Statistical Analysis Plan

POXEL

PXL065-003

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Reviewers

The following reviews of the SAP were conducted:

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Glossary of Abbreviations

Abbreviation	Term
AASLD	American Association for the Study of Liver Diseases
Adipo-IR	Adipose tissue insulin resistance
AE	Adverse event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Anti-HCV	Hepatitis C virus antibody
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BDRM	Blinded data review meeting
BMI	Body Mass Index
CGM	Continuous glucose monitoring
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease
CRF	Case report form
CRN	Clinical Research Network
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced liver fibrosis
EoS	End-of-Study
EoT	End-of-Treatment
ET	Early termination
FCS	Fully conditional specification
FDA	Food and Drug Administration
FFA	Free fatty acids
FIB4	Fibrosis 4
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase (GGT)
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B antigen
HDL-C	High-density lipoprotein cholesterol
HIV	Anti-human immunodeficiency virus
HOMA-IR	Homeostasis model assessment of insulin resistance
HOMA-β	Homeostasis model assessment of β-cell function
HR	Heart Rate
hsCRP	High-sensitivity C-reactive protein

ICF	Informed consent form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional review board
ITTS	Intent-to-treat set
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LFC	Liver Fat Content
LKAD	Last known assessment date
LLOQ	Lower limit of quantification
LSMs	Least Square Means
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
MRI-PDFF	Magnetic Resonance Imaging – Proton Density Fat Fraction
NAFLD	Non Alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
OAT	Organic Anion Transporter
OR	Odds ratio
PD	Protocol deviation
PDLC	Predefined Limits of Change
PK	Pharmacokinetic(s)
PPS	Per-protocol Set
pro-C3	N-terminal type III collagen propeptide
PT	Preferred term
QA	Quality Assurance
QD	*Quaque die*
QTcF	Fridericia corrected QT interval
QUICKI	Quantitative insulin sensitivity check index
RNA	Ribonucleic acid
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard Deviation
SEM	Standard error of the mean
SI	International system of units
SMBG	Self-Monitoring Blood Glucose
SOC	System Organ Class
SS	Safety Set
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, Figures and Listings
TSH	Thyroid-stimulating hormone
TZD	Thiazolidinedione
ULN	Upper Limit of Normal

ULOQ	Upper limit of quantification
WHO	World Health Organization
β-HCG	Serum B Human Chorionic Gonadotropin

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	17th December 2020	5.0
eCRF	24th Jan 2022	5.01
COVID-19 Memo	19th August 2020	1.0
Note to file – Handling for patients at site 065-S:	29th April 2022	1.0

2. Protocol Details

2.1 Study Objectives

Primary Objective

- To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on liver fat content (LFC) in nonalcoholic steatohepatitis (NASH) patients after 36 weeks of treatment.

Secondary Objectives

- To assess the safety and tolerability of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo in NASH patients after 36 weeks of treatment
- To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on metabolic and non-metabolic parameters in NASH patients after 36 weeks of treatment
- To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on histological changes in liver biopsy in NASH patients after 36 weeks of treatment
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- To describe PXL065 pre-dose plasma concentrations during the course of the treatment and the pre- and post-dose concentrations in NASH patients after 36 weeks of treatment

2.2 Overall Study Design Per Protocol

This study is a Phase 2, multi-center, double-blind, placebo-controlled, randomized study with 4 parallel groups in noncirrhotic, biopsy-proven NASH patients.

There will be a total of 3 study periods, as follows:

- Screening Period: maximum of 8 weeks

The screening period can be exceptionally extended after approval of the medical monitor and the POXEL medical representative, if there is no more than 10 weeks between MRI-PDFF and Randomization Visit (V1). Screen failure patients may be eligible for re-screening once approval is provided by the medical monitor and Poxel representative. Patients may only be re-screened once.

- Double-blind treatment period: 36 weeks
- Follow-up period: 2 weeks

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

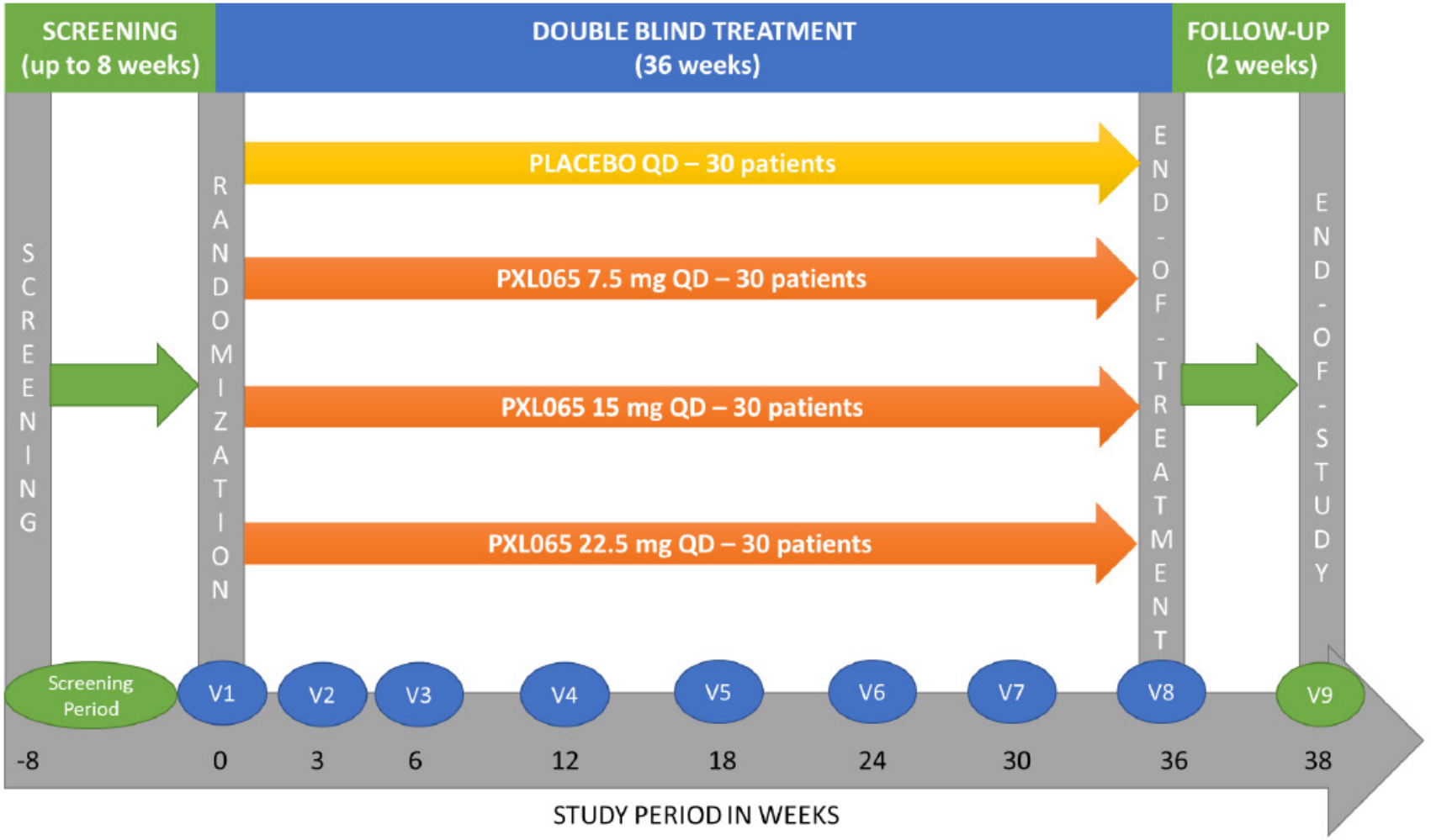
- PXL065 7.5 mg oral QD
- PXL065 15 mg oral QD
- PXL065 22.5 mg oral QD
- Placebo oral QD

Randomization will be stratified according to type 2 diabetes mellitus (T2DM) status (T2DM patients versus non-T2DM patients) and the NASH Clinical Research Network (CRN) fibrosis score (F1 versus F2/F3).

The diagram of the study design is shown in **Figure 1** and the visit schedule is displayed in Appendix A.

The duration of study for each patient from the first visit for the informed consent signature up to the end of the Follow-up period will be between 40-46 weeks. The end-of-study (EoS) is defined as the date of last visit of the last patient participating in the study.

