CLINICAL TRIAL PROTOCOL

NCT03763877

Trial Protocol Number	PXL770-004
Study Full Title	A randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL770 versus placebo after 12 weeks of treatment in patients with Nonalcoholic Fatty Liver Disease (NAFLD) with or without type 2 diabetes mellitus
Study Short Title	STAMP-NAFLD
Program Acronym	**STAMP** **ST**udy of **AMP** kinase activator
Phase	Phase IIa
Authors	Corporate confidential information
IND Number / Serial Number	140493 / 00013
EudraCT Number	N/A
Coordinating investigator	Corporate confidential information
Sponsor	POXEL S.A. 259-261, avenue Jean Jaurès 69007 Lyon France
Sponsor's Legal Representative (EU)	N/A
Trial Protocol Version	Version 6.0 / 24th July 2020
Replaces Trial Protocol Version	Version 5.0 / 20th November 2019
Current Protocol Amendment	No. 5
Previous Protocol Amendments	No. 4

Signature Page

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Investigator Signature

Study Title	A randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL770 versus placebo after 12 weeks of treatment in patients with Nonalcoholic Fatty Liver Disease (NAFLD) with or without type 2 diabetes mellitus
Protocol Version / Date	Version 6.0 / 24th July 2020
Study site Number	_____

Investigator (full name, title and academic degree) _____

_____

Address: _____

Phone: _____

Fax: _____

Email: _____

I, the undersigned, am responsible for the conduct of the study at this study site and affirm that:

- I understand and will conduct the study according to the protocol, any approved protocol amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and all applicable Regulatory Authority requirements and national laws.
- I will not deviate from the protocol, except where necessary to prevent immediate danger to patients.

_____ _____

Signature Date of Signature

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List of Abbreviations

ACC	Acetyl-CoA Carboxylase
Adipo-IR	Adipose tissue Insulin Resistance
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine amino Transferase
ALP	Alkaline Phosphatase
AMPK	5' adenosine monophosphate-activated protein kinase
ANCOVA	Analysis of Covariance
AST	Aspartate amino Transferase
AUC	Area under the concentration time curve
AUC_{inf}	Area under the concentration time curve extrapolated to infinity
βHCG	Human Chorionic Gonadotropin
BDRM	Blinded Data Review Meeting
Bid	Twice a day (*bis in die*)
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CAP	Controlled Attenuation Parameter
CHF	Congestive Heart Failure
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
C_{max}	Maximum concentration
C_{pre}	Predose concentration
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
DILI	Drug-Induced Liver Injury
DNL	De Novo Lipogenesis
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
ELAR	Expedited Liver Assessment Report
EoS	End-of-Study
EoT	End-of-Treatment
ET	Early Termination
FA	Fatty Acids
FDA	Food and Drug Administration
FFA	Free Fatty Acids

Fib-4	Fibrosis 4
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP1-RA	Glucagon-Like Peptide 1 – Receptor Agonist
GMP	Good Manufacturing Practice
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDL-c	High Density Lipoprotein-cholesterol
HIV	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
HSL	Hormone-Sensitive Lipase
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention-To-Treat
IWRS	Interactive Web Response System
LDL-c	Low Density Lipoprotein-cholesterol
LSM	Least Square Mean
MAD	Multiple Ascending Dose
MAR	Missing at random
MCP-1	Monocyte Chemoattractant Protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeat Measurement
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NAFL	Nonalcoholic Fatty Liver
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic steatohepatitis
NFS	NAFLD Fibrosis Score
NOAEL	No-observed-adverse-effect level
NYHA	New York Heart Association

PDFF	Proton Density Fat Fraction
PGC-1α	Peroxisome proliferator-activated receptor Gamma Coactivator 1-Alpha
PK	Pharmacokinetics
PPS	Per Protocol Set
PTCA	Percutaneous Transluminal Coronary Angioplasty
QD	Once a day (*Quaque die)*
QUICKI	Quantitative Insulin Sensitivity Check Index
RNA	Ribonucleic Acid
RS	Randomized Set
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SEM	Standard Error of the Mean
SGLT2-I	Sodium-Glucose-Co-Transportor-2 Inhibitor
SMBG	Self-Monitoring Blood Glucose
SOC	System Organ Class
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TBL	Total bilirubin
TE	Transient Elastography
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to reach the maximum concentration
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
VLDL	Very Low Density Lipoprotein
WHO	World Health Organization

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1 Synopsis

Protocol Number	PXL770-004
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Study Short Title	STAMP-NAFLD
Program Acronym	**STAMP** **ST**udy of **AMP** kinase activator
Sponsor	POXEL S.A.
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Study site(s)/Country	United States (US)
Planned Trial Period (first enrollment-last patient out)	Study start: Q1 2019 Study end: Q3 2020
Trial Objectives	**Primary objective** • To assess the effect of PXL770 versus placebo on hepatic steatosis in NAFLD patients at the daily dose of 250 mg once a day (QD) and twice a day (BID) and 500 mg QD after 12 weeks of treatment **Secondary objectives** • 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 • 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: - Liver enzymes - Lipid parameters - Glycemic parameters in fasting conditions - Biomarkers of inflammation - Biomarkers of fibrosis - Anthropomorphic parameters • To compare the 2 dose regimens of PXL770 (BID versus QD) on efficacy and safety parameters in NAFLD patients • 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

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Trial Design and Plan **(Design description in *Figure 1* and schedule of visits in *Table 1*)**	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 versus non-T2DM patients) Corporate confidential information
Planned Number of Patients	120 patients to be randomized in order to obtain at least 96 evaluable patients (24 patients per treatment group) accounting for a 20% drop-out rate. Corporate confidential information

Diagnosis and main Inclusion and Exclusion Criteria	**Inclusion criteria** 1. Capable of providing written informed consent. Male or female patients must have given written informed consent before any study-related activities are carried out 2. Age: ≥ 18 to ≤ 75 years at informed consent signature 3. Body mass index (BMI) ≥ 25 to ≤ 50 kg/m^2 at Screening Visit (V1) and Randomization Visit (V3) 4. Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73m² at Screening Visit (V1) calculated by the Chronic Kidney Disease – Epidemiology collaboration (CKD-EPI) formulae 5. For patients with T2DM: - Either naïve of treatment with no glucose lowering drug for the last 12 weeks prior to Screening Visit (V1) or under stable oral glucose lowering drug (mono- or bi-therapy) for the last 12 weeks prior to Screening Visit (V1) (See non-permitted concomitant medications in exclusion criteria #25) - Glycated hemoglobin (HbA1c) ≤ 9.0% at Screening Visit (V1) 6. Not applicable – intentionally left blank for data management purposes (consistency in eCRF capture of eligibility criteria historically) 7. Hepatic steatosis: - Evidenced by transient elastography (TE) with controlled attenuation parameter (CAP) ≥ 300 dB/m or by ultrasound or magnetic resonance imaging (MRI), performed within the last 12 weeks prior to Screening Visit (V1). If none of these assessments are available prior to Screening Visit (V1), TE with CAP ≥ 300 dB/m should be evidenced at Run-in Visit (V2) - Confirmed by MRI performed within 8 ± 4 days prior to Randomization Visit (V3) with a proton density fat fraction (PDFF) value ≥ 10% 8. Women of child-bearing potential (e.g. not surgically sterile or not postmenopausal) must have a negative serum pregnancy test at Screening Visit (V1) and a negative urine pregnancy test at Randomization Visit (V3) and must use an adequate method of contraception or be sexually abstinent. Adequate method of contraception includes, but is not limited to: oral, intramuscular, or implanted hormonal contraception, sexual partner with non-reversed vasectomy (with azoospermia in 2 tests), 2 barrier methods (e.g. condom, diaphragm, or spermicide), intrauterine device

