STATISTICAL ANALYSIS PLAN

Protocol Title:	A randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL770 versus placebo after 12 weeks treatment in patients with Nonalcoholic Fatty Liver Disease (NAFLD) with or without type 2 diabetes mellitus
Protocol Number:	PXL770-004
Protocol Version/Date:	Current: Version 6.0 / 24th July 2020 including memo to address COVID-19 elements
Investigational Product:	PXL770
Sponsor:	POXEL S.A. Immeuble Le Sunway 259-261 Avenue Jean Jaures 69007 Lyon France
SAP Version/Date:	Version 3.0 / 15-SEP-2020

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SIGNATURE PAGE

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Protocol Number:	PXL770-004

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

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3.0	15-Sep-2020	Final approved version.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
Adipo-IR	Adipose tissue Insulin Resistance
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration time curve
BDRM	Blinded Data Review Meeting
BID	Twice a day (*bis in die*)
BMI	Body Mass Index
CAP	Controlled Attenuation Parameter
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CRF	Case Report Form
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
eCRF	Electronic Case Report Form
ET	Early Termination
FFA	Free Fatty Acids
Fib-4	Fibrosis 4
FPG	Fasting Plasma Glucose
HbA1c	Glycated hemoglobin
HDL-c	High Density Lipoprotein-cholesterol
HOMA-β	Homeostasis Model Assessment of β-cell function
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HR	Heart Rate
hsCRP	High-sensitivity C-Reactive Protein
ICF	Informed Consent Form
INR	International Normalized Ratio
IQR	Inter-quartile range
ITTS	Intent-to-treat Set
LDL-c	Low Density Lipoprotein-cholesterol
LSM	Least Square Mean
MAR	Missing at Random

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MCP-1	Monocyte Chemoattractant Protein-1
MMRM	Mixed-Model Repeated Measures
MRI	Magnetic Resonance Imaging
NAFLD	Nonalcoholic Fatty Liver Disease
NFS	NAFLD Fibrosis Score
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PDFF	Proton Density Fat Fraction
PK	Pharmacokinetic
PPS	Per Protocol Set
PT	Prothrombin Time
QD	Once a day (*Quaque die*)
QUICKI	Quantitative Insulin Sensitivity Check Index
RS	Randomized Set
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SEM	Standard error of the mean
SS	Safety Analysis Set
T2DM	Type 2 Diabetes Mellitus
TE	Transient Elastography
TEAE	Treatment-emergent adverse event
TFL	Tables, Listings and Figures
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number PXL770-004. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

Primary	
Objective	**Endpoint**

To assess the effect of PXL770 versus placebo on hepatic steatosis in nonalcoholic fatty liver disease (NAFLD) patients at the daily dose of 250 mg once daily (QD) and twice daily (BID) and 500 mg QD after 12 weeks of treatment.	**Primary Endpoint**
	• Relative change (%) from baseline to Week 12/End of Treatment in the percentage of liver fat mass (assessed by Magnetic Resonance Imaging – Protein Density Fat Fraction [MRI-PDFF]).
	Key Secondary Endpoints
	• Change from baseline to Week 12/End of Treatment in the percentage of liver fat mass (assessed by MRI-PDFF).
	• Response defined as:
	  • an absolute reduction in liver fat mass (assessed by MRI-PDFF) of at least 5%.
	  • a relative reduction in liver fat mass (assessed by MRI-PDFF) of at least 30%.
	  • a relative reduction in liver fat mass (assessed by MRI-PDFF) of at least 50%.
	  • a liver fat mass value at Week 12/End of Treatment that is normalized, i.e. ≤ 5 %.

Secondary	
Objective	**Endpoint**
To assess the safety and tolerability of PXL770 versus placebo in NAFLD patients at the daily dose of 250 mg QD and BID and 500 mg QD after 12 weeks of treatment.	• Adverse events (AEs) • Physical examination • Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) • 12-lead electrocardiogram (ECG) • Biological parameters: biochemistry, hematology, coagulation and urinalysis • Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease

	– Epidemiology Collaboration (CKD-EPI) formula
To assess the effect of PXL770 versus placebo in NAFLD patients on metabolic and non-metabolic parameters at the daily dose of 250 mg QD and BID and 500 mg QD after 12 weeks of treatment:	Change and relative change (%) from baseline to each timepoint throughout the study in:
• Liver enzymes[A]	• Alanine amino Transferase (ALT) • Aspartate amino Transferase (AST)
• Lipid parameters	• Total cholesterol • High density lipoprotein-cholesterol (HDL-c) • Low density lipoprotein-cholesterol (LDL-c) • Triglycerides • Apo A1 • Apo B • Free fatty acids (FFA) • Glycerol • Adiponectin
• Glycemic parameters in fasting conditions	Measured metabolic parameters: • Fasting plasma glucose (FPG) • Glycated hemoglobin (HbA1c) • Serum insulin • C-peptide Calculated metabolic parameters: 1. Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) 2. Quantitative Insulin Sensitivity Check Index (QUICKI) 3. Homeostasis Model Assessment of β-cell function (HOMA-β) 4. Adipose tissue Insulin Resistance (Adipo-IR)
• Biomarkers of inflammation	• High-sensitivity C-Reactive Protein (hsCRP) • Fibrinogen • Monocyte chemoattractant protein-1 (MCP-1)
• Biomarkers of fibrosis	• NAFLD Fibrosis score (NFS) • Fibrosis-4 (Fib-4) score
• Anthropomorphic parameters[1]	• Body weight • Waist circumference • Waist-to-hip ratio
To compare the 2 dose regimens of PXL770 (BID versus QD) on efficacy and safety parameters in NAFLD patients.	Efficacy and safety parameters as described above.

To describe PXL770 pre-dose plasma concentrations during the course of the treatment and pre- and post-dose plasma concentrations after 12 weeks of treatment in NAFLD patients.	PXL770 plasma concentration at each applicable timepoints

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[A] The liver enzymes and anthropometric endpoints can be considered both efficacy and safety endpoints; details of these endpoints and their analysis will be discussed in the Efficacy Assessment section below.

2.2 Study Design

2.2.1 Overview

This study is a phase IIa, multi-center, double-blind, placebo-controlled, randomized study with 4 parallel groups in NAFLD patients.

There will be a total of 4 study periods, as follows:

- Screening period: maximum of 2 weeks
- Single-blind placebo Run-in period: 4 weeks
- Double-blind treatment period: 12 weeks
- Follow-up period: 1 week

Patients will be randomized in a 1:1:1:1 ratio to receive either:

- PXL770 250 mg QD
- PXL770 250 mg BID
- PXL770 500 mg QD
- Placebo

Randomization will be stratified according to type 2 diabetes mellitus (T2DM) status (T2DM patients vs non-T2DM patients)

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Patients will be assigned a unique randomization number at the Randomization Visit by Interactive Web Response System (IWRS). This randomization number identifies which record in the randomization list and therefore which treatment should be allocated to the patient.