Figure 1 Diagram of Study Design



2.3 Sample Size and Power

The sample size determination is based on the primary endpoint, i.e. the relative change in LFC (assessed by magnetic resonance imaging – proton density fat fraction [MRI-PDFF] from baseline to Week 36 (V8-End of Treatment [EoT]) ([LFC_{W36} – $LFC_{baseline}$] / $LFC_{baseline}$) and the primary objective, i.e. to demonstrate the superiority of at least one PXL065 dose to placebo as tested by the following null hypothesis (H_0) versus the alternative hypothesis (H_a):

$$H_0: \mu_{PXL065} - \mu_{placebo} = 0 \text{ versus } H_a: \mu_{PXL065} - \mu_{placebo} < 0$$

Where $\mu_{placebo}$ and μ_{PXL065} denote the mean relative change in the percentage of LFC from baseline to Week 36 in the PXL065 and placebo groups respectively.

The following assumptions will be considered for the sample size determination:

- No adjustment for multiple comparisons between PXL065 doses and placebo will considered and the usual nominal 1-sided alpha level of 0.025 (or equivalently the 2-sided level of 0.05) will be considered for each PXL065 dose vs placebo comparison
- A power of 90%
- An expected difference $\mu_{PXL065} - \mu_{placebo}$ of -30% for at least one PXL065 dose vs placebo comparison
- A standard deviation (SD) of the primary endpoint equal to 30%, as estimated from previous published data
- With these assumptions, a sample size of 23 patients per arm is needed to achieve 90% power for at least one PXL065 dose vs placebo comparison.

Assuming a dropout rate of 20%, around 30 patients per arm (120 = 4 x 30 patients in total) are needed to be randomized.

2.4 COVID-19

The COVID-19 memo provided alternative processes relative to those described in the protocol that may be used to conduct the study if needed to ensure subject safety and/or minimize impact on study integrity during the COVID-19 pandemic. For example, the screening window according to the memo can be extended from 8 weeks to 12 weeks. The visit window for Visit 2 and 3 can also be extended from +/- 4 days to 6 days. In addition, laboratory assessments can also be done locally if they cannot be collected for central laboratory testing and visits can be done virtually by phone or telehealth calls. However, if there are two consecutive virtual visits then the next one needs to be on-site.

Additional data related to COVID-19 will now also be collected for example, patients discontinuing due to COVID, patients failing screening due to COVID, patients missing visits due to COVID, interruption of study treatment due to COVID and missed visits due to COVID. This data will be presented in tables and listings.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

- Relative change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT)

3.2 Secondary Efficacy Endpoints

- Absolute change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT)
- Response defined as an absolute reduction in LFC ≥ 5% from baseline to Week 36
  (V8-EoT)
- Response defined as a relative reduction in LFC ≥ 30% from baseline to Week 36 (V8-EoT)
- Response defined as a relative reduction in LFC ≥ 50% from baseline to Week 36 (V8-EoT)
- Response defined as a LFC value at Week 36 (V8-EoT) that is normalized, i.e. ≤5%
- Change in the following parameters from baseline to Week 36 (V8-EoT):
  - Liver enzymes: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)
  - Percentage of responders as defined by the percentage of patient with normalization of liver enzymes in the subset of patients with increased baseline value
  - Measured glycemic parameters: Fasting plasma glucose (FPG), Glycated hemoglobin (HbA1c), serum insulin, C-peptide
  - Insulin resistance indexes: Homeostasis model assessment of insulin resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), Homeostasis model assessment of β-cell function (HOMA-β) and Adipose tissue insulin resistance (Adipo-IR)

Exploratory endpoints

Change from baseline in the following parameters at Week 36 (V8-EoT):

- Adiponectin
- Lipids: total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, free fatty acids (FFA)
- Biomarker of inflammation: High-sensitivity C-reactive protein (hsCRP)
- Biomarkers of fibrosis: N-terminal type III collagen propeptide (pro-C3), NAFLD Fibrosis score (NFS) and Fibrosis 4 (FIB-4) score and Enhanced Liver Fibrosis (ELF) score
- Histological change in liver biopsy:
  - Change in NAFLD Activity Score (NAS), in each component of NAS (steatosis, ballooning and inflammation) and in NASH CRN fibrosis score
  - Improvement in each component of NAS (steatosis, lobular inflammation and hepatocellular ballooning) by ≥ 1 point without worsening of fibrosis
  - Improvement in NAS by ≥ 2 points without worsening of fibrosis
  - Improvement in NASH CRN fibrosis score by ≥ 1 point

- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis)
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with improvement in NASH CRN fibrosis score by ≥ 1 point
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with no worsening in NASH CRN fibrosis score
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and improvement in NAS by ≥ 2 points with no worsening in NASH CRN fibrosis score

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3.3 Safety Variables

Safety and tolerability will be assessed on the following parameters:

- Adverse events (AEs)
- Physical examination
- Weight, waist and hip circumferences, and BMI
- Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR)
- Pitting edema assessment
- 12-lead electrocardiogram (ECG)
- Bone mineral density in postmenopausal women
- Biological parameters: biochemistry, hematology, coagulation
- Estimated Glomerular Filtration Rate (eGFR) (Chronic Kidney Disease – Epidemiology Collaboration [CKD-EPI] formula)
- Urinalysis

4. Pharmacokinetic Variables

Pharmacokinetics (PK) analysis will be done separately and consequently not reported in this SAP.

5. Analysis Populations

The analysis populations have been adapted due to data integrity being compromised at site 065-S.

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As a consequence, patients from site 065-S are excluded from principal analysis. Primary and some secondary endpoints will be analyzed including patients from site 065-S in a sensitivity analysis. Details of tables which will include site 065-S will be described in each dedicated part. In addition, site 065-S patients that did not complete the study will have treatment exposure end date coded as 23rd December 2021, corresponding with the site early termination date. This change will impact some derivations e.g., treatment-emergent AEs, duration of exposure, etc. Details of the quality issue and data handling at site 065-S are available in the note to file.

5.1 Screened Set

All patients except patients from site 065-S , who were screened for inclusion into the study will be included in the screened set. Patients who are rescreened will be considered once utilizing their most recent subject identifier.

5.2 Screened Set with Site 065-S

All patients who were screened for inclusion into the study will be included in the screened set with site 065-S . Patients who are rescreened will be considered once utilizing their most recent subject identifier.

5.3 Randomized Set (RS)

All patients except patients from site 065-S , considered as-randomized regardless of the treatment actually received.

5.4 Randomized Set with Site 065-S (RS-w-065-S)

All patients including patients from site 065-S , considered as-randomized regardless of the treatment actually received.

5.5 Safety Set (SS)

All randomized patients except patients from site 065-S , having received at least one dose of the IMP (either PXL065 or placebo) and considered as-treated will be included in the Safety set. The Safety set will be considered as the primary set for safety and tolerability analyses. Safety patients are analyzed according to their actual treatment received.

5.6 Safety Set with Site 065-S (SS-w-065-S)

All randomized patients including patients from site 065-S having received at least one dose of the IMP (either PXL065 or placebo) and considered as-treated will be included in the Safety set with site 065-S . The Safety set with site 065-S will be considered as the secondary set for some safety and tolerability analyses. Safety patients are analyzed according to their actual treatment received.

5.7 Intent-to-treat Set (ITTS)

The ITTS consists of all as-randomized patients excluding patients from site 065-S , having received at least one dose of the IMP (either PXL065 or placebo). Patients will be assigned to the treatment group as-randomized regardless of the treatment actually received. The ITTS will be considered as the primary set for efficacy analyses.

5.8 Intent-to-treat Set with Site 065-S (ITTS-w-065-S)

The ITTS-w-065-S consists of all as-randomized patients including patients from site 065-S , having received at least one dose of the IMP (either PXL065 or placebo). Patients will be assigned to the treatment group as-randomized regardless of the treatment actually received. The ITTS-w-065-S will be considered for the sensitivity analyses of the primary and secondary efficacy endpoints.

5.9 Per-Protocol Set (PPS)

The PPS consists of all ITTS-w-065-S patients without any important deviation of study procedures some of which include but are not limited to the following:

- Inclusion/Exclusion criteria likely to affect the primary efficacy endpoint satisfied
- Absence of relevant protocol violations with respect to factors likely to affect the primary efficacy endpoint where the nature of protocol violation will be defined before breaking the blind
- Adequate study medication compliance (80-120%) for the overall treatment period where patient has passed Week 12.
- Adequate measurement of the primary variable

The above criteria for the PPS are described in further detail in Section 5.10. Important protocol deviations (PDs) will be identified prior to breaking the blind. All important protocol deviations will be assessed for exclusion from the PPS during the blinded data review meeting (BDRM).

Patients in the PPS will be analyzed based on treatment actually received and actual strata rather than randomized.

5.10 Important Protocol Deviations Leading to Exclusion from the PP Analysis

All important and non-important protocol deviations are defined in a separate documentation where each PD's detection methods are indicated by monitoring or programming.

Only those important protocol deviations considered to have a major effect on the primary efficacy endpoint will lead to complete exclusion of the patient from the PPS.