	9. Male patients must have agreed on an effective contraception with their female partner
	Exclusion criteria Patients must not enter in the study and will not be randomized in the study if they fulfill any of the following Exclusion criteria: 1. Involvement in the planning and/or conduct of the study (applies to both POXEL and staff and/or staff at the study site) 2. Participation in another clinical study with intake of an investigational product during the last 12 weeks prior to Screening Visit (V1) 3. Previous participation in any clinical study with PXL770 intake ***Target disease exclusions*** 4. Evidence of another form of liver disease including but not limited to viral hepatitis, autoimmune hepatitis, alcoholic disease, cholestatic liver disease, Wilson's disease, Alpha-1-antitypsin deficiency, hemochromatosis or drug induced liver injury (DILI) 5. Evidence of liver cirrhosis on laboratory assessment or Transient Elastography ≥ 14 kPa at Run-in Visit (V2) 6. Aspartate amino transferase (AST) or alanine amino transferase (ALT) > 200 IU/L at Screening Visit (V1) 7. Evidence of hepatic impairment at Screening Visit (V1) as defined by the combination of at least two of the following parameters: - Total bilirubin (TBL) ≥ 1.3 mg/dL - Serum albumin < 3.5 g/dL - International Normalized Ratio (INR) ≥ 1.2 - Platelets < 150 G/L - Hemoglobin < 11 g/dL in females or < 12 g/dL in males - Presence of ascites 8. Bariatric surgery of any kind at any time prior to Randomization Visit (V3) or change in body weight greater than 5% within the last 12 weeks prior to the Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3) 9. Positive serologic evidence of current infectious liver disease including hepatitis B surface antigen (HBsAg), and/or anti-hepatitis C virus (HCV) antibody with detected circulating ribonucleic acid (RNA) at the Screening Visit (V1). 10. History of excessive alcohol intake defined by equal or greater than 21 units of alcohol/ week in males and equal or greater than 14 units of alcohol/ week in females for 2

	years prior to the Screening Visit (V1), where a unit of alcohol is equal to 10 g pure alcohol. ***Medical History and Concurrent Disease Exclusions*** *Cardiovascular diseases* 11. Any of the following disease within 24 weeks prior to Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3): - Myocardial infarction - Cardiac revascularization surgery (coronary artery bypass graft/percutaneous transluminal coronary angioplasty (CABG/PTCA)) - Unstable angina - Unstable congestive heart failure (CHF) - New York Heart Association (NYHA) Class III or IV - Transient ischemic attack, stroke or cerebrovascular disease 12. Unstable or undiagnosed arrhythmias, long QT syndrome, short QT syndrome, history of drug-induced Torsade de Pointe 13. Uncontrolled high blood pressure (BP): diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg with or without antihypertensive treatment at Screening Visit (V1) *Hematological and oncological diseases* 14. Malignancy within 5 years prior to Screening Visit (V1) (with the exception of treated basal cell carcinoma or treated squamous cell carcinoma of the skin) 15. History of haemoglobinopathies (e.g., sickle cell anemia or thalassemia, sideroblastic anemia) 16. Patient who donated blood products to a blood bank or who received blood transfusion within 12 weeks prior to Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3) *Endocrinological disease* 17. Diabetes other than T2DM 18. Uncontrolled hypothyroidism (thyroid stimulating hormone (TSH) > 2 x the upper limit of normal (ULN) at Screening Visit (V1)) ***Other exclusion conditions*** 19. Immunocompromised patients such as patients that underwent organ transplantation or were diagnosed with human immunodeficiency virus (HIV) 20. Any other known serious disease (such as major infection, clinically significant gastrointestinal disorder, major autoimmune disease…) or other disease which in the

	Investigator's opinion would exclude the patient from the study 21. Any current drug addiction 22. Mental handicap, limited capacity of recognition, inability to follow the study procedures as evaluated by the Investigator, or any history of clinically important emotional and/or psychiatric illness 23. Anorexia or bulimia 24. Known hypersensitivity to any of the constituents or excipients of the investigational medicinal product (IMP), or history of relevant drug and/or food allergies (e.g. anaphylactic, anaphylactoid reactions) 25. Use of non-permitted concomitant medication within 24 weeks prior to Screening Visit (V1) and at any time between the Screening Visit (V1) and the Randomization Visit (V3): - Pioglitazone, insulin, Glucagon-Like Peptide-1 Receptor Agonist (GLP1-RA), Sodium-Glucose-Co-Transportor-2 inhibitor (SGLT2-I), anticoagulants, amiodarone, bile salt chelators, methotrexate, equal or more than 400 U of vitamin E per day, corticosteroids with a systemic effect, or any other medications known to affect liver function / steatosis at the Investigator's discretion, . Corporate confidential information herbal drug or Chinese traditional medicines 26. Contraindications to MRI - Such as patients with pacemakers, metallic cardiac valves, magnetic material such as surgical clips, implanted electronic infusion pumps or other conditions that would preclude proximity to a strong magnetic field - History of extreme claustrophobia - The patient cannot fit inside the magnetic resonance scanner cavity 27. Pregnancy or lactation
Investigational Medicinal Product(s) (IMP): dose/ dosing schedule/ mode of administration	PXL770 capsules (capsules of 250 mg each) orally Placebo capsules orally Treatments to be administered in the 4 treatment groups: • PXL770 250 mg QD (morning) + placebo BID (morning and evening) • PXL770 250 mg BID + placebo BID

	• PXL770 500 mg QD (morning) + placebo QD (evening) • Placebo BID
Planned Study Duration per Patient	Study duration per patient (from Screening Visit (V1) up to End-of-study Visit (V8)) • Minimum: 17 weeks • Maximum: 19 weeks
Assessments for Efficacy	**Primary endpoint** Relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7) **Key secondary endpoints** • Absolute change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7) • Percentage of responders as defined by the percentage of patients who achieve a clinically meaningful reduction of at least 5 % (≥ 5%) in absolute liver fat mass (from baseline (Randomization Visit (V3)) as measured by MRI-PDFF at Week 12 (V7) • Percentage of responders as defined by the percentage of patients who achieve a relative reduction of at least 30% (≥ 30%) in liver fat mass (from baseline Randomization Visit (V3)) as measured by MRI-PDFF at Week 12 (V7) • Percentage of responders as defined by the percentage of patients who achieve a relative reduction of at least 50% (≥ 50%) in liver fat mass (from baseline Randomization Visit (V3)) as measured by MRI-PDFF at Week 12 (V7) • Percentage of responders as defined by the percentage of patients who achieve a liver fat mass value at Week 12 (V7) that is normalized, i.e. ≤ 5% **Secondary endpoints** Change from baseline (Randomization Visit (V3)) in the following parameters at Week 12 (V7): • Liver enzymes: ALT and AST • Measured metabolic parameters: Fasting plasma glucose (FPG), HbA1c, serum insulin, C-peptide, total cholesterol, high density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), triglycerides, Apo A1, Apo B, free fatty acids (FFA), glycerol and adiponectin • Calculated metabolic parameters: 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) • High-sensitivity C-reactive protein (hsCRP) and other markers of inflammation: fibrinogen and monocyte chemoattractant protein-1 (MCP-1) • Markers of fibrosis: NAFLD Fibrosis score (NFS) and Fibrosis 4 (Fib-4) score • Body weight, waist circumference and waist-to-hip ratio Corporate confidential information
Assessments for Safety	Safety and tolerability will be assessed on the following parameters: • Adverse events (AE) • Physical examination • Weight, waist and hip circumferences and BMI • Vital signs (systolic BP, diastolic BP, heart rate (HR)) • 12-lead electrocardiogram (ECG) • Biological parameters: biochemistry, hematology, coagulation • eGFR (CKD-EPI formula) • Urinalysis
Pharmacokinetics (PK)	A pre-dose sample will be drawn before the morning dose at V4, V5, V6 and V7, for the determination of PXL770 plasma concentrations. Corporate confidential information

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Other Assessment	Blood sample will be drawn in all patients for extra-samples at V3 and V7 to allow post-hoc testing of any additional safety and efficacy parameters or any potential biomarkers related to liver, cardiovascular diseases or metabolic diseases in relation with the drug target. In addition, blood sample will be drawn at V3 and V7 to allow post-hoc genetic and pharmacogenetic research on the DNA/RNA samples from patients who sign an optional, additional informed consent. The frozen samples will be stored centrally, and will be destroyed within 2 years after clinical study report finalization.
Statistical Methods	**Sample size calculation** Sample size determination is based on the primary endpoint, i.e. the relative percent change in liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3) to Week 12 (V7). Assuming an expected difference of 30% between at least one dose of PXL770 and placebo, a common standard deviation of 30% (estimated from previous published data [1]), a two-sided significance level of 0.05, 24 patients per treatment group are required to achieve a power of 90%. Given the early stage of development (i.e. a Phase II trial for internal decision), no adjustment for comparison multiplicity will be considered. The sample size is expanded to 30 patients per group to account for an expected 20% drop-out rate, which amounts to a total required number of 120 patients to be randomized. **Statistical methods** Full details of analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to the unblinding and locking of the database. Analyses sets • Screened Analysis Set: all patients who were screened for inclusion into the study • Run-in Safety Analysis Set (RISS): all patients having received at least one dose of the single-blind placebo run-in treatment. • Safety Set (SS): all randomized patients having received at least one dose of the IMP (either PXL770 or placebo) and considered as-treated. Primary set for safety analyses and tolerability will be analyzed on the Safety Set.