The randomization list will be generated by a independent statistician.

During the Single-blind placebo Run-in period, patients will take an oral dose of 2 capsules of placebo BID (4 capsules per day). The Single-blind placebo Run-in period will last for 4 weeks.

During the Double-blind treatment period, patients will take a total of 4 capsules per day (2 in the morning and 2 in the evening). The Double-blind treatment period will last for 12 weeks.

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The diagram of the study design is shown in Figure 1
Details of the Visit Schedule are included in Table 1.

The duration of study for each patient from the first visit for the informed consent signature (ICF) up to the end of the Follow-up period will be between 17 and 19 weeks.

The End-of-study is defined as the date of last visit of last patient participating in the study.

Alternative processes to mitigate the impact of COVID-19 pandemic on the conduct of this clinical trial and to eliminate apparent immediate additional risks to subjects may be implemented. Most notably for analysis, the double-blind treatment duration could be extended to a maximum duration of 20 weeks in total (i.e. 8 extra weeks) if Visit 7 (including MRI) could not be performed after 12 weeks of treatment. This prolongation should be as short as possible. An additional on-site visit or if not possible, phone contact or virtual visit including laboratory assessments (at central laboratory or if not possible at local laboratory) should be performed after 4 weeks (+/- 4 days) of treatment prolongation (i.e. Week 16). In case of temporary treatment interruption (≤ 3 weeks) due to IMP dispensation issues, the IMP must have been resumed for at least 2 weeks prior to performing the End of treatment MRI-PDFF.

Figure 1. Diagram of Study Design

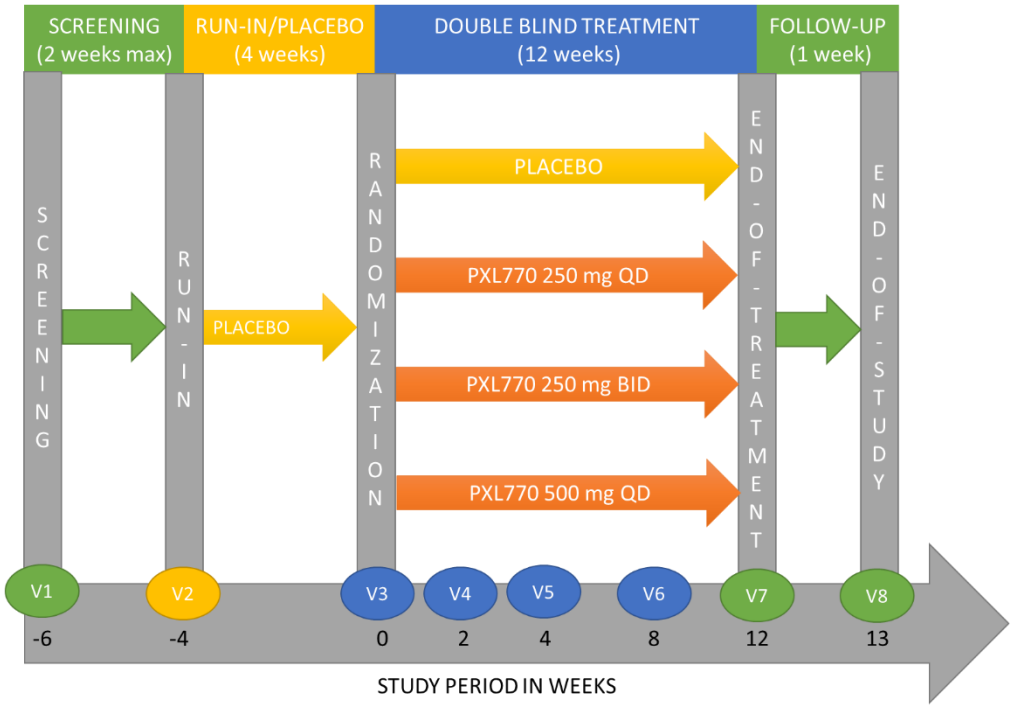

Table 1. Visit Schedule

	V1	V2	V3	V4	V5	V6	V7	V8	ET
	Screening	Run-in	Randomization	Week 2	Week 4	Week 8	Week 12 EoT	Week 13 EoS	-
Timeframe	**-6 weeks max + 2 days**	**-4 weeks**	**Day 0**	**Day 14**	**Day 28**	**Day 56**	**Day 84**	**Day 91**	**-**
Time windows	-	*Within 2W after V1*	*4W after V2 ± 2 days*	*2W after V3 ± 2 days*	*4W after V3 ± 2 days*	*8W after V3 ± 3 days[1]*	*12W after V3 ± 4 days[1]*	*1W after V7 ± 2 days*	*Within 11 days after IMP discontinuation*
Informed Consent	X								
IWRS log-on	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X	X	X						
Demography	X								
Medical history	X								
Adverse events	X	X	X	X	X	X	X	X	X
Prior medications	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Complete phys ex.[2,3]	X		X				X	X	X
Limited phys ex.[4]		X		X	X	X			
Vital signs[5]	X	X	X	X	X	X	X	X	X
ECG[14]	X		X	X	X	X	X[15]	X	X
hsCRP	X		X	X	X	X	X	X	X
FPG	X		X	X	X	X	X	X	X
HbA1c	X		X				X		X
Safety lab[8]	X		X	X	X	X	X	X	X
eGFR	X		X				X		X
Pregnancy test[12]	X		X	X	X	X	X	X	X
Viral screen lab[11]	X								
Measured metabolic param[6]			X		X	X	X		X
Calculated metabolic param[7]			X		X		X		X
Inflammatory biomarkers[9]			X				X		X
Fibrosis biomarkers[10]			X				X		X
Biobanking sampling			X				X		
Pharmacogenetic sampling[17]			X				X		
PK sampling[16]				X	X	X	X	X	
Transient Elastography[13]		X							
MRI-PDFF			X*				X**		
IMP compliance			X	X	X	X	X		X
IMP dispensing		X	X		X	X			
Patient Emerg. Card dispensing	X								
Diary dispensing		X	X		X	X			
Diary review			X	X	X	X	X		X
SMBG dispensing[18]		X							
SMBG measurements review[19]			X	X	X	X	X	X	X

X*: MRI-PDFF must be performed within 8 ± 4 days prior to Randomization Visit (V3); X**: MRI must be performed before or on the day of Week 12 (V7), i.e. 84 days (- 4 days) after Randomization Visit (V3).
ECG: electrocardiogram: eGFR: estimate glomerular filtration rate; EoS: End of Study; EoT: End of Treatment; ET: Early Termination; Emerg: Emergency; FPG: Fasting Plasma Glucose; HbA1c: glycated hemoglobin; hsCRP: High-sensitivity C-Reactive Protein; IMP: Investigational medicinal product; IWRS: Interactive Web Response System; lab: laboratory; MRI-PDFF: Magnetic Resonance Imaging – Proton Density Fat Fraction; param.: parameters; phys ex.: physical examination; PK: pharmacokinetics; SMBG: self-monitoring blood glucose; V: visit; W: week(s)

[1]: the interval between two on-site visits must not exceed 32 days.

