoglobin decrease >1 g/dL (compared to Baseline)
 - at least one haemoglobin decrease >1.5 g/dL (compared to Baseline)
 - at least one haemoglobin decrease >2 g/dL (compared to Baseline)
- related to aminotransferase (ALT, AST) elevation:
 - if mean pre-treatment ALT or AST <1.5xULN: at least one post-treatment ALT or AST ≥3xULN
 - if mean pre-treatment ALT or AST ≥1.5xULN: at least one post-treatment ALT or AST ≥3 x mean pre-treatment value or ALT or AST ≥300 IU/Lwith mean pre-treatment being the mean of all pre-treatment values (see the corresponding protocol section)
- related to hypoglycaemia:
 - at least one post-treatment glucose blood level < LLN
 - at least one post-treatment glucose blood level < LLN and assessed as clinically significant

The on-treatment period (see [Section 9.2](#)) will be considered.

12.6.9 Dietary and Lifestyle monitoring

For all patients, diet stability and exercise habits will be summarized and listed by treatment group at each applicable time points. The total counts and percentages of patients will be presented.

Dietary and lifestyle monitoring results based on CRFs in pre-baseline and post baseline time points will be listed for each patient.

13.0 References

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14.0 Glossary of Abbreviations

Glossary of Abbreviations:	
ADAPT	Age, Presence of Diabetes, [REDACTED] and Platelet Count
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APRI	Aspartate Aminotransferase-to-Platelet Ratio Index
AR(1)	Auto Regressive 1 st Order
ARH(1)	Heterogeneous Auto Regressive 1 st Order
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BMI	Body Mass Index
[REDACTED]	[REDACTED]
CI	Confidence Interval
[REDACTED]	[REDACTED]
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
DILI	Drug Induced Liver Injury
DRM	Data Review Meeting
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
[REDACTED]	[REDACTED]
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
[REDACTED]	[REDACTED]
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonists
HbA1c	Haemoglobin A1c
HDL	High-Density Lipoprotein
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	Heart Rate
IA	Interim Analysis
IAS	Interim Analysis Set

Glossary of Abbreviations:	
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IVA	Inventiva
INR	International Normalized Ratio
LDL	Low-Density Lipoprotein
LLN	Lower Limit of Normal
████	████████████████████
LSMean	Least Square Means
LST	Lead Biostatistician
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean Corpuscular Volume
MD	Medical Director
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Medical Monitoring Associate
MMRM	Mixed Models for Repeated Measures
████	██
NASH	Non-Alcoholic Steatohepatitis
NFS	Nafld Fibrosis Score
nMAR	Not Missing at Random
nTEAE	Non-Treatment Emergent Adverse Event
████	██
PLT	Platelet Count
PPAR	Peroxisome Proliferator-Activated Receptor
PPS	Per Protocol Set
PSO	System of Records For Protocol Deviations
PT	Preferred Term
PTEAE	Post-Treatment Emergent Adverse Event
QC	Quality Control
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

Glossary of Abbreviations:	
SAS®	Statistical Analysis Software
SAT	Subcutaneous Adipose Tissue
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Events
TFLs	Tables, Figures And Listings
TLR	Top Line Results
TIMP-1	Tissue Inhibitor Matrix Metalloproteinase 1
ULN	Upper Limit of Normal
UN	Unstructured
US	United States Of America
VAT	Visceral Adipose Tissue
WBC	White Blood Cells
WHO	World Health Organization