- Randomized Set (RS): all patients randomized and considered as randomized regardless of the treatment actually received.
- Intention-to-treat Set (ITTS): all patients having received at least one dose of the IMP (either PXL770 or placebo) and considered as randomized. Primary set for efficacy analyses.
- Per Protocol Set (PPS): ITT patients without any major violations.
- Pharmacokinetic (PK) population: all patients from the SS who have been treated with PXL770 according to the protocol and have provided at least one pre-dose PK assessment during the study.

Efficacy analyses

Primary Endpoint:

The primary endpoint, i.e. expressed as the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7), will be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo) and for stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and Corporate confidential information and baseline liver fat mass as a covariate. Least square means (LSMs) of the primary endpoint for treatment groups and pairwise differences in LSMs will be estimated along with their p-values and 95% confidence intervals.

Missing MRI-PDFF at Week 12 (V7) will be estimated using a multiple imputation method assuming missing at random (MAR) mechanism that will be detailed in the SAP. Missing baseline MRI-PDFF will not be estimated

Sensitivity analyses will be performed based on a rank analysis.

Subgroup analyses will be performed:

- within each T2DM status (T2DM patients versus non-T2DM patients). The treatment by T2DM status interaction will be tested.

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Key secondary Endpoints:

- *Absolute change in the percentage of liver fat mass from baseline (Randomization Visit (V3)) to Week 12 (V7)*: this will be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment, T2DM status (T2DM patients versus non-T2DM patients), site (main 1 vs main 2 vs main 3 vs others) and baseline liver fat mass. Least square means of the change in the percentage

	of liver fat mass for treatment groups (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo) and pairwise differences in LSMs will be estimated along with their p-values and 95% confidence intervals. • *Responders (as defined in the Assessment for Efficacy Section)* will be analyzed in a logistic regression model adjusting for treatment (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo), T2DM status (T2DM patients versus non-T2DM patients), site (main 1 vs main 2 vs main 3 vs others) and baseline liver fat mass. Pairwise differences in treatment groups will be estimated in this model as odds ratios along with their p-values and 95% confidence intervals. Methods handling missing MRI-PDFF at Week 12 (V7) and therefore the responder status at Week 12 (V7) will be detailed in the SAP. ***Other secondary Endpoints:*** The analysis of these secondary endpoints will be fully detailed in the SAP. ***Safety Endpoints:*** Safety endpoints will be analyzed with usual descriptive methods. ***PK Endpoints:*** Pharmacokinetic data (PXL770 concentrations) will be analyzed using a Population PK model. PK parameters will be listed and summarized by treatment groups and by visits/timepoints.

Figure 1. Diagram of Study Design

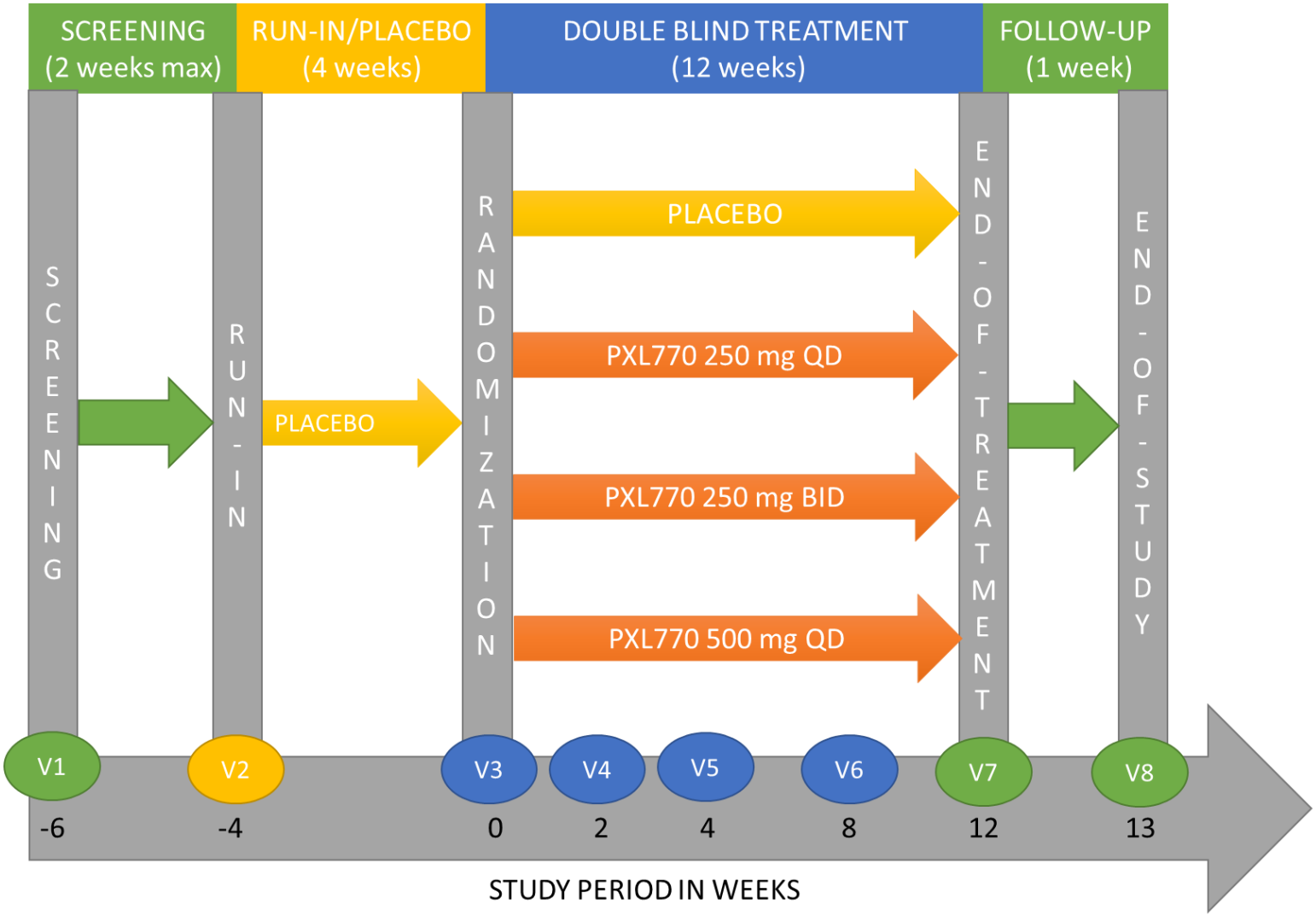

Table 1. Visit Schedule Chart

The visit schedule chart is the master representation of the clinical trial. In case of (apparent) inconsistencies in the clinical trial protocol, the information provided here is the binding one.

	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

	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*

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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: estimated 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; test; 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 Investigator; 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).
For the determination of these parameters, two blood samples should be collected at a 10-min interval.
[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 result, 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 Corporate confidential information
[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))
- At V8

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[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.

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2 Background Information

2.1 Scientific Rationale

Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease associated with fat accumulation in the liver exceeding 5% in people with no or little alcohol consumption [2]. The development of non-alcoholic steatohepatitis (NASH) is the result of both environmental (sedentary lifestyle and excessive calorie intake) and individual predispositions, which lead to adipose tissue expansion, insulin resistance, liver fat accumulation (steatosis or non-alcoholic fatty liver - NAFL) with potentially development of inflammation and fibrosis (NASH). The ultimate stage of cirrhosis contributes to hepatic impairment and development of hepato-carcinoma. NAFLD has shown a rapid increase in prevalence worldwide (25% in the global population) and is particularly important in subjects with obesity, metabolic syndrome and T2DM reaching 70% to 90% in these high-risk populations [3]. It is estimated that around 1.8 billion individuals have NAFLD worldwide [4]. Up to now, the best therapeutic approach for NAFLD consists in diet and exercise. This approach has proven an efficacy evidenced by improvement of liver biopsy [5]. However, these important lifestyle modifications are difficult to achieve and to sustain for the wide majority of the population [6]. Although the initial description was published in 1980 [7], its full spectrum and impact as a major chronic liver disease have only been recognized for the past 2 decades [8]. To date, no pharmacological agent has proven a clinically meaningful benefit/risk profile as potential drug for NAFLD, and, to date, no drug has been recognized as standard pharmacotherapy and approved in this indication. Hence, there is an unmet medical need for pharmacological agents for management of NAFLD patients.