[2]: includes head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems.
[3]: includes height, weight, body mass index (BMI), waist and hip circumferences for Screening Visit (V1) and weight, BMI, waist and hip circumferences for other visits.
[4]: includes general appearance, the cardiovascular system as well as reported symptoms by the patient to the Investigatory; includes weight, waist and hip circumferences.
[5]: includes one measurement of heart rate and three measurements of blood pressure in supine position.
[6]: includes serum insulin, C-peptide, total cholesterol. Low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol; triglycerides, Apo A1, Apo B, free fatty acids (FFA), glycerol and adiponectin.
[7]: includes Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Check Index (QUICKI), Homeostasis Model Assessment of β-cell function (HOMA-β) and Adipose tissue Insulin Resistance (Adipo-IR).
[8]: includes biochemistry, hematology, coagulation and urinalysis.
[9]: includes fibrinogen and Monocyte Chemoattractant Protein-1 (MCP-1).
[10]: includes Non-Alcohol Fatty Liver Disease (NAFLD) Fibrosis score (NFS) and Fibrosis-4 (Fib-4) score.
[11]: includes Hepatitis B surface antigen (HBsAg), Hepatitis C virus antibody (anti-HCV), in case of positive results, reflex test of HCV circulating ribonucleic acid (RNA), anti-human immunodeficiency virus (HIV) 1 and 2.
[12]: for female patients of child-bearing potential only, serum pregnancy test (Human Chorionic Gonadotropin (β-HCG)) at Screening Visit (V1), End-of-study Visit (V8) and Early termination Visit (ET) and urine pregnancy test at all other visits where a pregnancy test is planned.
[13]: if required as per inclusion criterion #7, transient elastography should include Controlled Attenuation Parameter (CAP) assessment.
[14]: includes single ECG at Screening Visit (V1) and triplicate ECGs at the other visits.
[15]: ECG should be performed at pre-dose and 2h post-dose (i.e. before the PK sampling and the glucose and fructose load (if applicable)).
[16]: blood sampling should be performed at the following timepoints:
For all randomized patients:
- At V4, V5 and V6: pre-dose
- At V7: pre-dose Corporate confidential information
- At V8.

[17]: Optional collection of DNA/RNA sample.
[18]: SMBG dispensed to T2DM patients only. SMBG to be brought back to the study site at each visit for measurement review. SMBG will be kept by the patient after the end of his/her study participation.
[19]: For T2DM patients only.

2.2.2 Sample Size Determination

Sample size determination is based on the primary endpoint, i.e. the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline to Week 12/End of Treatment. The primary objective is to show the superiority of at least one PXL770 dose over placebo with regard the primary endpoint and the following assumptions:

- Superiority design of PXL770 compared to placebo
- 2-sided alpha = 0.05
- Power of 90%
- Expected difference of 30% between at least one PXL770 dose and placebo
- Relative change in percentage liver fat mass: standard deviation (SD) = 30%, estimated from previous published data[1]
- No adjustment for multiple comparisons between PXL770 doses and placebo was considered

With these assumptions, the sample size is 24 evaluable patients in each group to achieve a 90% power for each pairwise comparison.

Assuming a dropout rate of approximately 20%, 120 patients in total (30 patients per arm) are to be randomized in the study.

In the event that the drop-out rate exceeds 20% and the initial planned number of 120 randomized patients does not allow to obtain at least 96 evaluable patients, up to 20 additional patients could be randomized.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of double-blind study treatment. The day of the first dose of study treatment will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

Analysis Day will be calculated as:

Date of assessment – date of first dose of study treatment

+ 1 (if date of assessment ≥ date if first dose of study treatment)

3.1.2 Definition of Baseline

Baseline for all efficacy and safety variables will be defined as the value obtained at the Randomization Visit (Day 1) prior to the first dose of double-blind study treatment. If the measurement at this visit is missing, the last measurement prior to the first dose of double-blind study treatment will be used as baseline.

3.1.3 Analysis Visits

For the primary endpoint, liver fat mass (assessed by MRI-PDFF), analysis visits will be assigned according to the labelled visit: Baseline or Week 12/End of Treatment. Even if MRI-PDFF is assessed after treatment extension, it will be included for analysis. However, note that the Week

12/End of Treatment assessment must meet each of the following criteria in order to be included for analysis:

- Must be performed within 14 days (inclusive) of the last dose of study treatment. It may be performed more than 14 days prior to last dose of study treatment, but cannot be performed more than 14 days after last dose of study treatment in order to be included for analysis.
- The MRI analysis day must be between 8 and 20 weeks (57 and 141 days), inclusive.

Other efficacy assessment and safety assessment analysis visits will be assigned according to the labelled visit as well. In addition to maximize the data available for assessments with regular scheduled visits, where possible, results from early termination (ET) and unscheduled visits will be allocated to a post-baseline scheduled visit according to the following rules and visit windows described in the table below (defined as the halfway point between the target visit days). If a valid value exists for the scheduled visit to which the ET/unscheduled visit has been allocated then the value from the scheduled visit will be used in the analysis, otherwise the values from the ET/unscheduled visits will be used in the analysis for the particular scheduled visit.

Note that Visit 7 for subjects that extended treatment due to COVID-19 will be handled similar to unscheduled/ET visits. It will not be set to Week 12 by default. It will be checked for an analysis visit window according to the table below. For example, Visit 7 may be treated as Week 20 for these subjects.

If there is more than one assessment within a visit window, then the analysis visit will be assigned by the following priorities:

1. Use the assessment from the visit with the matching visit label.
2. Use the visit closest to the target visit day; in the case of ties, use the earlier visit.

Further details of analysis visit assignment will be provided in the Analysis Data Model (ADaM) Specifications.