The following criteria have been identified as important protocol deviations leading to exclusion from the PPS as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

Note: Emergency unblinding may lead to a patient being removed from PPS even if it is not included as a PD.

5.10.1 Failure of Inclusion/Exclusion Criteria

Non-compliance with Inclusion / Exclusion criteria leading to exclusion from PPS will be described in the BDRM minutes.

Per protocol, if a patient who does not meet the inclusion/exclusion criteria mistakenly enters the double-blind treatment period, a discussion should occur between the POXEL Medical Representative, the Medical Monitor and the Investigator regarding whether to continue or discontinue the IMP, based on patient's safety and study's consideration. In situations where an agreement cannot be reached, the patient should be withdrawn from the study. In such case, patients will be considered as withdrawn from the study due to protocol deviation (GCP non-compliance) and may be excluded from PPS.

5.10.2 Prohibited Medications

Prohibited medications leading to exclusion from PPS will be described in the BDRM minutes. Per protocol, patients must not take any of the following licensed medications from the Randomization Visit (V1) up to Week 38 (V9-EoS):

- Any medication containing pioglitazone (e.g. Actos®, Actoplus Met®, Duetact®, Oseni®) or other approved or experimental TZD (e.g. rosiglitazone (Avandia®), leriglitazone (MIN-102), MSDC-0602K), or PPARγ agonists
- Any other antidiabetic drug except those permitted in the inclusion criterion #5 (Protocol Section 5.1 Inclusion critera: Metformin, sitagliptin, alogliptin, empagliflozin, canagliflozin, and dapagliflozin)
- Topiramate
- Amiodarone
- Bile salt chelators
- Methotrexate
- Chronic corticosteroids (> 2 consecutive weeks) with a systemic effect (e.g. oral or intravenous administrations) at doses ≥10 mg/day of oral prednisone (or equivalent)
- Equal or more than 800 U of vitamin E per day
- Orlistat
- Obeticholic acid
- Any other medications (including vitamins, herbal and dietary supplements) known to affect liver function/steatosis at the Investigator's discretion

5.10.3 Accidental or Emergency Unblinding During Treatment Period

If the treatment code for a patient is inadvertently revealed to one or more site staff or project team members who should have remained blind until database lock, this will lead to patient exclusion from the PPS.

If it becomes necessary for the investigator to unblind a specific patient in an emergency because of a safety concern, this will exclude the patient from the PPS.

5.10.4 Errors in Treatment Allocation During Treatment Period

Some patients may have received the wrong IMP treatment at one or more study visits due to randomization, packaging or dispensing errors.

If the wrong treatment was received at all or most visits, then the patient should be assigned to the actual or predominant treatment received in the PPS analysis at all visits (in contrast to the randomized treatment for the ITTS-w-065-S /ITTS analysis).

If the wrong treatment was received at a single visit, then the patient should be assigned to the randomized treatment in the PPS analysis at all visits, possibly with exclusion of the patient from the PPS if this is considered of sufficient concern for key efficacy conclusions.

Impact of incorrect IMP administration on efficacy analysis will be discussed and decided prior to database lock and unblinding at the BDRM.

5.10.5 Adequate Study Medication Compliance

The acceptable overall compliance will be within 80% - 120% (≥80% - ≤120%). If at any visit the compliance does not fall within this range, it must be reported as a protocol deviation (if it occurs anytime during treatment period), however, this may not necessary mean that the patient will be excluded from the PPS and will be reviewed by the study team at the BDRM.

5.10.6 Assessment of Important Protocol Deviations

Important protocol deviations which require clinical or medical monitoring interpretation will be reviewed periodically during the protocol deviations review by the team.

All-important protocol deviations leading to exclusion from the PPS occurring during the study will be reviewed and approved by Poxel prior to unblinding during the BDRM.

Should additional important protocol deviations leading to exclusion from the PPS, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding) they will be documented in a SAP amendment/updated Important Protocol Deviations Designation and Escalation document and included in all relevant protocol deviation reviews and approvals.

6. DATA Handling

6.1 Time Points and Visit Windows

Day 1 is defined as the day of randomization. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

To maximize the data available for analysis, where possible, results from ET and Unscheduled Visits will be allocated to scheduled visit according to the following rules and visit windows described in Table 2.

- 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.
- If more than one ET/Unscheduled Visit is allocated to the same scheduled visit (and no valid value from the scheduled visit is available) then the closest visit value will be used in the analysis for the scheduled visit.

Visit Windowing rules are defined according to parameters groups in **Table 1Table 1 - Visit window groups** and the windows in **Table 2**.

Double-blind treatment period is defined as the period between the randomization visit (V1) and the EoT visit (V8). Follow-up period is defined as the period between the EoT visit (V8) and the EoS visit (V9).

Table 1 - Visit window groups

Visit window group	Visits	Parameters
Group 1	All visits	Pitting edema assessment, vital signs and body measurements, physical examination
Group 2	Screening, V1, V4, V6, V8	HbA1c
Group 3	Screening, V1, V4, V6, V8, V9	Safety lab, FPG
Group 4	Screening, V1, V5, V8, V9	ECG
Group 5	Screening, V8	DXA, MRI-PDFF, Liver biopsy
Group 6	Screening, V1, V8	eGFR
Group 7	Screening, V1, V5, V9	Pregnancy test
Group 8	V1, V4, V6, V8	Measured metabolic parameters, insulin resistance indexes
Group 9	V1, V8	Fibrosis biomarkers, biobanking sampling

Table 2 - Visit windows

Visits	Study day [a]	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	Group 9
Screening	N/A	-∞ to -1	-∞ to -1	-∞ to -1	-∞ to -1	-∞ to -1	-∞ to -1	-∞ to -1		
Randomization	1	1 to 12	1 to 43	1 to 43	1 to 64		1 to 127	1 to 64	1 to 43	1 to 127
Week 3	22	13 to 33								
Week 6	43	34 to 64								
Week 12	85	65 to 106	44 to 127	44 to 127					44 to 127	
Week 18	127	107 to 148			65 to 190			65 to 197		
Week 24	169	149 to 190	128 to 211	128 to 211					128 to 211	
Week 30	211	191 to 232								
Week 36	253	233 to 260	212 to ∞	212 to 260	191 to 260	79 to ∞	128 to ∞		212 to ∞	128 to ∞
Week 38	267	261 to ∞		261 to ∞	261 to ∞			198 to ∞		

[a] Relative to the date of randomization (Day 1)

6.2 Handling of Dropouts

A patient who discontinues study participation prematurely for any reason after randomization is defined as a "dropout". Patients who drop out will not be replaced.

A patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" in this study is regarded a screen failure.

In all cases, the reason for withdrawal must be entered in the eCRF and in the patient's medical records.

6.3 Handling of Patients from Site 065-S

Patients included at site 065-S will be presented in all listings and in specific tables of interest.

6.4 Handling of Rescreened Patients

Patients who are rescreened will be presented once in summary tables utilizing the most recent subject identifier. Both new and old subject identifier will be presented in listings.

6.5 Handling of Missing Data

In order to achieve the goal of a well conducted clinical trial according to International Council on Harmonization Good Clinical Practice, every effort should be made to collect all data (i.e., if a patient misses a scheduled assessment, the site personnel should contact the patient and request him/her to come to the clinic for the visit). However, despite best efforts, it may be inevitable that missing or incomplete data are reported. All missing or partial data will be presented in the patient data listings, as they were recorded on the eCRF.

6.5.1 Safety Variables

Incomplete adverse event start or stop dates and concomitant medication start or stop dates will be imputed to determine treatment-emergent AE and concomitant medication as described in **Table 3**. Missing or partial dates will be presented in the patient data listings as they were recorded on the CRFs.

Table 3 - Imputation Rules for Incomplete Dates for AE and Concomitant Medication

	Missing	Scenario	Imputation
Start date (AE, concomitant medication)	Day	Event month&year < month&year of first dose	last day of the month
		Event month&year = month&year of first dose	first dose date
		Event month&year > month&year of first dose	first day of the month
	Day / Month	Event year < year of first dose	December 31
		Event year = year of first dose	first dose date
		Event year > year of first dose	January 01
	Complete missing		AE: first dose date Conmed: no imputation
Stop date (AE, concomitant medication)	Day	Event month&year < month&year of last known assessment date (LKAD)	last day of the month
		Event month&year = month&year of LKAD	date of LKAD
		Event month&year > month&year of LKAD	no imputation
	Day / Month	Event year < year of LKAD	December 31
		Event year = year of LKAD	date of LKAD
		Event year > year of LKAD	no imputation
	Complete missing		date of LKAD

Note: If first dose date is missing, use randomization date for the imputation.
If the imputed start date is after the stop date, the start date will be imputed to equal the stop date.
If the imputed stop date is before the start date, the stop date will be imputed to equal the start date.