The pathogenesis of NALFD is primarily driven by the progressive expansion of the adipose tissue secondary to poor lifestyle, triggering a low-grade inflammation state responsible for insulin resistance. Insulin resistance enhances fatty acids (FAs) release from the adipose tissue (lipolysis) towards the liver, FAs synthesis from carbohydrate in the liver (DNL), both promoting unexpected FAs accumulation in the liver (steatosis). Steatosis can stay uncomplicated for decades, but in a subset of subjects, inflammatory processes will develop leading to hepatocellular injuries and promoting fibrosis (steatohepatitis).

5' adenosine monophosphate-activated protein kinase (AMPK) is an energy sensor that regulates cellular metabolism in multiple peripheral tissues (liver, adipose tissue, muscle, pancreatic β cells…). When activated under low energy condition, AMPK stimulates catabolic pathways to produce energy (glucose uptake and lipid oxidation) while turning off energy consuming processes (gluconeogenesis and FA synthesis), in order to restore energy balance. In addition or in parallel to its metabolic effect, AMPK activation has been shown to have anti-inflammatory effects, improving the cellular functional environment. It is already well-established that AMPK activation by pharmacological compounds (metformin, thiazolidinediones), adipokines (leptin, adiponectin)

or physical activity causes many beneficial metabolic changes in subjects with metabolic syndrome. New drugs that directly activate AMPK are expected to improve both glucose and lipid homeostasis and may bring a substantial improvement in the treatment of NAFLD.

PXL770 is a new chemical entity from a new class of drug. It is a direct AMPK activator and is currently under development in the treatment of NAFLD.

2.2 PXL770

2.2.1 Non-clinical Information

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Corporate confidential information

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For the most comprehensive nonclinical and clinical information regarding the efficacy and safety of PXL770, please refer to the latest version of the Investigator's Brochure (IB) for PXL770. The term of "POXEL" used throughout the protocol refers to the Sponsor entities listed in the Contact Information page(s), which will be provided in *Annex 1. Sponsor, Coordinating Investigators, Investigators and Study Administrative Structure.*

2.3 Research Hypothesis

After 12 weeks of double-blind treatment, we aim to show superiority in liver fat mass reduction, assessed by MRI-PDFF, achieved with PXL770 compared to placebo in NAFLD patients.

3 Study Objectives

3.1 Primary Objective

To assess the effect of PXL770 versus placebo on hepatic steatosis in NAFLD patients at the daily dose of 250 mg QD and BID and 500 mg QD after 12 weeks of treatment

3.2 Secondary Objectives

- 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
- 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:
    - Liver enzymes
    - Lipid parameters
    - Glycemic parameters in fasting conditions
    - Biomarkers of inflammation
    - Biomarkers of fibrosis
    - Anthropomorphic parameters
- To compare the 2 doses regimens of PXL770 (BID versus QD) on efficacy and safety parameters in NAFLD patients
- 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.

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4 Study Design

4.1 Study Design and Schedule

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
- PXL700 250 mg BID
- PXL770 500 mg QD
- Placebo

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients)

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The diagram of the study design is shown in *Figure 1* and the visit schedule is tabulated in *Table 1* and in *Figure 2*.

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.

4.2 Rationale for Study Design, Doses and Control Group

This study is a phase IIa, multi-center, double-blind, placebo-controlled, randomized, parallel-group study in NAFLD patients to assess the efficacy, safety and tolerability of PXL770 administered as monotherapy, following International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP).

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5 Study Population

Each patient must meet all the applicable Inclusion criteria and none of the Exclusion criteria for this study. No waiver will be granted to this rule. Re-screening will not be allowed.

5.1 Inclusion Criteria

1. Capable of providing written informed consent. Male or female patients must have given written informed consent before any study-related activities are carried out
2. Age: ≥ 18 to ≤ 75 years at informed consent signature
3. BMI ≥ 25 to ≤ 50 kg/m^2 at Screening Visit (V1) and Randomization Visit (V3)
4. eGFR ≥ 60 mL/min/1.73m² at Screening Visit (V1) calculated by the CKD-EPI formulae
5. For patients with T2DM:
   - Either naïve of treatment with no glucose lowering drug for the last 12 weeks prior to Screening Visit (V1) or under stable oral glucose lowering drug (mono- or bi-therapy) for the last 12 weeks prior to Screening Visit (V1) (See non-permitted concomitant medications in exclusion criteria #25)
   - HbA1c ≤ 9.0% at Screening Visit (V1)
6. Not applicable – intentionally left blank for data management purposes (consistency in eCRF capture of eligibility criteria historically)
7. Hepatic steatosis:
   - Evidenced by TE with CAP ≥ 300 dB/m or by ultrasound or MRI, performed within the last 12 weeks prior to Screening Visit (V1). If none of these assessments are available prior to Screening Visit (V1), TE with CAP ≥ 300 dB/m should be evidenced at Run-in Visit (V2)
   - Confirmed by MRI performed within 8 ± 4 days prior to Randomization Visit (V3) with a PDFF value ≥ 10%
8. Women of child-bearing potential (e.g. not surgically sterile or not postmenopausal) must have a negative serum pregnancy test at Screening Visit (V1) and a negative urine pregnancy test at Randomization Visit (V3) and must use an adequate method of contraception or be sexually abstinent. Adequate method of contraception includes, but is not limited to: oral, intramuscular, or implanted hormonal contraception, sexual partner with non-reversed vasectomy (with azoospermia in 2 tests), 2 barrier methods (e.g. condom, diaphragm, or spermicide), intrauterine device
9. Male patients must have agreed on an effective contraception with their female partner

Patients who were screened failed due to ALT values as per protocol versions prior to version 5.0 can be rescreened one time for this study.

5.2 Exclusion Criteria

Exclusion criteria

Patients must not enter in the study and will not be randomized in the study if they fulfill any of the following Exclusion criteria:

1. Involvement in the planning and/or conduct of the study (applies to both POXEL and staff and/or staff at the study site)
2. Participation in another clinical study with intake of an investigational product during the last 12 weeks prior to Screening Visit (V1)
3. Previous participation in any clinical study with PXL770 intake

Target disease exclusions

4. Evidence of another form of liver disease including but not limited to viral hepatitis, autoimmune hepatitis, alcoholic disease, cholestatic liver disease, Wilson's disease, Alpha-1-antitypsin deficiency, hemochromatosis or DILI
5. Evidence of liver cirrhosis on laboratory assessment or TE ≥ 14 kPa at Run-in Visit (V2)
6. AST or ALT > 200 IU/L at Screening Visit (V1)
7. Evidence of hepatic impairment at Screening Visit (V1) as defined by the combination of at least two of the following parameters:
   - TBL ≥ 1.3 mg/dL
   - Serum albumin < 3.5 g/dL
   - INR ≥ 1.2
   - Platelets < 150 G/L
   - Hemoglobin < 11 g/dL in females or < 12 g/dL in males
   - Presence of ascites
8. Bariatric surgery of any kind at any time prior to Randomization Visit (V3) or change in body weight greater than 5% within the last 12 weeks prior to the Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3)
9. Positive serologic evidence of current infectious liver disease including HBsAg, and/or anti-HCV antibody with detected RNA at the Screening Visit (V1).
10. History of excessive alcohol intake defined by equal or greater than 21 units of alcohol/ week in males and equal or greater than 14 units of alcohol/ week in females for 2 years prior to the Screening Visit (V1), where a unit of alcohol is equal to 10 g pure alcohol.