Analysis Visit	**Target Analysis Day**	**Visit Windows (Analysis Days)**				
		Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
Baseline[a]	1	1	1	1	1	
Week 2	15	2 – 22				1 – 22
Week 4	29	23 – 43	2 – 43	2 - 43		23 – 43
Week 8	57	44 – 71	44 - 71			44 – 71
Week 12	85	72 – 99	72 - 99	44 - 99	58 - 99	72 – 89
Week 16	113	100 – 127	100 – 127	100 – 127	100 – 127	
Week 20	141	128+	128+	128+	128+	
Week 12/End of Treatment	The last post-dose observation within 7 days (inclusive) of last dose of double-blind study treatment will be used. This will be an added visit in the analysis database (i.e. a Week 12 or Week 20 result may be used).					
End of Study	The last observation after last dose of double-blind study treatment will be used.					
Week 13	92					90+

[a] Baseline is defined as assumed to occur on Day 1 but will be defined as detailed in section 3.1.2.

All efficacy assessments (excluding the End of Study analysis visit) must be within 7 days (inclusive) of last dose of double-blind study treatment to be used for analysis. There is no upper limit for what may be used for the End of Study analysis visit.

Group 1 refers to liver enzymes, FPG, hsCRP, anthropometric parameters, physical examination, vital signs, 12-lead ECG and biological parameters (biochemistry, hematology, coagulation and urinalysis).
Group 2 refers to lipids and the measured metabolic parameters (serum insulin and C-peptide).
Group 3 refers to the calculated metabolic parameters.
Group 4 refers to the biomarkers of inflammation and fibrosis, HbA1c and eGFR.
Group 5 refers to PK sampling

3.1.4 Change and Relative Change from Baseline

Change from baseline will be derived for each analysis visit as visit value minus baseline.

Relative change from baseline will be derived for each analysis visit as 100 * [(visit value minus baseline)/baseline].

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, standard deviation, standard error of the mean (SEM), median, Q1 and Q3, minimum, and maximum.

3.1.6 Hypothesis Testing

Unless stated otherwise, tests will be performed at the nominal alpha two-sided level of 0.05. 95% two-sided confidence intervals will also be reported.

Given the early stage of development (i.e. a Phase II trial), no adjustment for multiplicity will be considered. Hence, pairwise comparisons between PXL700 doses (250 mg QD, 250 mg BID and 500 mg QD) vs placebo and pairwise comparisons between active doses will be tested at the two-sided nominal level of significance of 0.05.

3.1.7 Handling of Dropouts and Missing Data

Few missing data are expected and, unless stated otherwise, they will not be replaced.

3.2 Analysis Populations

3.2.1 Screened Analysis Set

The Screened Analysis Set is defined as all patients who were screened for inclusion into the study.

3.2.2 Run-in Safety Analysis Set (RISS)

The Run-in Safety Analysis Set (RISS) is defined as all patients having received at least one dose of the single-blind placebo run-in treatment. The population will be used to assess exposure and compliance with the single-blind placebo run-in treatment only.

3.2.3 Safety Analysis Set (SS)

The Safety Analysis Set (SS) is defined as all randomized patients having received at least one dose of the double-blind study treatment (either PXL770 or placebo) and considered as-treated. All safety and tolerability data will be analyzed on the Safety Analysis Set.

3.2.4 Randomized Set (RS)

The Randomized Set (RS) is defined as all as-randomized patients. Patients will be assigned to the treatment group as randomized for the Randomized Set.

3.2.5 Intent-To-Treat Set (ITTS)

The Intent-To-Treat Set (ITTS) is defined as all randomized patients having received at least one dose of the double-blind study treatment (either PXL770 or placebo). Patients will be assigned to the treatment group as-randomized for the ITT Set. The ITTS will be considered as the primary set for efficacy analysis.

Additionally, some summaries and analyses may be performed on the ITTS excluding subjects whose study treatment period was extended due to COVID-19 pandemic circumstances. The subjects excluded will be defined as those that have checked “study treatment period was extended due to COVID-19 pandemic circumstances” on the eCRF *and* their overall double-blind study treatment duration is >98 days.

3.2.6 Per Protocol Set (PPS)

The Per Protocol Set (PPS) is defined as all patients in the ITT who complete the double-blind treatment period and have an overall treatment duration ≥8 weeks (≥56 days) without any CSR reportable protocol deviations (PD) that is deemed to affect the primary efficacy endpoint of MRI-PDFF.

CSR reportable PDs likely to affect the primary efficacy endpoint include the following categories (see Protocol Deviation Plan for further details):

- A patient who did not meet entry criteria;
- A patient who developed withdrawal criteria but were not withdrawn;
- A patient who received the wrong treatment or incorrect dose;
- A patient who was non-compliant with double-blind study treatment (overall <80% or > 120% compliant, or <70% compliant in the last visit interval prior to End of Treatment MRI assessment);
- A patient who received prohibited concomitant medications that affect the primary efficacy assessment (MRI-PDFF);
- A patient who missed the primary efficacy assessment (MRI-PDFF) at baseline or Week 12/End of Treatment. Subjects with extended treatment may be included in the PPS. The MRI must be performed within 14 days (inclusive) of the last dose of study treatment in order to be included.

During the Blind Data Review Meeting (BDRM), all patients with a CSR reportable protocol deviation will be reviewed and assessed for inclusion into the PP Analysis Set; this review will be carried out by the Sponsor and Medical Monitor and agreed upon prior to database lock.

3.2.7 Pharmacokinetic (PK) Population

The Pharmacokinetic (PK) population is defined as those patients from the Safety Analysis Set who have been treated with PXL770 according to the protocol and have provided at least one pre-dose PK assessment during the study.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

A patient who fails during the screening period (between V1 and V2) is deemed to be a screen failure. A patient who fails during the Run-in period (between the Run-in (V2) and run-in kit dispensed, and Randomization (V3) Visits), prior to randomization is deemed to be a run-in failure.

Note that subjects may rescreen. Subjects that screen fail twice will only be counted once according to their 2nd reason for screen failure for summary, but all reasons will be listed. If a subject rescreens and successfully enters the Run-in period, they will not be counted as a screen failure for summary, although their reason for initial screen failure will be listed.

The reason given for each screen failure and each run-in failure will be summarized and listed separately. The listings for screen failures and run-in failures will include date of screening, date of screen/run-in failure and the primary reason for screen/run-in failure.