6.5.2 Laboratory Values

For laboratory values below the lower limit of quantification (LLOQ) like "<xxx" or "≤xxx", or above the upper limit of quantification (ULOQ) like ">xxx" or "≥xxx", LLOQ or ULOQ (xxx) will be used for calculation of descriptive statistics. The original laboratory values ("<xxx", "≤xxx", ">xxx" or "≥xxx") are presented in the listing.

6.5.3 Type 2 Diabetes Diagnosis

Partial dates for diagnosis of type 2 diabetes will be handled in the following way,

- Missing day only: Impute using the last day of the month
- Missing day and month: Impute using the last day of the year

If the imputed date goes beyond the informed consent date, then impute to the date of informed consent.

7. Statistical Methods

7.1 General Principles

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

The following principles will be applied to all tables, figures and listings (TFLs) unless otherwise stated:

Principle	Value
Significant tests	Two-sided and use a 5% significance level for main effect
Treatment group labels and order presented	PXL065 7.5mg QD PXL065 15 mg QD PXL065 22.5mg QD Placebo
Visit labels presented	Tables and Figures: Week XX Listings: Screening Randomization (V1) Week 3 (V2) Week 6 (V3) … Week 36 (V8-EoT) End of Study (V9-EoS) Early termination Unscheduled
Tables	Data in summary tables presented by treatment group, assessment (where applicable) and analysis visit (where applicable).
Listings	All data collected presented by treatment group, patient, nominal visit, Date unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of patients/observations (N) Mean SD standard error of the mean (SEM), median interquartile range (25^{th} percentile, 75^{th} percentile) (Q1, Q3) minimum and maximum
Descriptive summary statistics for categorical variables	Frequency counts and percentages: n (%)
Denominator for percentages	Number of patients in the analysis population, unless stated otherwise in table shell(s).
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one treatment group.

Principle	Value
Display for 0 percentages	Leave blank
Display to one more decimal place than collected value	Mean SEM Mean Difference Median Interquartile range (Q1, Q3)
Display to 2 more decimal places than collected value	SD Confidence Intervals (CI)
Limit of precision for displays	3 decimal places
Date Format for the presentation in the listings	DDMMMYYYY

The baseline value is defined as last scheduled or unscheduled value collected prior to the first dose of IMP treatment, scheduled on Randomization Visit (V1). Assessments carried out on day of first treatment administration are considered to have taken place before the IMP administration, if the corresponding times have not been recorded.

7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized (for screened set and screened set with site 065-S) by treatment group and overall and will include the number and percentage of patients:

- Screened;
  - Discontinued during screening period;
    - Discontinued during screening period due to COVID-19
- Randomized into double-blind period
  - Randomized but did not receive a dose of IMP
  - Randomized and received at least one dose of IMP;
    - Randomized but discontinued IMP/Study;
      - Patients whose primary reason for withdrawal was due to COVID-19 pandemic circumstances;
      - Patients who had study treatment temporarily interrupted due to COVID-19 pandemic circumstances
      - Randomized but not completed due to Site Early Termination;
    - Completed double-blind period
      - Patients who had study treatment temporarily interrupted due to COVID-19 pandemic circumstances
- Entered into follow-up period

- Discontinued during follow-up period;
  - Patients whose primary reason for withdrawal was due to COVID-19
- Completed follow-up period

In addition, the number and percentage of patients who discontinue early, including a breakdown of the primary reasons for discontinuation from study, will be presented.

A summary of the reasons for screen failure will be produced.

A summary table of randomized patients by site and treatment group will be provided for the randomized set.

A summary table of patients included in each study population (RS, Safety, ITT, PPS) will be produced for the Randomized set and Randomized set with site 065-S . A listing of patients included from each population will be produced, for the Randomized set with site 065-S .

In addition, a summary table and listing will be produced for discrepancies between the stratification factors in the database and Interactive Web Response System (IWRS).

A listing of IMP kit numbers and assignments will be produced for the Randomized set with site 065-S .

7.3 Protocol Deviations

All protocol deviations (important and non-important) will be listed by treatment group for the Randomized set with site 065-S .

All-important protocol deviations leading to exclusion from the PPS (see Section 5.10) will be listed for the ITTS-w-065-S and summarized by treatment group for the ITTS.

The protocol deviations will be identified before data are unblinded near database lock.

7.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed for the ITTS-w-065-S and summarized by treatment group and overall for the ITTS. Standard descriptive statistics will be presented for:

- Sex;
- Race (American Indian or Alaska Native, Asian, African American, Native Hawaiian or Other Pacific Islander, White, Other);
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, not stated, unknown);
- Age (years) at screening (derived on eCRF);
- Age group (years) at screening (<65 years, ≥ 65 years) ;
- Height (cm) at screening visit;
- Weight (kg) at baseline;
- Body mass index (BMI) (kg/m^2) (derived on eCRF) at baseline;
- BMI (<median, ≥ median) at baseline;

- Child-bearing potential (yes, no, not applicable);
- Randomization strata of T2DM status (T2DM patients, non-T2DM patients);
- Randomization strata of NASH CRN fibrosis scoring system (F1, F2/F3);
- Baseline LFC (%) (<median, ≥ median);
- Baseline LFC (%);
- Baseline ALT (U/L);
- Baseline HbA1c (%);
- Baseline FPG (mmol/L);
- Previously diagnosed with type 2 diabetes mellitus (Yes, No);
- Diabetes duration (Years);
- Patient currently treated for diabetes (Yes, No);
- Alcohol status (Never, former, current);
- If former or current, alcohol units consumed per week;
- Habitual cigarette smoking status (Never, former, current);
- If former or current, number of cigarettes per day;
- Other habitual tobacco or nicotine use (Never, former, current);
- Any history of drug abuse (Yes, No);
- Site pooling (Investigators speciality [Hepatologist, Others]);

The demographic and baseline characteristics table will be repeated in 4 additional populations in the ITTS: Diabetic patients, non-diabetic patients, F1 patients and F2/F3 patients. All of these populations will be based on the randomization strata. The derivation of the medians for BMI and LFC will be based on the subset populations.

For randomization strata, the stratification factors as used in the IWRS randomization will be summarized.

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

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

Demographic and baseline characteristics table will also be repeated in ITTS-w-065-S

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.0].

All medical history will be listed for Safety set with site 065-S , and the number and percentage of patients with any medical history will be summarized for Safety set by system organ class (SOC) and preferred term (PT) for each treatment group sorting by descending overall frequency of SOC, and within SOC by descending incidence of PT.

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with IMP treatment will be coded by using the World Health Organization (WHO) Drug Dictionary [Version WHODrug Mar 2020], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are defined as medications taken within 28 days prior to informed consent form (ICF) signature and stopped before or on ICF signature date.

Concomitant medications are medications that are ongoing before and continue after the ICF signature

New medications are medications that are prescribed during the study (Starting after ICF signature).

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

Prior, concomitant and new medications will be listed for the Safety set with site 065-S and summarized separately for the Safety set, with summary tables displayed by treatment group.

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 indication, WHO ATC-Level 1, WHO ATC-Level 3, therapeutic class, and PT. The number and percentage of patients using medication for each different indication will also be displayed.

7.5 Measurements of IMP Treatment Compliance

7.5.1 Compliance

Overall compliance based on IMP accountability will be presented for the double-blind treatment period by treatment group.

Compliance will be calculated using the following formula based on accountability records on the eCRF:

$$\frac{\text{Number of tablets taken} \times 100}{\text{Theoretical number of tablets to be taken during the period (based on visit days)}}$$

Compliance as recorded in the eCRF will also be presented for each visit:

- Randomization Visit (V1) to V3, V3 to V4, V4 to V5, V5 to V6, V6 to V7 and V7 to V8

Percentage compliance will be listed for the Safety set with site 065-S and summarized descriptively by treatment group for the ITTS and Safety set.

The following percentage compliance categories will also be presented:

- <80.0%
- ≥80.0% and ≤120.0%
- >120.0%

7.5.2 Overdose

This study will be blinded during the treatment period. Since the daily dose received will be unknown up to the end of the study, an overdose can only be identified relying on the number of tablets administered over a defined period of time.

An overdose is defined as any dose greater than the daily dose prescribed, equivalent to the intake of 3 or more tablets per day, in any of the treatment groups.

Overdose events will be listed for the Safety set with site 065-S .

Cases of overdose may constitute AEs or serious adverse events (SAEs) and will also be presented in the relevant AE/SAE summaries and listings, see Adverse Events (section 7.7.2) below.