Medical History and Concurrent Disease Exclusions

Cardiovascular diseases

11. Any of the following disease within 24 weeks prior to Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3):
    - Myocardial infarction
    - Cardiac revascularization surgery (CABG/PTCA)
    - Unstable angina

- Unstable CHF
- NYHA Class III or IV
- Transient ischemic attack, stroke or cerebrovascular disease

12. Unstable or undiagnosed arrhythmias, long QT syndrome, short QT syndrome, history of drug-induced Torsade de Pointe
13. Uncontrolled high BP: diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg with or without antihypertensive treatment at Screening Visit (V1)

Hematological and oncological diseases

14. Malignancy within 5 years prior to Screening Visit (V1) (with the exception of treated basal cell carcinoma or treated squamous cell carcinoma of the skin)
15. History of haemoglobinopathies (e.g., sickle cell anemia or thalassemia, sideroblastic anemia)
16. Patient who donated blood products to a blood bank or who received blood transfusion within 12 weeks prior to Screening Visit (V1) or between Screening Visit (V1) and Randomization Visit (V3)

Endocrinological disease

17. Diabetes other than T2DM
18. Uncontrolled hypothyroidism (TSH > 2 x ULN at Screening Visit (V1))

Other exclusion conditions

19. Immunocompromised patients such as patients that underwent organ transplantation or were diagnosed with HIV
20. Any other known serious disease (such as major infection, clinically significant gastrointestinal disorder, major autoimmune disease…) or other disease which in the Investigator's opinion would exclude the patient from the study
21. Any current drug addiction
22. Mental handicap, limited capacity of recognition, inability to follow the study procedures as evaluated by the Investigator, or any history of clinically important emotional and/or psychiatric illness
23. Anorexia or bulimia
24. Known hypersensitivity to any of the constituents or excipients of the IMP, or history of relevant drug and/or food allergies (e.g. anaphylactic, anaphylactoid reactions)
25. Use of non-permitted concomitant medication within 24 weeks prior to Screening Visit (V1) and at any time between the Screening Visit (V1) and the Randomization Visit (V3):
    - Pioglitazone, insulin, GLP1-RA, SGLT2-I, anticoagulants, amiodarone, bile salt chelators, methotrexate, equal or more than 400 U of vitamin E per day, corticosteroids with systemic effect, or any other medications known to affect liver function / steatosis at the Investigator's discretion, Corporate confidential information , any herbal drug or Chinese traditional medicines
26. Contraindications to MRI

- Such as patients with pacemakers, metallic cardiac valves, magnetic material such as surgical clips, implanted electronic infusion pumps or other conditions that would preclude proximity to a strong magnetic field
- History of extreme claustrophobia
- The patient cannot fit inside the magnetic resonance scanner cavity

27. Pregnancy or lactation

5.3 Restrictions during the Study

Patients must make every attempt to maintain the same diet/exercise treatment through the study.

Patients must be in a fasting condition at least 10 hours (during which only water is permitted) prior to all on-site study visits except at V2.

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To respect *Inclusion criteria #8*, women of child-bearing potential must immediately contact the Investigator if they suspect they might be pregnant or if they have changed, or plan to change their birth control method.

Patients should not donate blood or blood products, sperm or oocytes during the study.

Any modifications or deviations regarding these restrictions must be documented in the patient file.

5.4 Patients Incorrectly Enrolled in the Single-blind Placebo Run-in Period or Incorrectly Randomized

Patients who fail to meet the Inclusion/Exclusion criteria must not, under any circumstances, enter the Single-blind placebo Run-in period, or enter the Double-blind treatment period.

5.4.1 Patients Incorrectly Enrolled in the Single-blind Placebo Run-in Period

If a patient who does not meet the Inclusion/Exclusion criteria mistakenly enters the study and performs the Single-blind placebo Run-in period, the POXEL Medical Representative and the Medical Monitor should be immediately informed. This patient will be immediately withdrawn from the study and will be considered as screen failure.

5.4.2 Patients Incorrectly Randomized

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.

5.5 Criteria for Screen-failure

Patients who are withdrawn from the study between the Screening Visit (V1) and the Randomization Visit (V3) will be considered as screen failure.

Patients must be screen-failed in the event of any of the following:

1. Target hepatic steatosis not met (as defined in Section *5.1 Inclusion Criteria, Inclusion Criteria #7*)
2. Target eGFR not met (as defined in Section *5.1 Inclusion Criteria, Inclusion Criteria #4*)
3. Other Inclusion criteria not met (as defined in Section *5.1 Inclusion Criteria*)
4. Occurrence of an Exclusion criteria (as defined in Section *5.2 Exclusion Criteria*)
5. Occurrence of an AE or SAE which is clinically relevant and affects patient's safety, if withdrawal from the study is considered necessary by the Investigator or POXEL Medical Representative
6. Occurrence of pregnancy
7. Important protocol deviation if withdrawal from the study is considered necessary by the Investigator or POXEL Medical Representative/designee
8. Intake of non-permitted drug (as defined in Section *6.5 Non-permitted Medicines*) if withdrawal from the study is considered necessary by the Investigator or POXEL Medical Representative/designee
9. Withdrawal of patient informed consent
10. Lost to follow-up

The reason for screen failure must be documented in source documents and reported in the electronic Case Report Form (eCRF) and interactive web response system (IWRS). If more than one reason is given, the Investigator should make all efforts to establish the main reason.

Patients should return at study site to bring back the remaining IMP Run-in kits, the patient diary dispensed and the SMBG device, if applicable. The Investigator will perform the IMP accountability; verify the patient diary, AE and concomitant medications and SMBG measurements if applicable. The SMBG device will be kept by the patient after the end of his/her study participation if applicable. This information will be recorded in the patient file and in the eCRF.

Patients will then be referred to their physician for the pursuit of routine medical care.

5.6 Criteria for Withdrawal from the Study for Randomized Patients during the Double-blind Treatment Period

5.6.1 Criteria for withdrawal from the study

Patients may withdraw from the study at any time at their own request.

The Investigator must temporarily interrupt or permanently discontinue the IMP if continued administration of the IMP is believed to be detrimental to the patient well-being.

IMP should be discontinued and the patient should be withdrawn from the study in the event of any of the following:

1. Occurrence of an AE or SAE which is clinically relevant and affects patient's safety, if discontinuation of the IMP is considered necessary by the Investigator or POXEL Medical Representative
2. Occurrence of DILI (as defined in Section *8.3.8.2 DILI*)
3. Occurrence of pregnancy
4. Important protocol deviation if discontinuation of IMP is considered necessary by the Investigator or POXEL Medical Representative/designee
5. Intake of non-permitted drug (as defined in Section *6.5 Non-permitted Medicines*) if discontinuation of IMP is considered necessary by the Investigator or POXEL Medical Representative/designee
6. Requirement of an emergency unblinding (as described in Section *6.3.3.2 Emergency Unblinding*
7. Withdrawal of patient informed consent
8. Lost to follow-up
9. Sponsor decision (as defined in Section *5.7 Discontinuation of the Study*)

In case of temporary discontinuation of the IMP, the decision to resume the IMP should be taken in agreement by the Investigator, POXEL Medical Representative and Medical Monitor.

5.6.2 Procedure for withdrawal from the study

In the case of discontinuation of IMP for any reason listed in Section *5.6.1 Criteria for withdrawal from the study* except SAE leading to death and lost to follow-up**, patients will be asked to perform an Early Termination Visit within 11 days after the IMP discontinuation. At the Early Termination Visit, patients will be considered as withdrawn patients.** This visit will allow the Investigator to check the medical status of the patient and the patient to return all the IMP blister cards (used and unused), his/her patient diary and the SMBG device for review if

applicable. The SMBG device will be kept by the patient after the end of his/her study participation if applicable. Investigator will complete the eCRF (Early Termination Visit section).

The reason and date for withdrawal from the study must be documented in source documents, in the eCRF and reported in the IWRS. If more than one reason of study withdrawal is given, the Investigator should make all efforts to establish the main reason.

If there is any medical reason for withdrawal from the study, the patient will remain under the supervision of the Investigator until satisfactory health has returned. The Investigator must make every effort to collect the information related to the outcome of the event. This information is recorded in the part of eCRF dedicated to AEs. If the Investigator cannot organize a follow-up visit to collect this information, he/she must try to call the patient and/or his/her treating physician. If the IMP is discontinued as a result of a SAE, the procedure described in Section *8.3.6.4 Procedure for Reporting Immediately Reportable Events (IREs= SAEs and Pregnancy)* is to be implemented.

If patients are lost to follow-up, all reasonable means of contact must be used. In addition, a letter must be sent to the patient and a copy filed in the patient file (if allowed by site's Standard Operating Procedures). All the attempts (at least 3 by telephone by the Investigator or Clinical Research Coordinator (CRC) at study site) must be recorded in the patient file and reported in the eCRF.

Irrespective of the withdrawal reasons, any withdrawal is to be notified immediately to the Medical Monitor and Poxel Medical Representative.

5.7 Discontinuation of the Study

The whole study may be discontinued by POXEL in the event of any of the following:

- New information leading to unfavorable risk-benefit ratio of IMP, e.g. due to:
  - Occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of known adverse reactions, or
  - Other unfavorable safety findings
- POXEL's decision that continuation of the study is unjustifiable for medical or ethical reasons
- Poor enrollment of patients making completion of the study within an acceptable time frame unlikely
- Discontinuation of development of the POXEL's IMP

Competent Authorities and institutional review boards/ethics committees (IRBs/ECs) will be informed about the discontinuation of the study in accordance with applicable regulations.