A patient disposition summary for Screening and Run-in will be provided for the Screened Analysis Set and will include the following categories:

- Patients who were screened for inclusion into the study
- Patients who failed screening (and reasons for screen failure)
- Patients who entered the run-in period
- Patients who failed during run-in (and reasons for run-in failure)
- Patients who were randomized

A patient disposition summary for the Treatment Period will be provided for the Randomized Set and repeated for the PPS and will include the following categories:

- Patients who were randomized
- Patients who received at least one dose of double-blind study treatment
- Patients who completed the double-blind period (i.e. Visit 7)
- Patients who withdrew from the double-blind period (and reasons for withdrawal)
- Patients who completed the follow-up period (i.e. completed the study overall)
- Patients who withdrew from the follow-up period (and reasons for withdrawal)
- Patients who had study treatment temporarily interrupted due to COVID-19 pandemic circumstances
- Patients who stopped study treatment due to COVID-19 pandemic circumstances
- Patients whose study treatment period was extended due to COVID-19 pandemic circumstances
- Patients whose primary reason for withdrawal was due to COVID-19

Disposition events during the screening or run-in periods will be summarized overall. Disposition events from the Randomization Visit (V3) onwards will be summarized by treatment group and overall.

A disposition listing containing the randomization details (randomized treatment group and date of randomization), dates of first and last dose of study treatment and completion status (with date and reasons for withdrawal for patients who withdrew) will be provided for all patients in the Randomized Set.

3.3.2 Protocol Deviations

Counts and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized by treatment group and overall for the Randomized Set. A separate summary table will also be produced for the CSR reportable protocol deviations that led to exclusion from the Per Protocol Set. A separate summary table will also be produced for all protocol deviations, CSR reportable or not, that were due to COVID-19 pandemic circumstances.

A listing of CSR reportable deviations will also be produced for the Randomized Set.

Inclusion/Exclusion criteria deviations will also be listed for the Randomized Set; an additional listing for the Non-randomized patients will also be presented.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by treatment group and overall. Only counts will be displayed for the Screened Analysis Set, the Run-in Safety Analysis Set and the Randomized Set. The denominator for the other Analysis Sets will be based on the Randomized Set.

A listing of analysis set inclusion will also be provided.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment group and overall for the ITT Set.

Demographic characteristics include age, gender, childbearing potential, if female, ethnicity and race.

Baseline characteristics include:

- Stratification variables – T2DM status Corporate confidential information
- Diabetes disease history –history of disease, duration of disease, currently treated
- Hepatic Steatosis Disease history – duration of disease
- Cardiovascular disease (hypertension and dyslipidemia) history – history of disease, duration of disease, currently treated
- Liver fat mass (%) as assessed from MRI-PDFF
- Anthropometric parameters –weight and Body Mass Index (BMI)
- Alcohol, tobacco and drug use
- Liver enzymes – ALT, AST
- Glycemic parameters - HbA1c, FPG

3.3.5 Medical History

Separate listings for Hepatic Steatosis, Diabetes, Cardiovascular Disease (Hypertension and Dyslipidemia) and Other Medical History will be provided for the Randomized Set.

Other Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 COVID-19 update. The number and percentage of patients with medical history will be summarized by preferred term within system organ class and treatment group for the Randomized Set and presented by descending overall frequency of SOC, and within SOC by descending incidence of PT.

3.3.6 Concomitant Medications

Concomitant medications will be coded using the WHODrug Dictionary version Sep2018G B3. For summary purposes, medications will be considered prior medications if they were taken within 28 days prior to ICF signature and stopped before or on ICF signature date. Medications that are ongoing before and continue after the ICF signature will be considered as concomitant medications. Medications that were prescribed during the study (from the ICF signature to End-of study Visits) will be considered as new medications. If a subject rescreens, the later ICF signature date will be used as reference. If a subject rescreens, the medications initially reported for the subject in their first screening will not be reported for summary purposes; only the medications from their rescreening will be used for summary.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior, concomitant or new. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication stop date is incomplete, the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

The number and percentage of patients taking prior, concomitant and new medications by preferred term within Anatomical Therapeutic Chemical (ATC) Classification Systems levels 1, 3 and 4 will be summarized by double-blind treatment group and in total based on the Safety Analysis Set.

3.3.7 Study Treatment Exposure and Compliance

3.3.7.1 Single-Blind Placebo Run-In

The number of days of exposure to the single-blind placebo run-in treatment will be listed and summarized for the Run-In Safety Analysis Set. Exposure, in days, will be calculated as the difference in dates between the first and last dose of single-blind placebo run-in treatment plus 1. If these dates are partial or missing, they will be imputed for the purpose of calculating exposure. Details of the imputation will be described in the programming specifications.

Percent compliance will be calculated as:

$$\frac{\text{Number of single blind placebo run in capsules taken x 100}}{\text{Theoretical number of single blind placebo run in capsules to be taken during the run in treatment period}}$$

The number of single-blind placebo run-in capsules taken will be derived by adding the number of actual morning and evening capsules taken as recorded on the electronic Case Report Form (eCRF). If this is not recorded, then the estimated number of capsules taken, as recorded on the eCRF, will be used.

The theoretical number of single-blind placebo run-in capsules to be taken will be derived as the difference in dates between Visit 2 and Visit 3 multiplied by 4. If the Visit 3 date of visit is missing,

it will be imputed using the screen failure date for the purpose of calculating the theoretical number of capsules.

Percent compliance with the single-blind run-in study treatment will be summarized overall for the Run-In Safety Population using descriptive statistics.

3.3.7.2 Double-Blind Study Treatment

Days of overall exposure to double-blind study treatment will be summarized by treatment group for the Safety Analysis Set using descriptive statistics. Exposure, in days, will be calculated as:

date of last dose of double-blind study treatment – date of first dose + 1

If these dates are partial or missing, they will be imputed for the purpose of calculating exposure. Details of the imputation will be described in the programming specifications.

Note that the exposure calculation is intended to describe the length of time a patient was exposed to double-blind study treatment and therefore does not take double-blind study treatment interruptions into account.

In addition, a contingency table will be provided to display the number and percentage of patients with exposure in the following categories:

- ≤4 weeks (≤30 days)
- >4 to ≤8 weeks (31 - 59 days)
- >8 to ≤12 weeks (60 days – 88 days)
- >12 to ≤16 weeks (89 – 116 days)
- >16 weeks (>116 days)

In addition, exposure will be calculated per visit interval using the same intervals as the compliance calculations. If mid-study administration dates are partial or missing, they will be imputed using the visit dates for the purpose of calculating exposure.

Percent compliance will be calculated as:

$$\frac{\text{Number of capsules taken x } 100}{\text{Theoretical number of capsules to be taken during the period (based off on} - \text{site visit days)}}$$

The number of capsules taken will derived by adding the number of actual morning and evening capsules taken as recorded on the electronic Case Report Form (eCRF). If this is not recorded, then the estimated number of capsules taken, as recorded on the eCRF, will be used only if it is the last study drug return.