7.6 Efficacy

7.6.1 Primary Endpoint

7.6.1.1 Primary Analysis

The primary evaluation of efficacy will be based on MRI-PDFF. The primary endpoint will be the relative change in the percentage of LFC from baseline to Week 36 (V8-EoT) in the ITTS.

For patients who withdraw from the study at or after Week 12 (V4), the LFC will be assessed at ET as far as possible. With the assumption that the LFC assessed at or after Week 12 (V4) reflects what could have been observed at Week 36 (V8-EoT), the missing LFCs at Week 36 (V8-EoT) will be estimated by this value. For patients who withdraw before Week 12 (V4) or withdraw without any LFC assessment at or after Week 12 (V4), LFC missing values at Week 36 (V8-EoT) will be imputed using a multivariate imputation approach by fully conditional specification (FCS) regression method assuming missing at random (MAR) mechanism. The set of variables included in the multiple imputation model will be randomized treatment, type 2 diabetes mellitus status (T2DM patients versus non-T2DM patients), NASH CRN fibrosis scoring system (F1 versus F2/F3), and baseline LFC. The number of imputed datasets generated will be 1000 with the burn-out iterations set at 100. A minimum value of 0 and a maximum value of 50 will also be applied to restrict imputed LFC values, see

Appendix B: Sample SAS® code for analyses of efficacy endpoints for example SAS code.

Each of the complete datasets after imputation will then be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment and for randomization stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline LFC as a continuous covariate in the ITTS. Results from each complete dataset will be combined using Rubin's rule to provide the least square means (LSMs) for treatment groups at Week 36, standard error of the LSM, pairwise differences (PXL065 7.5 mg QD, 15 mg QD and 22.5 mg QD versus placebo) in LSMs, p-values and 95% CIs, see

Appendix B: Sample SAS® code for analyses of efficacy endpoints for example SAS code.

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

In addition, descriptive statistics on the non-imputed LFC and percentage changes from baseline will be calculated by visit within each treatment group.

A listing of LFC data will be produced for the ITT set with site 065-S .

7.6.1.2 Sensitivity Analysis for the Primary Analysis

The imputation method described in the primary analysis will be repeated and each of the complete datasets after imputation will then be analyzed with non-parametric pairwise Wilcoxon tests stratified according to T2DM status and NASH CRN fibrosis scoring system. Hodges-Lehmann midpoint estimates along with their 95% confidence intervals will also be provided for the ITTS for each imputed data set and then combined using Rubin's rule, see Appendix C for example SAS code.

7.6.1.3 Other Analyses for the Primary Endpoint

The same statistical analyses described in Sections 7.6.1.1 and 7.6.1.2 will be repeated for the ITTS-w-065-S .

Additionally, analyses described in Sections 7.6.1.1 and 7.6.1.2 will be repeated without the multivariate imputation on missing Week 36 data for the ITTS and the PPS.

7.6.1.4 Subgroup Analysis

Subgroup analyses will be performed for the primary endpoint for the following subgroups:

- Baseline age group (<65 years, ≥ 65 years) ;
- Baseline BMI (<median, ≥ median);
- Sex (female and male);
- Randomization strata of T2DM status (T2DM patients, non-T2DM patients);
- Randomization strata of NASH CRN fibrosis scoring system (F1, F2/F3);
- Baseline LFC (<median, ≥ median);
- Site pooling. (Investigators specialty [Hepatology, Other]);

For each subgroup, the LSM differences and the 90% CI will be presented. The subgroup by treatment interaction will be tested at the nominal alpha level of 0.1. The subgroup analysis will be performed on the ITTS.

7.6.2 Secondary Endpoints

7.6.2.1 Absolute Change in LFC

The absolute change in LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT) will be analyzed in ANCOVA model adjusting for treatment, T2DM status (T2DM patients versus non-T2DM patients), and NASH CRN fibrosis scoring system (F1 versus F2/F3) and for baseline LFC as a continuous covariate. The method applied to missing data for the primary endpoint in Section 7.6.1.1 will also be utilized for this secondary endpoint. LSMs for treatment groups, standard error of the LSM, pairwise differences (PXL065 7.5 mg QD, 15 mg QD and 22.5 mg QD versus placebo) in LSMs, p-values and 95% CIs will

be presented. In addition, descriptive statistics for LFC and change from baseline will be calculated by visit within each treatment group.

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

The analysis described in Section 7.6.1.2 and 7.6.1.3, except for the ITTS-w-065-S will also be done for this secondary endpoint.

7.6.2.2 Analysis of Responders

The 4 types of responders that will be analyzed are:

- Absolute reduction in LFC ≥ 5% from baseline to Week 36 (V8-EoT)
- Relative reduction in LFC ≥ 30% from baseline to Week 36 (V8-EoT)
- Relative reduction in LFC ≥ 50% from baseline to Week 36 (V8-EoT)
- LFC value at Week 36 (V8-EoT) that is normalized, i.e. ≤5%

For each response, responder rate will be provided within each treatment group. The stratified Cochran-Mantel-Haenszel (CMH) will primarily be used to analyze the responders, stratifying for T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3). Each PXL065 treatment group will be compared with placebo. The odds ratios (ORs), 95% CIs for the ORs, and p-values will be displayed for the ITTS. In addition, the number of responder's and non-responders will be displayed for each treatment group, see

Appendix B: Sample SAS® code for analyses of efficacy endpoints for example SAS code.

The binary response will also be analyzed using a logistic regression model adjusting for treatment, stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline LFC as a continuous covariate. Pairwise differences for each PXL065 treatment group vs placebo will be estimated in the model as ORs along with their p-values and 95% CI. The binary response will also be analyzed using the approach proposed by Ge et al. (2011), see Appendix C: Ge et al. code.

For each type of responder and analysis described above (CMH and logistic regression), two different methods of data handling will be applied:

- Multiple imputation as per Section 7.6.1.1
- No imputation and analysis set restriction (Restricting analysis to only include patients with Week 36 assessments)

Analysis of responder defined as relative reduction in LFC ≥ 30% from baseline to Week 36 (V8-EoT), will be repeated in the ITTS-w-065-S , using multiple imputation as per Section 7.6.1.1.

7.6.2.3 Other Secondary Continuous Endpoints

Efficacy will be further assessed based on the following secondary continuous endpoints:

- Liver enzymes: ALT, AST, GGT, ALP
- Measured glycemic parameters: FPG, HbA1c, serum insulin, C-peptide
- Insulin resistance indexes: HOMA-IR, QUICKI, HOMA-β, Adipo-IR

The change from baseline (Randomization Visit [V1]) to Week 36 (V8) will be analyzed using a Mixed Model for Repeated Measures (MMRM) for the secondary continuous parameters with fixed effects for treatment, stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), baseline endpoint specific parameter value, time-point, and treatment by time-point interaction. Covariance parameters will be estimated via the REML method. Compound symmetry will be used for the covariance structure. The Kenward and Roger's method for evaluating the degrees of freedom will also be used. Example SAS code is shown in Appendix C.

All patients in the ITTS with non-missing baseline data and at least one post-baseline data are included in the analysis mode, which uses values at all time points with data available. The MMRM analyses will use observed data only, no imputations of data will be performed.

The LSMs for change from baseline at Week 36 and LSM differences for change from baseline between PXL065 treatment groups and placebo will be presented along with 95% CIs and the comparison p-value. A two-sided nominal significance level of 0.05 will be used for treatment comparison.

In addition, the results and changes from baseline at scheduled visits will be summarized by treatment group and visit using standard descriptive statistics for the ITTS.

The same statistical analyses described above will be repeated for the ITTS-w-065-S for the following secondary continuous endpoints:

- Liver enzymes: ALT, AST

- Measured glycemic parameters: FPG, HbA1c

A listing of secondary continuous efficacy endpoint data will be produced for the ITT set with site 065-S .

7.6.2.4 Other Secondary Categorical Endpoint

The other secondary categorical endpoint is responders with the following criteria:

- Patients with normalization of liver enzymes in the subset of patients with increased baseline value

Normalization of liver enzymes (ALT, AST, GGT or ALP) will be analyzed in the subset of patients with baseline greater than the upper reference range for the respective liver enzyme parameter. Patients will be classed as responders if the liver enzyme normalizes, i.e. decreases to < upper reference range at a post baseline visit.

Responder rate will be provided within each treatment group. Patients who have no assessments at a particular visit will be defined as non-responders. The stratified CMH will primarily be used to analyze the responders, stratifying for T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3). Each PXL065 treatment group will be compared with placebo. The OR, 95% CIs for the OR, and p-values will be displayed for the ITTS. In addition, the number of responders and non-responders will be displayed for each treatment group, see Appendix C for example SAS code.