The study may be terminated or suspended upon request of Competent Authorities.

5.8 Replacement Policy

Patients who withdrew from the study for any reason will not be replaced.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

According to the Article 2(d) of Directive 2001/20/EC, the definition of an "Investigational Medicinal Product (IMP)" is a pharmaceutical form of an active substance or placebo tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form" [9].

In this study, the terminology IMP refers both to PXL770 or placebo.

The IMP administered are Corporate confidential information The capsules are packaged in blisters. A description of the two types of capsules, PXL770 and placebo, is given in the IB [10].

All IMPs will be produced in accordance with Good Manufacturing Practice (GMP) and Annex 13 of GMP dedicated to IMP.

6.1 Description of Investigational Medicinal Product

PXL770 capsules will contain 250 mg of PXL770 plus the excipients. The active pharmaceutical ingredient is the Corporate confidential information . Placebo capsules will contain excipients alone, as described in the IB [10]. Both capsules have the same shape, size and appearance (including the same color, smell and taste).

6.2 Dosage and Administration

PXL770 and/or placebo capsules will be taken BID with a glass of water. An optimal interval between the two IMP intakes would be 12 ± 2 hours. The interval of IMP intakes must not be less than 6 hours.

To harmonize IMP intake, it is recommended to take IMP at least 15 min before a meal in the morning time and in the evening time.

No IMP should be taken in the morning at home before each on-site visit. IMP will be taken at study site after all visit assessments are performed as specified in *Table 1*.

Patients will be provided with the patient diary (paper format) as specified in *Table 1*. IMP intake (date and time) will be documented by the patients in the patient diary.

The patient diary is to be returned at each visit together with the IMP kit(s) (used and unused).

6.2.1 Single-blind Placebo Run-in Period

At Run-in Visit (V2), patients will start 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 from Run-In Visit (V2) to Randomization Visit (V3).

First dose intake of IMP will be taken by the patient in the evening time on the day of Run-in Visit (V2). Last IMP intake will be at study site on the day of Randomization Visit (V3) (morning time; after completion of all pre-dose assessments).

6.2.2 Double-blind Treatment Period

The Double-blind treatment period starts on the day of the Randomization Visit (V3) (evening time), following randomization to one of the 4 double-blind treatment groups in this study. On the day of Randomization Visit (V3), the first dose of Double-blind treatment period IMP will be taken by the patient in the evening.

To ensure a double-blind design, regardless of the treatment group, all patients will take an oral dose of 2 capsules BID of either placebo and/or PXL770 250 mg depending on the group they have been allocated to:

Table 2. Treatments to be administered in the 4 treatment groups

Treatment Group	Number of Capsules (Total = 4 Capsules/Day)
PXL770 250 mg QD (250 mg/day)	- 1 capsule of PXL770 250 mg + 1 capsule of placebo in the morning - 2 capsules of placebo in the evening
PXL770 250 mg BID (500 mg/day)	- 1 capsule of PXL770 250 mg + 1 capsule of placebo in the morning - 1 capsule of PXL770 250 mg + 1 capsule of placebo in the evening
PXL770 500 mg QD (500 mg/day)	- 2 capsules of PXL770 250 mg in the morning - 2 capsules of placebo in the evening
Placebo	- 2 capsules of placebo in the morning - 2 capsules of placebo in the evening

The Double-blind treatment period will last for 12 weeks after Randomization Visit (V3).

The last dose of each IMP kit should be taken by the patient at site in the morning of the visit after completion of all pre-dose assessments. Then, the first dose from the new IMP kits dispensed during the visit should be taken in the evening time on the day of the visit.

Last IMP intake will be at study site on the day of End-of-treatment Visit (V7) (morning time; after completion of all pre-dose assessments).

6.2.3 Follow-up Period

The Follow-up period starts at the end of the 12-week Double-blind treatment period. At the End-of-treatment Visit (V7), patients will not receive an IMP kit and consequently they will not take IMP during the follow-up period.

The Follow-up period will last for 1 week.

6.3 Treatment Assignment and Blinding

Allocation of patients to treatment groups will proceed through the use of an IWRS and will be performed according to the IWRS manual.

6.3.1 Patient Numbering

Patients will be identified during the whole study (V1 to V8) by a patient number assigned at Screening Visit (V1).

The patient number consists of a unique 5-digit number using the schema XX-YYY. The first 2 digits (XX) indicate the pre-defined study site number. The last 3 digits (YYY) identify the patient within the study site. The first patient entered in a study site will be assigned the number 001, the second will be assigned the number 002, and so on. For example, patient 04-001 will be the first patient screened at study site 04. So that each patient is numbered uniquely across all clinical databases (IWRS, eCRF…).

Upon ICF signature by the patient and the Investigator, the Investigator (or designee) will register the patient in the IWRS. The patient number will be created and allocated automatically by the IWRS. Once assigned, the patient number must not be reused for any other patient and the patient number for this patient must not be changed.

6.3.2 Treatment Assignment or Randomization

Single-blind placebo Run-in period

At Run-in Visit (V2), once eligibility criteria have been checked by the Investigator, the Investigator (or designee) will log on to the IWRS to confirm the patient eligibility and enter the patient into the Single-blind placebo Run-in period for 4 weeks.

Double-blind treatment period

At Randomization Visit (V3), after re-confirming the eligibility criteria, the Investigator (or designee) will log on to the IWRS to re-confirm the eligibility and enter the patient into the Double-blind treatment period. Patients will be randomized in a 1:1:1:1 ratio to receive either PXL770 250 mg QD, 250 mg BID, 500 mg QD or placebo for 12 weeks.

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients) at Randomization Visit (V3) : Corporate confidential information

Patients will be assigned a unique randomization number at the Randomization Visit (V3) by IWRS. This randomization number identifies which record in the randomization list and therefore which treatment will be allocated to the patient.

The randomization list will be generated and kept by the statistical department by a statistician independent of the project team. A copy will be provided to in charge of medication packaging and logistics, and to the bioanalytical laboratory in charge of the PK assessments on samples from patients receiving PXL770.

During the Double-blind treatment period, at each on-site visit (except at Week 2 (V4)) after all visit assessments and safety evaluation are performed, the Investigator (or designee) will log on to the IWRS for IMP kit allocation.

All confirmation reports generated by IWRS must be stored at least in the patient file.

6.3.3 Treatment Blinding

6.3.3.1 Method of Blinding

The study will be conducted using a Double-blind design with a placebo capsule that has the same shape, size and appearance (including the same color, smell and taste) as the PXL770 capsules. Whatever the dose group they will be assigned to, patients will receive the same number of capsules (PXL770 and/or placebo) in order to keep the blind, both during the Single-blind placebo Run-in period and the Double-blind treatment period.

PXL770 and placebo capsules will be identical in packaging, labelling, schedule of administration and appearance. Traceability of the IMP kit content is ensured by the IMP kit number and the randomization list.

Blinded IMP will be assigned according to a computerized randomization list using the IWRS. The IWRS will assign IMP kits containing blinded medication for each patient at each visit requiring IMP kit dispensation.

6.3.3.2 Emergency Unblinding

Only in case of emergency, the Investigator is authorized to access the IWRS's randomization system using the randomization code break provided at the beginning of the study.

Code-breaking can be accessed via internet. The exact description of the treatment assigned to the individual patient will be accessible. A code-break can thus be made for any patient without affecting the double-blind nature of the study. Patients IMP information may only be accessed in the event of an emergency and out of necessity to know the identity of the allocated IMP in order to institute appropriate therapeutic management. The Investigator is obliged to make every effort to discuss the code-break with POXEL before code breaking. **Once the code is broken for a patient, this patient must discontinue IMP, perform Early termination Visit and withdraw from the study.**

In the event that a code-break is performed, the Investigator will receive a confirmation by email from IWRS. The Investigator must document on the confirmation printout the reason for the code-break, and sign the document. The document has to be kept in a safe place until the end of the study. Once a code has been broken, the Investigator must confirm the unblinding to the Clinical Research Associate (CRA), the Medical Monitor and the Poxel Medical Representative within 24 hours in writing.

POXEL and / or its designee(s) will also receive an authorization to access IWRS's randomization information and will be attributed a specific access code that can be used if a suspected Serious Adverse Reaction (SAR) occurs, to assess the expectedness of the reaction. Suspected Unexpected Serious Adverse Reactions (SUSARs) need to be reported according to regulatory requirements (see Section *8.3.6.4 Procedure for Reporting Immediately Reportable Events (IREs = SAEs and Pregnancy)*).