The theoretical number of capsules to be taken will be derived from the date of first dispensation visit to the date of last return visit of the double-blind study treatment, assuming 4 capsules are taken per day. In other words, on-site visit dates are used in the calculation by visit interval and overall. These visit intervals will be based on actual data reported, not the planned visit schedule. In other words, a wider interval may be used if study drug was not returned at an intermediate visit. Or unscheduled visits may be used, if reported. If a subject early withdrawals, the last study drug return visit date will be used. Days of exposure by visit will use the same visit intervals as are used for compliance.

Percent compliance with the study treatment will be summarized by treatment group for the Safety Population using descriptive statistics. Additionally, the number and percentage of patients within each treatment group with overall compliance in the following categories will be provided:

- <80%
- 80-120%
- >120%

3.4 Efficacy Assessment

In general, efficacy data will be summarized by treatment group. All efficacy data will be listed for the Randomized Set.

3.4.1 Analyses of Liver Fat Mass Assessed by MRI-PDFF

Summary statistics for liver fat mass at baseline, Week 12/End of Treatment and the change and relative change from baseline will be provided for the ITT and PP Analysis Sets.

3.4.1.1 Primary Efficacy Analysis

The primary efficacy endpoint is the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline to Week 12/End of Treatment.

The primary analysis of the primary endpoint will be performed on the ITT set using an analysis of covariance (ANCOVA) model with treatment (PXL770 doses of 250 mg QD, 250 mg BID, 500 mg QD and placebo) and stratification factors – T2DM status (T2DM patients vs non-T2DM patients) Corporate confidential information as factors and baseline liver fat mass as a covariate. The least square means (LSMs) for liver fat mass within the treatment groups and pairwise differences in LSMs will be estimated along with their 95% confidence intervals (CIs) and p-values. Sample SAS code:

```
/************************************************************
TRTPN: 0=Placebo, 1=PXL770 250 mg QD, 2=PXL770 250 mg BID,
       3=PXL770 500 mg QD
T2DM: T2DM status stratification factor
      (T2DM patients vs non-T2DM patients)
```

Corporate confidential information

```
PCHG: Relative change from baseline to Week 12/End of Treatment
      in liver fat mass
BASE: Baseline liver fat mass
************************************************************/
proc glm;
    class TRTPN T2DM
    model PCHG = T2DM        TRTPN BASE / p;
    lsmeans TRTPN / stderr pdiff cl;
    estimate "PXL770 250 mg QD : Placebo"  TRTPN -1 1 0 0;
    estimate "PXL770 250 mg BID : Placebo" TRTPN -1 0 1 0;
    estimate "PXL770 500 mg QD : Placebo"  TRTPN -1 0 0 1;
    run;
```

The ANCOVA model validity will be checked using appropriate plots (studentized residuals vs predicted values, etc.).

Missing MRI-PDFF at Week 12/End of Treatment will be estimated using a multiple imputation method (fully conditional specification method as well) assuming missing at random (MAR) mechanism. Missing baseline MRI-PDFF will not be estimated.

The multiple imputation procedure and the analysis will be conducted in three separate steps: 1) Multiple Imputation 2) ANCOVA Model based analysis by Imputed data set 3) combination of results using Rubin's rule. PROC MIANALYZE

1. Multiple imputation (using SAS PROC MI): since there is only one post randomization visit (Week 12/End of Treatment) for MRI assessment, the missing pattern is monotone. The imputation model will include treatment, stratification factors (T2DM status Corporate confidential |), and baseline liver fat mass and the fully conditional specification (FCS) method as well will be used. Missing data will be imputed 100 times to generate 100 imputed data sets. The seed will be 7704. Sample SAS code is below.

```
/*************************************************************
TRTPN: 0=Placebo, 1=PXL770 250 mg QD, 2=PXL770 250 mg BID,
       3=PXL770 500 mg QD
T2DM: T2DM status stratification factor
      (T2DM patients vs non-T2DM patients)
```

Corporate confidential information

```
Baseline: Baseline liver fat mass
Week_12: Week 12/End of Treatment liver fat mass
*************************************************************/
proc mi nimpute=100 seed=7704
    minimum=(. . . 10 0) maximum=(. . . 100 100);
    class TRTPN T2DM
    var TRTPN T2DM        Baseline Week_12;
    FCS reg(Week_12 = TRTPN T2DM        Baseline);

    run;
```

2. Analysis of imputed data sets: imputed data sets will then be analyzed separately using the same model for the primary endpoint analysis (ANCOVA model).
3. Combination of estimates across imputed datasets (using SAS PROC MIANALYZE): this will be performed using Rubin's rule and the overall treatment estimates vs placebo along with their 95% CI and p value will be provided.

3.4.1.2 Sensitivity Analyses for Primary Efficacy Endpoint

The same ANCOVA model with multiple imputation will be conducted on the ITTS excluding subjects whose study treatment period was extended due to COVID-19 pandemic circumstances.

The same ANCOVA analysis will be repeated on the PPS (of note, as patients with missing MRI assessments will be excluded from the PPS, no multiple imputation is necessary). A sensitivity analysis will be performed on the ITT whereby patients with missing Week 12/End of Treatment liver fat mass will have their Week 12/End of Treatment value imputed using the Baseline Carried Forward Method (i.e. assuming no change). A similar ANCOVA model to that described for the primary analysis will be used.

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An unstratified Wilcoxon based sensitivity analysis will also be performed and the Hodges-Lehmann estimate along its their 95% confidence intervals will also be provided. These analyses will be performed on the ITT and PP Sets without replacement of missing data.

3.4.1.3 Subgroup Analyses for Primary Efficacy Endpoint

The primary analysis for the relative change in liver fat mass will be performed for the ITT Analysis Set for the following subgroups:

- Within each T2DM status (T2DM patients vs non-T2DM patients).
  Corporate confidential information

A forest plot will be provided displaying the 3 estimates (PXL770 groups) vs placebo with their 95% CI by factor level (i.e. by TD2M status) along with the factor by treatment interaction test p-value for each factor.

3.4.1.3.1 Key Secondary Efficacy Analysis: Absolute Change in Liver Fat Mass Assessed by MRI-PDFF

The change from baseline to Week 12/End of Treatment in liver fat mass will be analyzed with the same approach proposed for the analysis of the primary endpoint (including sensitivity analyses).

3.4.1.3.2 Key Secondary Efficacy Analysis: Analysis of Responders

Four types of responders will be proposed and analyzed:

- Response defined as an absolute reduction in liver fat mass (from baseline (Randomization Visit [V3]) to Week 12 [V7]/End of Treatment) higher than or equal to 5% (≥ 5 %).
- Response defined as a relative reduction in liver fat mass (from baseline [Randomization Visit {V3}] to Week 12 [V7]/End of Treatment) higher than or equal to 30% (≥ 30 %).
- Response defined as a relative reduction in liver fat mass (from baseline [Randomization Visit {V3}] to Week 12 [V7]/End of Treatment) higher than or equal to 50% (≥ 50 %).
- Response defined as a liver fat mass value at Week 12 (V7)/End of Treatment that is normalized, i.e. lower than or equal to 5% (≤ 5 %).