7.6.2.5 Subgroup Analysis

Analysis of responder defined as relative reduction in LFC ≥ 30% from baseline to Week 36 (V8-EoT), will have a subgroup analysis performed using multiple imputation as per Section 7.6.1.1 for the following groups:

- Randomization strata of T2DM status (T2DM patients, non-T2DM patients)
- Randomization strata of NASH CRN fibrosis scoring system (F1, F2/F3)

The MMRM analysis described in Section 7.6.2.3 will have subgroup analysis performed for the following parameters and subgroups in the ITT Set:

- ALT (U/L)
    - Randomization strata of T2DM status (T2DM patients, non-T2DM patients)
    - Randomization strata of NASH CRN fibrosis scoring system (F1, F2/F3)
- AST (U/L)
    - Randomization strata of T2DM status (T2DM patients, non-T2DM patients)
    - Randomization strata of NASH CRN fibrosis scoring system (F1, F2/F3)
- FPG (mmol/L)
    - Randomization strata of T2DM status (T2DM patients, non-T2DM patients)
- HbA1c (%)
    - Randomization strata of T2DM status (T2DM patients, non-T2DM patients)

7.6.3 Exploratory Endpoints

The analyses described in Section 7.6.2.3 will be repeated for the ITTS for the following endpoints:

- Adiponectin
- Lipids (Percentage change): total cholesterol, LDL-c, HDL-c, triglycerides, FFA
- Biomarker of inflammation: hsCRP

For lipids (total cholesterol, LDL-C, HDL-C, triglycerides and FFA) summary statistics will be provided for both, absolute and percent change from baseline.

Biomarkers of fibrosis (pro-C3, NFS, FIB-4 and ELF score) will be analyzed using a linear regression with the following covariates, treatment, T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline endpoint specific parameter value. LSMs for treatment groups, standard error of the LSM, pairwise differences (PXL065 7.5 mg QD, 15 mg QD and 22.5 mg QD versus placebo) in LSMs, p-values and 95% CIs will be presented. In addition, descriptive statistics for each parameter and change from baseline will be calculated by visit within each treatment group.

The change from baseline in NAS, in each component of NAS (steatosis, ballooning and inflammation), total NAS score and in NASH CRN fibrosis score will be analyzed using a non-parametric ANCOVA method of Koch, Tangen, Jung, and Amara (Koch et al), with fixed effects for treatment, stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), baseline endpoint specific parameter value. This analysis will be performed using the SAS macro for non-parametric randomization-based ANCOVA 'NParCov4'. An example of the SAS code is given below:

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Note: The variance under the null (HYPOTH=NULL) will be the structure for producing p-values, while the variance under the alternative (HYPOTH=ALT) will be used for computing confidence intervals.

Total NAS score is the sum of three scores:

- Steatosis (0-3)

- Ballooning (0-2)
- Inflammation (0-3)

The statistical model will be used to calculate the treatment difference (PXL065 - placebo), 95% CI and p-value at Week 36

The number of percentage of patients in each category below from baseline to Week 36 will also be presented by treatment group on the ITTS:

- Improvement in each component of NAS (steatosis, lobular inflammation and hepatocellular ballooning) by ≥ 1 point without worsening of fibrosis
- Improvement in NAS ≥ 2 points without worsening of fibrosis
- Improvement in NASH CRN fibrosis score by ≥ 1 point
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis)
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with improvement in NASH CRN fibrosis score by ≥ 1 point
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with no worsening in NASH CRN fibrosis score
- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and improvement in NAS ≥ 2 points with no worsening in NASH CRN fibrosis score

For each response, responder rate will be provided within each treatment group for patients with Week 36 assessments. The stratified Cochran-Mantel-Haenszel (CMH) will primarily be used to analyze the responders, stratifying for T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3). Each PXL065 treatment group will be compared with placebo. The odds ratios (ORs), 95% CIs for the ORs, and p-values will be displayed for the ITTS. In addition, the number of responder's and non-responders will be displayed for each treatment group, see for example SAS code.

A listing of these endpoints will also be produced for the ITTS-w-065-S .

In addition, the following categories will be summarized for responders/non-responders by treatment group in the ITTS in the subpopulation of responders for LFC (defined as patients with a Relative Reduction in LFC (%) ≥ 30% at Week 36):

- NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with No Worsening in NASH CRN Fibrosis Score from Baseline to Week 36
- Improvement in NASH CRN Fibrosis Score of At Least One Point from Baseline to Week 36

7.7 Safety

7.7.1 Extent of Exposure

Duration of exposure will be listed for the Safety set with site 065-S and summarized using descriptive statistics for each treatment group for the Safety set, based on dosing records of the IMP medication on the eCRF. Duration of exposure will be calculated as follows:

Date of Last Study Drug Administration – Date of First Study Drug Administration + 1.

7.7.2 Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [Version 23.0] and classified as either pre-treatment AEs, treatment-emergent AEs (TEAEs) or post-treatment AEs as follows:

- Pre-treatment AEs are events that start after the patient is included into the study (Date of ICF signature) and prior to the date of first dose of IMP
- TEAEs are events with start date and time on or after the date and time of first dose of IMP and up to 7 days post-IMP discontinuation, or events with start date and time prior to the date and time of first dose of IMP whose severity or relationship to IMP worsens on or after the date and time of first dose of IMP up to 7 days post-IMP discontinuation. TEAEs also include AEs that are considered by the Investigator as related to IMP treatment, or with unknown/missing relationship to IMP treatment that start 8 days post IMP discontinuation.
- Post-treatment AEs are AEs that start 8 days after IMP discontinuation, with the exclusion of those AEs that are considered by the Investigator as related to IMP treatment.

Summary tables of pre-treatment AEs, TEAEs and post-treatment AEs by treatment group will be produced for the Safety set. No statistical comparisons of AEs between treatment groups will be performed.

All pre-treatment AEs, TEAEs, and post-treatment AEs will be listed by treatment group for the Safety set with site 065-S . Details of SAEs, AEs leading to permanent discontinuation of IMP, AEs resulting in death, and adverse events of special interest (AESI) will be listed separately.

Assessment of AE severity will be based on the Common Terminology Criteria for AEs (CTCAE, version 5).

The relationship between a TEAE and IMP treatment is assessed as unrelated or related. A treatment-related TEAE is a TEAE considered by the Investigator as related to IMP treatment.

Overview tables will summarize the number and percentage of patients with at least one of the following AEs, where patients with more than one AE in a particular category are counted only once in that category:

- any pre-treatment AEs, TEAEs, post-treatment AEs

- any pre-treatment AEs, TEAEs, post-treatment AEs by severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- treatment-related TEAEs
- treatment-related TEAEs by maximum severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- TEAEs leading to IMP treatment discontinuation
- SAEs
- treatment-related treatment-emergent serious AEs (TESAEs) by maximum severity (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- SAEs leading to death
- TESAEs leading to IMP treatment discontinuation
- TEAEs related to study procedures
- Treatment-emergent AESI's (Heart failure, Pitting edema, Bladder cancer, Bone fracture, Drug-induced liver injury – DILI)

The overview table will also summarize the number of events for the same categories in the Safety set.

Overview table for TEAEs will be repeated in the Safety set with site 065-S .

The number and percentage of patients reporting each pre-treatment AEs, TEAE, post-treatment AEs will be summarized by SOC and PT. Tables will be sorted by descending overall frequency of SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- Pre-treatment AEs, TEAEs, post-treatment AEs by SOC and PT
- TEAEs related to IMP treatment, by SOC and PT
- TEAEs causing discontinuation from IMP treatment, by SOC and PT
- TEAEs related to IMP treatment and causing discontinuation from IMP treatment, by SOC and PT
- TEAEs, by severity, SOC and PT
- Pre-treatment SAEs, TESAEs, post-treatment SAEs, by SOC and PT
- TESAEs related to IMP treatment, by SOC and PT
- Pre-treatment AEs, TEAEs, post-treatment AEs leading to death, by SOC and PT
- Pre-treatment AEs, TEAEs, post-treatment AESIs 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.

Additionally, the number and percent of each AE will be summarized for each treatment group, by descending overall frequency of SOC and PT (sorted by descending overall total), displaying the number of observed events for each PT.

TEAEs that are described as cardiovascular will also be summarized for each treatment group, by descending overall frequency of SOC and PT (sorted by descending overall total) displaying number of observed events for the Safety set.

Summary tables, will be repeated in the Safety set with site 065-S for:

- TEAEs by SOC and PT
- TEAEs related to IMP treatment, by SOC and PT
- TESAEs by SOC and PT

7.7.2.1 Hypoglycemia

T2DM Patients are requested to immediately perform a finger stick glucose measurement with the self-monitoring blood glucose (SMBG) device provided for this study (unless CGM is used) if any symptoms occur that may be related to hypoglycemia and to avoid any delay in treating these symptoms. After the recovery of the symptoms, patients may report all the symptoms, date and time, dietary intake states, time of the recovery in the patient diary as well as blood glucose values if available.