6.4 Concomitant Medications and Therapies

The use of any systemic medication will be restricted during the study, with the exception of ongoing authorized medications, and/or potential medications that could be required for the patient's welfare, apart from contra-indicated medications as listed in Section *6.5 Non-permitted Medicines*.

As far as possible, no change should be made to the dosing of these concomitant medications from the ICF signature to the End-of-study Visit (V8). Patients must not take any unlicensed medication, i.e. other investigational drugs except PXL770 or placebo, during their participation in the study.

Medications taken within 28 days prior to ICF signature and stopped before or on ICF signature date will be considered as prior medication.

Medications that are ongoing before and continue after the ICF signature will be considered as concomitant medication.

Medications that will be prescribed during the study (from the ICF signature to End-of-study Visit (V8)) will be considered as new medication.

Any concomitant medication must be recorded in the corresponding section of the eCRF, its dose, dosage form, frequency, date of onset and stop date of the medication, indication, reason and route used. Patients should inform the Investigator of any change in their usual treatment and any change should be recorded. All patients will be questioned about concomitant medication at each study visit.

6.5 Non-permitted Medicines

Patients must not take any of the following licensed medication within the 24 weeks prior to the Screening Visit (V1):

- Pioglitazone
- Insulin
- GLP1-RA
- SGLT2-I
- Anticoagulant agents
- Amiodarone
- Bile salt chelators
- Methotrexate
- Equal or more than 400 U of vitamin E per day
- Corticosteroids with significant systemic effect (e.g. oral or intravenous administrations)
- Any other medications known to affect liver function / steatosis at the Investigator's discretion

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- Any herbal drug or Chinese traditional medicines

If, during the study, the administration of a non-permitted concomitant drug occurs or becomes necessary, e.g. because of AE, the Investigator together with the POXEL Medical Representative and Medical Monitor will decide whether the patient can continue the IMP.

6.6 Packaging and Labeling

PXL770 and placebo capsules will be packaged in appropriate blister and will be labeled in English with respect to the regulatory requirements in the US.

Blister: A blister contains 32 capsules corresponding to 8 days of BID treatment. The morning and evening doses will be clearly identified. The patient must strictly follow these indications.

IMP kit: An IMP kit contains 4 blisters (128 capsules – 32 days).

- During the Single-blind placebo Run-in period, 1 IMP kit containing 4 blisters (total of 4 blisters – 128 capsules – 32 days) will be dispensed at Run-in Visit (V2).
- During the Double-blind treatment period, 1 IMP kit containing 4 blisters (total of 4 blisters – 128 capsules – 32 days) will be dispensed at each dispensing visit.

IMP kit numbering

The IMP kit number will identify medication packs.

Packaging and labeling will be in accordance with applicable US regulatory requirements.

6.7 Management of IMP

The Investigator (or designee) will be responsible for the IMP storage, dispensing, stock inventory, accountability and return in the view of destruction of all IMP kits.

6.7.1 Shipment of IMP

The depot will store and supply IMPs to the study sites. The shipments will contain the IMP kits as agreed upon for the timely completion of the clinical study, once the necessary regulatory documents have been received.

6.7.2 Supply and Receipt of IMP

Upon receipt of IMP, the Investigator (or designee) will check for accurate delivery and acknowledge receipt via IWRS. The receipt and inventory of IMP in the study site is tracked in IWRS. Furthermore, IMP stock at study site must be followed and documented by the Investigator (or designee) on a Master Accountability log throughout the whole duration of the study.

IMP resupply will be managed automatically through IWRS.

6.7.3 Storage of IMP

The Investigator (or designee) will ensure that all IMPs are stored under recommended storage conditions and in accordance with applicable US regulatory requirements. IMP must be carefully and safely stored at the study site, and separately from other drugs, in a locked area under the responsibility of the Investigator (or designee). Only the Investigator (or designee) will have access to this room.

The storage condition of IMP will be indicated in the pharmacy manual.

The Investigators (or designee) are reminded to check temperature daily (e.g. manually) and before the first dispensation of the day, at least on every working day (i.e. manually or by using alarm system to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of IMP. Any temperature excursions should be addressed according to the procedures described in the pharmacy manual.

Under no circumstances, the Investigator is allowed to use IMP in conditions other than described in the protocol and the pharmacy manual otherwise the insurance coverage will become null and void.

It must be ensured at the study site that IMP is not dispensed to a patient with an expiry date prior to the date of the patient's next on-site visit. The IMP expiry date might be extended after the drug stability has been re-analyzed. In such case, IMP should then be re-labeled before dispensation. The re-labeling of the medication will be performed by an authorized person at the US depot, following appropriate instructions and documented. Further details of procedures will be described in the pharmacy manual.

6.7.4 Dispensing, Accountability and Compliance of IMP

IMP dispensing

Only the IMP kit number assigned by the IWRS will be dispensed to the patient. The dispensing of the IMP will be carefully recorded on the appropriate drug accountability logs provided by

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IMP accountability

The Investigator (or designee) must maintain an accurate record as follows:

- Master Accountability log recording IMP receipt, dispensing and return by the CRA to the depot for destruction. The global stock at study site level must be carefully tracked and documented on this log. The Investigator (or designee) should ensure that this stock is consistent with the inventory described in IWRS.

- Subject Accountability log recording IMP dispensing and IMP return by patient detailed in terms of number of capsules.

For both logs, dates, quantities, dose, batch numbers, expiry dates and initials of the Investigator (or designee) must be recorded.

The supplies, inventory and accurate IMP documentation must be available for monitoring visit, audit by the designated representatives of POXEL or inspection by regulatory authorities, upon request.

Any unused IMP must not be discarded or used for any other purpose than the present study. IMP that has been dispensed to a patient must not be re-dispensed to the patient neither to a different patient.

IMP compliance

Compliance will be calculated by the Investigator (or designee) from Run-in Visit (V2) to Randomization Visit (V3) for the Single-blind Run-in period and from Randomization Visit (V3) to End-of-treatment Visit (V7) (from Day 0 to Week 12) for the Double-blind treatment period based on the patient diary and IMP kits returned by the patient.

The Investigator (or designee) must document the IMP compliance in source document and in the eCRF. In case of inconsistency between data in the patient diary and IMP returned, the Investigator (or designee) should question the patient and the reported compliance will be based on Investigator judgment.

The compliance will be calculated using the following formula based on the medication returned:

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

* 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.

The acceptable 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 during Double-blind treatment period) and the Investigator must remind the patient to follow the IMP instructions.

6.7.5 Return and Destruction of IMP

The Investigator (or designee) will reconcile capsules returned by the patients with the Subject Accountability Logs. The CRA will verify and confirm this reconciliation by checking IMP accountability logs and all IMP returns (both unused and used kits). Thereafter, the CRA will place IMP kits in sealed containers to be sent to a predefined location designated by POXEL, for interim storage. The description of IMP kits returned will be recorded on a form completed by the CRA and signed by the Investigator (or designee). The allowed number of sealed container returns by the study site is described in the pharmacy manual.

Upon database lock and after green light from POXEL, the company in charge of IMP destruction will proceed with IMP kits destruction (both unused and used). They should provide certificates of destruction including but not limited to destruction dates, quantities and batch numbers.

6.8 Overdose

The packaging has been designed to prevent any overdose with a clear indication on the blisters of the morning and evening dose to be taken per day. Moreover, to limit the risk of overdosing while still allowing some flexibility in the Double-blind treatment period duration, only 1 extra daily dose is available per week. In total, 4 extra daily doses are provided between 2 on-site visits (4 weeks). For Week 2 (V4, 2 weeks after randomization), patients will have to come at the visit with the IMP kit but no other kit will be provided. Patients will continue to use the IMP kit provided at Randomization Visit (V3) until Week 4 (V5, 4 weeks after randomization).

6.8.1 Preclinical and Clinical Status

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6.8.2 Overdose Definition

Based on available data, an overdose is considered as any dose greater than the highest daily dose administered as single or repeated doses in the phase I study

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However, this study will be blinded during the Double-blind treatment period. As 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 capsules administered over a defined period of time.

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Error in dosing schedule may happen as for instance misdosing (i.e. 4 capsules QD in place of 2 capsules BID). In such cases, dosing error will be recorded in the patient file by the Investigator and reported as a protocol deviation by the CRA. Patient will be retrained by the Investigator and it will be documented in source documents.

In any case, these overdoses based on number of capsules will need to be confirmed at the end of the study, once unblinding and identification of the treatment group will allow real dose calculation.

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Conclusion on overdose will be included in the final study report.