The number and percentage of responders will be summarized by treatment group.

The response will be analyzed in a logistic regression model adjusting for treatment, stratification factors (T2DM status Corporate confidential information) and baseline liver fat mass using the ITT Analysis Set. Pairwise differences in treatment groups will be estimated in this model as odds ratios along with their 95% CIs and p-values. A multiple imputation procedure similar to that proposed for the analysis of the primary endpoint will be proposed to impute missing MRI-PDFF at Week 12/End of Treatment. Imputed values will be used to classify patients as responders or not. Of note, Missing baseline MRI-PDFF will be not replaced and patients without baseline MRI-PDFF will be not taken into account in the analysis.

A sensitivity analysis will be proposed considering patients with missing MRI-PDFF either at baseline or at Week 12/End of Treatment as non responders.

If needed, Firth's penalized likelihood approach will be used to address the quasi-complete separation in the logistic regression analysis.

3.4.2 Analyses of Other Efficacy Endpoints

All other secondary efficacy endpoints will be summarized and analyzed based on the ITT Analysis Set. Descriptive statistics of the baseline change from baseline and/or relative change from baseline to each post-baseline visit will be presented by treatment group for each secondary efficacy parameter.

3.4.2.1 Liver enzymes

The change (and relative change) from baseline in ALT and AST at Weeks 2, 4, 8 and 12/End of Treatment will be analyzed using a Mixed Model for Repeated Measures (MMRM) assuming MAR mechanism. Hence, no imputation of missing data will be performed. The factors in the model will be treatment group, stratification factors (T2DM status Corporate confidential information), baseline value, visit, treatment by visit and baseline by visit interactions. An unstructured covariance matrix will be used (TYPE=UN). The LSMs for change from baseline at each post-baseline visit will be estimated and compared between treatment groups. Sample SAS code is below.

```
/*************************************************************************
      USUBJID = Unique subject identifier
      T2DM = T2DM status (T2DM patients vs non-T2DM patients)
       Corporate confidential information
      CHG = observed change from baseline
      BASE = baseline value
      TRTPN = treatment identifier, e.g. 0 (Placebo), 1 (PXL770 250 mg QD),
              2 (PXL770 250 mg BID), 3 (PXL770 500 mg QD)
      AVISITN = analysis visit (weeks 2, 4, 8, and 12/End of Treatment)
*************************************************************************/
proc mixed;
    class USUBJID T2DM        TRTPN AVISITN;
    model CHG = T2DM        TRTPN BASE AVISITN TRTPN*AVISITN BASE*AVISITN /
          ddfm=KR;
    Repeated AVISITN / TYPE=UN sub=USUBJID;
    lsmeans AVISITN*TRTPN / cl pdiff slice=AVISITN;
    run;
```

3.4.2.2 Measured Metabolic Parameters

3.4.2.2.1 Lipid Parameters

The change (and relative change) from baseline in Total Cholesterol, HDL-c, LDL-C, Triglycerides, Apo A1, Apo B, FFA, Glycerol and Adiponectin at Weeks 4, 8 and 12/End of Treatment will be analyzed using the same MMRM model for the analysis of liver enzymes.

3.4.2.2.2 Other measured metabolic parameters

The change from baseline in FPG at Weeks 2, 4, 8 and 12/End of Treatment will be analyzed using the same MMRM model for the analysis of liver enzymes.

The change from baseline in HbA1c at Week 12/End of Treatment will be analyzed using an ANCOVA model. No imputation will be performed. The factors in the model will be treatment group, stratification factors (T2DM status Corporate confidential information and the baseline HbA1c value.

The change from baseline in serum insulin and C-peptide, at Weeks 4, 8 and 12/End of Treatment will be analyzed using the same MMRM model for the analysis of liver enzymes.

3.4.2.3 Calculated Metabolic Parameters

The change from baseline in HOMA-IR, QUICKI, HOMA-β and Adipo-IR assessed at Weeks 4 and 12/End of Treatment will be analyzed using a MMRM model similar to the analysis of liver enzymes.

3.4.2.4 hsCRP

The change from baseline in hsCRP at Weeks 2, 4, 8 and 12/End of Treatment will be analyzed the same MMRM model for the analysis of liver enzymes.

3.4.2.5 Other Inflammatory Biomarkers

The change from baseline in fibrinogen and MCP-1 at Week 12/End of Treatment will be analyzed using the ANCOVA model for the analysis of the change in HbA1c.

3.4.2.6 Fibrosis Biomarkers

The change from baseline in NFS and Fib-4 score at Week 12/End of Treatment will be analyzed using the ANCOVA model for the analysis of the change in HbA1c.

3.4.2.7 Body weight, waist circumference and waist-to-hip ratio

The change (and relative change) from baseline in body weight, waist circumference and waist-to-hip ratio at Weeks 2, 4, 8 and 12/End of Treatment will be analyzed using the same MMRM model for the analysis of liver enzymes.

3.5 Pharmacokinetic Assessment

For all patients in the Randomized Set, pre-dose pharmacokinetic (PK) samples will be taken at Weeks 2, 4, 8 and 12. Corporate confidential information
A PK sample will also be taken at Week 13.

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Plasma concentrations of PXL770 will be summarized by visit and time point for the PK Population; results will be displayed by treatment group. In addition to the standard summary statistics, geometric mean and CV will also be presented for the plasma concentrations.

3.6 Safety Assessment

The safety data for this study include Adverse Events (AEs), vital signs, ECGs, physical examinations and safety laboratory assessments. The safety data will be summarized based on the Safety Analysis Set and presented by treatment group. Missing values will not be imputed.

3.6.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

For analysis, a treatment emergent AE (TEAE) is defined as any AE that occurred for the first time after the first dose of double-blind study treatment or existed prior to the first dose and worsened after the first dose. AE worsening applies to severity, or relationship to study treatment. If part of the date/time for the onset/end of an AE is missing, but the existing parts allow determination of timing of AE onset relative to the first dose of double-blind study treatment, then the AE will be classified as treatment-emergent or not per review of the existing parts of the date/time. If timing of the AE onset/end relative to the first dose of double-blind study treatment is missing, then the AE will be assumed to be treatment-emergent.