Only symptoms and/or plasma glucose concentration values deemed by the Investigator to meet the definition of hypoglycemia should be reported on the AE section of the eCRF.

Hypoglycemia will be reported as recommended by the FDA guidance [2]:

- Probable symptomatic hypoglycemia: Hypoglycemia evidenced only by symptoms without blood glucose measurement
- Asymptomatic Hypoglycemia: Hypoglycemia evidenced only by plasma glucose concentration of less than 70 mg/dL (3.9 mmol/L) and not accompanied by typical symptoms of hypoglycemia
- Documented Symptomatic Hypoglycemia: Hypoglycemia evidenced both by typical symptoms and plasma glucose concentration of less than 70 mg/dL (3.9 mmol/L)
- Severe Hypoglycemia: Hypoglycemia requiring assistance of another person to administer carbohydrate or glucagon or other procedure

In case of AE of hypoglycemia, the Investigator should query the patient to understand the clinical context that may have explained a low glucose value (exercise, missing meal, timing of drug intake and SMBG). All these data should be reviewed by Medical Monitor.

Summary tables of probable symptomatic hypoglycemia, asymptomatic hypoglycemia, documented symptomatic hypoglycemia and severe hypoglycemia by treatment group will be produced for the Safety set.

Hypoglycemic events will be hardcoded with SOC "Metabolism and nutrition disorders" and PT "Hypoglycaemia".

Hypoglycemia events will be listed for the Safety set with site 065-S .

7.7.3 Laboratory Evaluations

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

Laboratory data will be summarized using standard descriptive statistics for each treatment group, by scheduled visit for the Safety population.

7.7.3.1 Standard Safety Laboratory Panel

Data for the following hematology, biochemistry, urinalysis and coagulation received from central laboratory will be listed for the Safety set with site 065-S and summarized by treatment group and visit for the Safety set. Local laboratory results will be listed only.

Hematology	Biochemistry	Urinalysis
Erythrocytes Hemoglobin Hematocrit Red Blood Cell Morphology Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Leucocytes Differential blood count (lymphocytes, monocytes, eosinophils, basophils, neutrophils/ absolute values and percentages should be given) Thrombocytes	Blood Urea Nitrogen Creatinine Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphate Total protein Albumin Uric acid Creatine phosphokinase AST ALT GGT Total bilirubin ALP hsCRP TSH (during Screening Period only)	pH Specific gravity Protein Glucose Ketones Nitrites Urobilinogen Blood Leucocytes If the dipstick result is abnormal: microscopic examination of the sediment for blood cells, cylinders, etc.

Coagulation
Activated Partial Thromboplastin Time (aPTT) Prothrombin Time International Normalized Ratio (INR)

Values outside the normal range will be categorized as H (above the normal range) or L (below the normal range) based on the central laboratory's normal reference range. Laboratory data will be summarized by visit using standard descriptive statistics. Changes from baseline will also be summarized.

The following elevations will be assessed:

Predefined Limits of Change (PDLC)	
ALT (SGPT) (U/L)	Value >3xULN
ALT (SGPT) (U/L)	Value >5xULN
ALT (SGPT) (U/L)	Value >8xULN
AST (SGOT) (U/L)	Value >3xULN
AST (SGOT) (U/L)	Value >5xULN
AST (SGOT) (U/L)	Value >8xULN
Total Bilirubin (µmol/L)	Value >2xULN

Predefined Limits of Change (PDLC)	
ALP (U/L)	Value >2xULN

A listing of patients with elevated PDLC criteria will be produced for Safety set with site 065-S .

7.7.3.2 eGFR

Data for eGFR received from central laboratory will be listed and summarized by treatment group and visit. Local laboratory results will be listed only.

eGFR will be calculated using the chronic kidney disease – epidemiology collaboration (CKD-EPI) formula, as follows [14]:

141 x min(Scr/κ,1)α x max(Scr/κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if black]

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

CKD stages are defined as:

- CKD stage 1 (eGFR ≥90 mL/min/1.73m^2)
- CKD stage 2 (eGFR ≥60 to <90 mL/min/1.73m^2)
- CKD stage 3a (eGFR ≥45 to <60 mL/min/1.73m^2)
- CKD stage 3b (eGFR ≥30 to <45 mL/min/1.73m^2)
- CKD stage 4 (eGFR ≥15 to <30 mL/min/1.73m^2)
- CKD stage 5 (eGFR <15 mL/min/1.73m^2)

Shift tables from baseline will be presented at each post-baseline visit showing the number of patients per treatment group with each populated CKD stage for the Safety set.

eGFR data will be summarized by treatment group and visit using standard descriptive statistics, changes from baseline will also be summarized. Summary tables will be produced for the Safety set.

A listing of eGFR data will be produced for the Safety set with site 065-S .

7.7.3.3 Viral Infection Screen Panel

Data for viral infection screen panel received from central and local laboratory will be listed by treatment group and visit for Safety set with site 065-S .

Hepatitis screening	**HIV screening**
Hepatitis B antigen (HBsAg) Hepatitis C virus antibody (anti-HCV), in case of positive result, reflex test of HCV circulating Ribonucleic acid (RNA)	Anti-human immunodeficiency virus (HIV) 1 and 2

7.7.3.4 Serum and Urine Pregnancy Test

For female patients of child-bearing potential only, a serum B Human Chorionic Gonadotropin (β-HCG) test or a urine pregnancy test will be performed.

Additional serum pregnancy testing should be performed during the study whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Serum and Urine pregnancy test results will be summarized for the Safety set.

Serum and Urine pregnancy test results, and immediate pregnancy reporting will be listed for the Safety set with site 065-S .

7.7.4 Bone Mineral Density

For postmenopausal women only, a standard dual-energy X-ray absorptiometry (DXA) testing will be performed during the study.

If possible, all DXA testing for a given patient (historical testing or testing performed during study) should be performed at the same facility and using the same procedure.

Bone mineral density will be summarized by visit using standard descriptive statistics for each treatment group, changes from baseline will also be summarized. Summary tables will be produced for the Safety set.

Bone mineral density test results will also be listed for the Safety set with site 065-S .

7.7.5 Vital Signs and Body Measurements

The following vital sign and body measurements will be taken during the study:

- height (cm)
- weight (kg)
- waist circumference (cm)
- hip circumference (cm)
- Waist-to-hip ratio [Derived as waist circumference (cm)/hip circumference (cm)]
- heart rate (bpm)
- SBP (mmHg) with 3 readings
- DBP (mmHg) with 3 readings

The following vital sign results are derived on the eCRF:

- calculated BMI (kg/m^2)
- mean SBP (mmHg)
- mean DBP (mmHg)

Vital signs data and changes from baseline in vital signs will be summarized visit by using standard descriptive statistics for each treatment group the Safety set. For summaries, the average of the 3 blood pressure readings will be used.

Summary table on weight will be repeated in the Safety set with site 065-S .

The MMRM analysis described in Section 7.6.2.3 will be repeated for the Safety set, Safety set with site 065-S and ITTS for weight (kg).

A listing of vital signs data will be produced for the Safety set with site 065-S .

7.7.6 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- heart rate (bpm);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Fridericia corrected QT (QTcF) interval (msec);

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant"). Any new clinically significant findings or worsening of abnormalities previously recorded as Medical History on the ECG will be reported as AEs, and followed up and/or treated locally until the AE has resolved or the condition has stabilized.

The ECG measurements and changes from baseline in ECG will be listed for the Safety set with site 065-S and summarized by treatment group and visit using standard descriptive statistics for the Safety set.

The Investigator assessment will be listed for the Safety set with site 065-S and the number and percentage of subjects within each assessment category will be tabulated for each treatment group by visit for the Safety set.

Summary tables will be produced for the Safety set.

A listing of ECG measurements and findings will be produced for the Safety set with site 065-S .

7.7.7 Physical Examination

Any new clinically significant abnormal findings or worsening of conditions previously recorded as medical history should be documented in the source documents and reported in the eCRF as AE.

Physical examination date will be listed for the Safety set with site 065-S .

7.7.8 Pitting Edema

Shift tables from baseline will be presented at each post-baseline visit showing the number of patients per treatment group with each populated grade for the Safety set.

A listing will also be provided for the Safety set with site 065-S .

7.7.9 Other Safety Variables

Blood (total, plasma and serum) samples for supplementary tests will be collected at particular visits to enable post-hoc testing of any additional efficacy and safety parameters or any potential biomarkers related to liver, cardiovascular diseases or metabolic diseases in relation with the drug target. The samples will be stored until

further use. All the biobanking samples will be destroyed within 2 years after the final study report is issued.

7.8 Interim Analysis

Not applicable

8. Changes in Planned Analysis

- Changes from SAP v2.0 (12May2022) to SAP Final v3.0 (12Aug2022):
  - Treatment exposure end date coded as 23rd December 2021 per NTF for patients that did not complete the study at site 065-S
  - PPS description updated following the BDRM
  - Removal of analyses utilizing multiple imputation on the PPS
  - Multiple imputation method updated to consider a minimum and maximum value
  - CMH and logistic regression analysis removed for "Patients without any MRI assessments on treatment being classified as non-responders"
  - Analysis on biopsy exploratory endpoints updated to consider only patients with Week 36 assessments
  - EoS Visit end date removed for derivation of new medications
- Changes from SAP v1.0 (03Dec2020) to SAP Final v2.0 (17May2022):
  - Updates per issue with site 065-S
    - Section 1 updated to mention note to file for the handling of site 065-S
    - Analysis populations section includes description of the issue with site 065-S and the handling of the analysis sets
    - Section 7 updated to specify which analyses are done with and without site 065-S
    - Updates to disposition table
    - Additional MMRM analysis for weight (kg)
    - Section 7.6.2.5 added for new subgroup analyses on secondary endpoints
  - Updates per dry run 1
    - Rescreened patients excluded from screened set
    - Demographics - BMI and Weight at baseline rather than randomization
    - Updates to TEAE overall table
    - Inclusion of urine pregnancy summary and listing
    - Inclusion of immediate pregnancy reporting listing
  - Updates per protocol amendment 5
    - Additional section for handling of rescreened patients
    - Removal of albuminuria/creatininuria ratio
    - Updates to prohibited medication
  - Imputation rules added for type 2 diabetes diagnosis
  - PK analysis is now being reported separately

  - References to Covance updated to Labcorp/Labcorp Drug Development
- Approval of SAP version 1.0 dated 03Dec2020

9. Data Issues

Issues concerning site 065-S have been documented in Section 5 and in a note to file.

10. References

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11. Appendix A: Visit Schedule Chart

	Screening Period	V1	V2	V3	V4	V5	V6	V7	V8	V9	ET
		Randomization	Week 3	Week 6	Week 12	Week 18	Week 24	Week 30	Week 36 EoT	Week 38 EoS	-
Timeframe	-8 weeks max	Day 1	Day 22	Day 43	Day 85	Day 127	Day 169	Day 211	Day 253	Day 267	-
Time windows	-	*Within 8W after ICF signature*	*3W after V1 ± 4 days*	*6W after V1 ± 4 days[1]*	*12W after V1 ± 6 days[1]*	*18W after V1 ± 6 days[1]*	*24W after V1 ± 6 days[1]*	*30W after V1 ± 6 days[1]*	36W after V1 ± 6 days[1]	*2W after V8 ± 3 days*	*Within 8 days after IMP discontinuation*
General Activities											
Informed consent	X										
IWRS log-on	X	X	X	X	X	X	X	X	X	X	X
Patient Emergency Card dispensing	X										
Inclusion/Exclusion	X	X									
Randomization		X									
IMP dispensing		X		X	X	X	X	X			
IMP compliance				X	X	X	X	X	X		X
Diary dispensing		X		X	X	X	X	X			
SMBG dispensing[2]		X									
Diary review (+SMBG review if T2DM)			X	X	X	X	X	X	X	X	X
AASLD lifestyle guidance[3]		X	X	X	X	X	X	X	X	X	X
History and Clinical Investigations											
Demography	X										
Medical history	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Prior medications	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Complete phys ex.[4]	X	X							X	X	X
Limited phys ex.[4]			X	X	X	X	X	X			
Pitting edema assessment	X	X	X	X	X	X	X	X	X	X	X
Vital signs and body measurements[5]	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X				X			X	X	X
DXA[6]	X								X		
Central Laboratory											
MRI-PDFF[7]	X								X		X
Liver Biopsy[8]	X								X		
Viral screen lab[9]	X										
Safety lab[10]	X	X			X		X		X	X	X
eGFR	X	X							X		
Pregnancy test[11]	X	X				X				X	X
FPG	X	X			X		X		X	X	X
HbA1c	X	X			X		X		X		X
Measured metabolic param[12]		X			X		X		X		X
Insulin resistance indexes[13]		X			X		X		X		X
Fibrosis biomarkers[14]		X							X		
Biobanking sampling		X							X		
PK sampling[15]					X		X		X		

AASLD: American Association for the Study of Liver Diseases; AE: adverse event; DXA: dual-energy X-ray absorptiometry; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EoS: End-of-Study Visit; EoT: End-of-Treatment Visit; ET: Early Termination Visit; FPG: Fasting Plasma Glucose; HbA1c: glycated hemoglobin; hsCRP: High-sensitivity C-Reactive Protein; ICF: informed consent form; 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;T2DM: Type 2 Diabetes mellitus V: visit; W: week(s)

[1]: The interval between 2 on-site visits must not exceed 48 days.
[2]: SMBG device dispensed to T2DM patients only. SMBG devices to be brought back to the study site at each visit for measurement review. SMBG device will be kept by the patient after the end of his/her study participation. Continuous Glucose Monitoring (CGM) is accepted and no SMBG device needs to be dispensed in this case.
[3]: Investigators will explain AASLD guidance regarding diet and exercise at Randomization Visit (V1). Investigators will collect the compliance to this guidance at each subsequent visit.
[4]: The complete physical examination will include head, ears, eyes, nose, mouth, skin, cardiovascular and lung examinations, lymph nodes, gastrointestinal, musculoskeletal and neurological systems. The limited physical examination will be focused on general appearance, the cardiovascular system as well as towards patient reported symptoms.
[5]: Vital signs and labs body measurements include: heart rate and 3 blood pressure measurements in supine or sitting position, and, height (during Screening Period only), body weight, BMI, waist and hip circumferences.
[6]: Postmenopausal women must have BMD T-score results assessed by standard DXA testing within 6 months prior to Randomization Visit (V1). If there is no available BMD T-score within this period, a DXA testing must be performed during the Screening Period only after receiving confirmation of eligibility on history, clinical examination and labs. DXA testing must also be performed before (within 8 days) or on the day of Week 36 (V8-EoT).
[7]: MRI-PDFF must be performed only after receiving confirmation of eligibility on history, clinical examination and labs during Screening Period. MRI-PDFF must also be performed before (within 8 days) or on the day of Week 36 (V8-EoT). MRI-PDFF must also be performed at Early termination Visit (ET) only for patients who withdraw from the study at or after Week 12 (V4) and only when the IMP was discontinued less than 14 days before the ET Visit.
[8]: Eligibility is to be confirmed based on all assessments before performing liver biopsy and/or sending material to histopathology laboratory. A qualifying liver biopsy is required within 6 months prior to the Randomization Visit (V1). If no appropriate historical liver biopsy material is available, a liver biopsy must be performed during Screening Period. A second liver biopsy must be performed before (within 8 days) or on the day of Week 36 (V8-EoT).
[9]: The viral infection screen panel includes hepatitis screening (hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV) and in case of positive result, reflex test of HCV circulating ribonucleic acid (RNA), anti-human immunodeficiency virus (HIV) 1 and 2)
[10]: The standard safety laboratory panel (blood and urine) includes hematology, biochemistry, coagulation and urinalysis

[11]: For female patients of child-bearing potential only. Serum pregnancy test (Human Chorionic Gonadotropin (β-HCG)) during Screening Period, End-of-study Visit (V9) and Early Termination Visit (ET) and urine pregnancy test at Randomization Visit (V1) and Week 18 (V5).
[12]: Measured metabolic parameters include serum insulin, C-peptide, adiponectin, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, free fatty acids (FFA)
[13]: Insulin resistance indexes include Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostasis Model Assessment of β-cell function (HOMA-β) and Adipose Tissue Insulin Resistance (Adipo-IR)
[14]: Fibrosis biomarkers include: N-terminal type III collagen propeptide (pro-C3), Nonalcoholic Fatty Liver Disease (NALFD) Fibrosis Score (NFS), Fibrosis 4 (FIB-4) score and Enhanced Liver Fibrosis (ELF) score
[15]: One pre-dose blood sample will be drawn just before the IMP daily intake at, Week 12, Week 24 and Week 36 (visits V3, V4, V6 and V8-EoT) and one sample between 1h and 4h post-dose at Week 36 (last IMP intake, V8- EoT).

12. Appendix B: Sample SAS® code for analyses of efficacy endpoints

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13. Appendix C: Ge et al. code

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