A summary overview of all AEs will be provided, which presents the number and percentage of patients in each treatment group from the Safety Analysis Set, including number of events, satisfying each of the following categories:

- Any Adverse Event
- Any non-TEAE
- Any TEAE
- Maximum severity of TEAEs
- Study-medication related TEAEs
- Maximum severity of study-medication related TEAEs
- TEAEs of special interest – Drug Induced Liver Injury (DILI), sourced from the End of Study eCRF reason for withdrawal
- All serious AEs (SAEs)
- All serious TEAEs (TESAEs)
- All study treatment-related TESAEs
- TEAEs leading to death
- TEAEs leading to temporary interruption
- TEAEs leading to study treatment discontinuation

Adverse events will be coded using MedDRA v23.0 COVID-19 update. The number and percentage of patients with AEs, including the number of AEs, will be summarized by their MedDRA preferred term within system organ class and treatment group. For patient count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) from the same patients will only be counted once. Similar summaries will be presented for each of the categories above.

The number and percentage of patients with TEAEs will be summarized by reported maximum severity within each MedDRA preferred term within system organ class and by treatment group. Similar summaries will be provided for study-medication related TEAEs.

Detailed listings will be provided for all AEs; separate listings will be provided for non-TEAEs and TEAEs. Separate listings will also be provided for AEs of Special Interest, SAEs, AEs leading to study treatment discontinuation and AEs leading to death.

Note that if there is an occurrence of suspected DILI, sites are instructed to enter the AE (e.g. elevated ALT) and also fill out the DILI eCRF. Only if it is a confirmed DILI event will the reason for withdrawal be “occurrence of DILI”. In order to avoid the appearance of duplicate AEs, the information from the DILI eCRF will not be included in the TFLs.

3.6.2 Clinical Laboratory Tests

Biochemistry, hematology, coagulation and urinalysis will be collected at the Screening, Randomization, Weeks 2, 4, 8, 12 and 13 and at the Early Termination Visits.

Biochemistry parameters include: Albumin, Alkaline phosphatase (ALP), Amylase, Bicarbonate, Blood Urea Nitrogen, Calcium, Chloride, Creatine phosphokinase, Creatinine, eGFR (using CKD-EPI formula), Gamma-glutamyl transferase, Inorganic phosphate, Lipase, Potassium, Sodium, Total bilirubin, Total protein and Uric acid.

Hematology parameters include: Differential blood count (lymphocytes, monocytes, eosinophils, basophils, neutrophils – absolute values and percentages), Erythrocytes, Hemoglobin, Hematocrit, Leucocytes, Mean corpuscular volume, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Red Blood Cell Morphology, and Thrombocytes.

Coagulation parameters include: activated Partial Thromboplastin Time (aPTT), International Normalized Ratio (INR) and Prothrombin Time (PT).

Urinalysis parameters include: Blood, Glucose, Ketones, Leucocytes, Nitrites, pH, Protein, Specific gravity and Urobilinogen.

Descriptive statistics of each safety laboratory parameter will be presented for baseline values and for values and the change from baseline at each post-baseline visit.

Values outside the normal range (N) will be categorized as H (above the normal range) or L (below the normal range) based on the central laboratory's normal reference range. Shift tables will be presented for Alkaline Phosphatase, Creatine Phosphokinase, eGFR (using CKD-EPI formula), Gamma-Glutamyl Transferase (GGT) and Total Bilirubin. The shift tables will show the shift from baseline to the last on-treatment value and will present the number of patients per treatment group with N, H or L.

3.6.3 Vital Signs

Vital signs will be measured at the Screening, Run-in, Randomization, Weeks 2, 4, 8, 12 and 13 and at the Early Termination Visits. Vital signs parameters include systolic and diastolic blood pressure and heart rate. At each visit, three measurements for blood pressure will be taken, the average of the three measurements will be used in the analysis.

Descriptive statistics of each vital signs parameter will be presented for baseline values and for values and the change from baseline at each post-baseline visit. These will be presented by treatment group for each parameter using the Safety Analysis Set.

3.6.4 Electrocardiograms

ECGs will be performed at the Screening, Randomization, Weeks 2, 4, 8, 12, 13 and at the Early Termination Visits. A single ECG will be performed at the Screening Visit, and in triplicate at all other visits. The average of the triplicate measurements will be used in the analysis.

Descriptive statistics of each ECG parameter will be presented for baseline values and for values and the change from baseline at each post-baseline visit. Overall interpretation will also be summarized at each post-baseline visit. These will be presented by treatment group for each parameter using the Safety Analysis Set.

3.6.5 Physical Examinations

A complete physical examination will be carried out at the Screening, Randomization, Weeks 12 and 13 and at the Early Termination Visits. A limited physical examination will be carried out at the other study visits (i.e. Run-in, Weeks 2, 4 and 8).

A complete listing of the physical examination results will be provided.

4 ANALYSIS TIMING

4.1 Dry Runs/Blinded Data Reviews

Two dry run of all analysis tables, figures and listings (TFLs) will be provided:

- The first will occur approximately 3 months prior to database lock with the main aim for the Sponsor to review TFL layout, etc.
- The second will occur after soft lock, approximately 2 weeks prior to database lock for blinded data review.

Draft TFLs will include text in the titles or on the cover page of the compiled document to indicate that they are draft and use dummy treatment assignments (e.g., Table 14.1.1.1 - DRAFT/DUMMY TREATMENT ASSIGNMENTS APPLIED).

4.2 Blinded Data Review Meeting (BDRM)

Prior to database lock, a BDRM will be scheduled during which the blinded data will be reviewed, and decisions will be made as to whether patients will be included or excluded from the Per Protocol Analysis Set.

4.3 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Topline TFLs will be provided approximately 1 week after database lock and unblinding and pre-final TFLs will be provided approximately 3 weeks after database lock and unblinding.

4.4 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, Study Data Tabulation Model (SDTM) data and ADaM data along with associated files will be provided. Associated files may include: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

For calculation of study drug compliance, the Protocol states “In case of IMP temporary interruption requested by the Investigator (e.g. due to AE), the duration of the temporary interruption should be deducted from the theoretical number of capsules to be taken during the

period." This rule will not be applied; compliance will be calculated without regard to temporary interruptions requested by the Investigator. Temporary interruptions (documented for SAEs and in the free text fields of the study drug return pages) will only be considered for the review of the protocol deviations reported in case of compliance below 80%.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patients and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. Harrison, S.A., et al., *NGM282 for treatment of non-alcoholic steatohepatitis: a multicenter, randomized, double-blind, placebo-controlled, phase 2 trial.* Lancet, 2018. **391**(10126): P. 1174-1185.
2. Matsuda, M. and R.A. DeFronzo, *Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp.* Diabetes Care, 1999. **22**(9): p. 1462-70.