6.8.3 Reporting

Any suspicion of overdose, when occurring in the Double-blind treatment period, whether or not associated with an AE (serious or non-serious) must be reported to POXEL in an expedited manner.

6.8.4 Treatment

No specific antidote is currently available for PXL770 and only symptomatic therapy is possible.

7 Study Procedures

At each visit, it will be recommended to perform the assessments in the following order: ECGs, vital signs and blood samplings. Blood sampling for PK analysis should be collected nearest to the scheduled time point.

7.1 Screening Period, Screening Visit (V1): On-site Visit

Eligible patients (see definition in section *5.1 Inclusion Criteria*) will be informed about the study in detail and sign the ICF prior to any study-related procedure. Re-screening will not be allowed.

The Screening period starts from the date of ICF signature.

On the basis of the findings from the assessments made at this visit, the Investigator will decide whether the patient is to be included in the study.

The following procedures will be completed:

- Obtain written ICF
- Register the patient in the IWRS to retrieve his/her patient study number
- Review Inclusion and Exclusion criteria
- Obtain demography (year of birth, age, gender, ethnic origin, race, child-bearing potential if woman)
- Obtain complete medical history (including liver disease history, diabetes history, history of drug abuse, alcohol and tobacco consumption)
- Collect AE
- Obtain complete prior and concomitant medication history of all prescription or nonprescription drugs, dietary and herbal supplements taken within 28 days prior this visit
- Conduct complete physical examination including height, weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine single 12-lead ECG
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG and HbA1c
    - Standard safety laboratory panel (blood and urine)
    - eGFR using the CKD-EPI formula

- Serum pregnancy test (if applicable)
- Viral infection screen panel

- Dispense patient emergency card

In case the patient is not fasting in the morning of the Screening Visit (V1), the visit should proceed according to the protocol description, with the exception of the laboratory sampling which can be postponed up to 3 days later. The reason for this should be carefully mentioned in the patient file.

7.2 Single-blind Placebo Run-in Period, Run-in Visit (V2): On-site Visit

Run-in Visit (V2) will take place within maximum 2 weeks after the Screening Visit (V1).

The following procedures will be completed:

- Log on to IWRS to confirm patient eligibility and retrieve IMP kit number assigned by the system
- Review Inclusion and Exclusion criteria
- Collect AE
- Collect concomitant medication
- Conduct limited physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform Transient elastography. If required as per inclusion criterion #7, this TE should include CAP measurement
- Dispense placebo capsules for 4 weeks and patient diary
- Dispense self-monitoring blood glucose (SMBG) device only for T2DM patients

During the Single-blind placebo Run-in period starting from V2 to V3, the patient must undergo an MRI with PDFF evaluation within 8 ± 4 days prior to Randomization Visit (V3).

7.3 Double-blind Treatment Period

7.3.1 Randomization Visit (V3) (Day 0): On-site Visit

Randomization Visit (V3) will take place 4 weeks (± 2 days) after the Run-in Visit (V2).

The following procedures will be completed:

- Log on to IWRS to confirm patient eligibility and retrieve IMP kit number assigned by the system
- Review Inclusion and Exclusion criteria **including review of MRI-PDFF performed within 8 ± 4 days prior to this visit**

- Collect AE
- Collect concomitant medication
- Conduct complete physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG and HbA1c
    - Standard safety laboratory panel (blood and urine)
    - eGFR using the CKD-EPI formula
    - Urine pregnancy test (if applicable)
    - Measured metabolic parameters
    - Calculated metabolic parameters
    - Inflammatory biomarkers
    - Fibrosis biomarkers
    - Biobanking sampling
    - Blood sampling for DNA/RNA (only for patients who have signed the additional, specific consent form)
- Review the patient diary dispensed at Run-In Visit (V2)
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for the period Run-In Visit (V2) to Randomization Visit (V3)
- Dispense placebo and/or PXL770 capsules for 4 weeks and patient diary

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7.3.2 Week 2 (V4): On-site Visit

Week 2 (V4) will take place 2 weeks (± 2 days) after Randomization Visit (V3).

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- Collect AE
- Collect concomitant medication
- Conduct limited physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG
    - Standard safety laboratory panel (blood and urine)
    - Urine pregnancy test (if applicable)
    - PK sampling
- Review the patient diary dispensed at Randomization Visit (V3)
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for the period Randomization Visit (V3) to Week 2 (V4)

7.3.3 Week 4 (V5): On-site Visit

Week 4 (V5) will take place 4 weeks (± 2 days) after Randomization Visit (V3).

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Collect AE
- Collect concomitant medication
- Conduct limited physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG
    - Standard safety laboratory panel (blood and urine)

  - Urine pregnancy test (if applicable)
  - Measured metabolic parameters
  - Calculated metabolic parameters
  - PK sampling
- Review the patient diary dispensed at Randomization Visit (V3)
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for the period Week 2 (V4) to Week 4 (V5)
  - Dispense placebo and/or PXL770 capsules for 4 weeks and patient diary

7.3.4 Week 8 (V6): On-site Visit

Week 8 (V6) will take place 8 weeks (± 3 days) after Randomization Visit (V3). The interval between V5 and V6 must not exceed 32 days.

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Collect AE
- Collect concomitant medication
- Conduct limited physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
  - hsCRP
  - FPG
  - Standard safety laboratory panel (blood and urine)
  - Urine pregnancy test (if applicable)
  - Measured metabolic parameters
  - PK sampling
- Review the patient diary dispensed at Week 4 (V5)
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for the period Week 4 (V5) to Week 8 (V6)
- Dispense placebo and/or PXL770 capsules for 4 weeks and patient diary

7.3.5 Week 12 – End-of-treatment Visit (V7): On-site Visit

End-of-treatment Visit (V7) will take place 12 weeks (± 4 days) after Randomization Visit (V3). The interval between V6 and V7 must not exceed 32 days.

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- Collect AE
- Collect concomitant medication
- Conduct complete physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs

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- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG and HbA1c
    - Standard safety laboratory panel (blood and urine)
    - Urine pregnancy test (if applicable)
    - eGFR using the CKD-EPI formula
    - Measured metabolic parameters
    - Calculated metabolic parameters
    - Inflammatory biomarkers
    - Fibrosis biomarkers
    - Biobanking sampling (including optional collection of blood sample for DNA/RNA (only for patients who have signed the additional, specific consent form)
- Perform PK samplings at pre-dose :

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- Perform MRI with PDFF evaluation before or on the day of Week 12 (V7), i.e. 84 days (- 4 days) after Randomization Visit (V3)
- Review the patient diary dispensed at Week 8 (V6)
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for the period Week 8 (V6) to End-of-treatment Visit (V7)

7.4 Follow-up Period, End-of-study Visit (V8): On-site Visit

End-of-study Visit (V8) will take place 1 week (± 2 days) after End-of-treatment Visit (V7).

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- Collect AE
- Collect concomitant medication
- Conduct complete physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG
    - Standard safety laboratory panel (blood and urine)
    - Serum pregnancy test (if applicable)
    - PK sampling
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations
- Refer patient to his/her previous physician for the pursuit of his/her routine medical care

7.5 Withdrawal of Patients (Early termination Visit): On-site Visit

The following procedures will be completed during an on-site visit within 11 days after the IMP discontinuation:

- Log on to IWRS to register patient withdrawal date
- Collect AE
- Collect concomitant medication

- Conduct complete physical examination including weight, BMI, waist and hip circumferences
- Record supine vital signs (BP and HR)
- Perform standard supine triplicate 12-lead ECGs
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - hsCRP
    - FPG and HbA1c
    - Standard safety laboratory panel (blood and urine)
    - eGFR using the CKD-EPI formula
    - Serum pregnancy test (if applicable)
    - Measured metabolic parameters
    - Calculated metabolic parameters
    - Inflammatory biomarkers
    - Fibrosis biomarkers
- Review the patient diary dispensed at the previous visit
- For T2DM patients, review SMBG measurements performed according to the Investigator (or designee) recommendations.
- Record IMP compliance for previous period
- Refer patient to his/ her previous physician for the pursuit of his/her routine medical care

8 Study Assessments

Every effort should be made to ensure that protocol-required tests and procedures are completed as described.

8.1 Blood Volume

The total blood sampling volume for individual patients in this study will be described in the central laboratory manual.

Additional blood samples may be taken for safety assessments at times specified by the Investigator (in case of safety issue for example) with the agreement of POXEL Medical Representative.

8.2 Efficacy Assessment

8.2.1 Liver fat mass assessed by MRI-PDFF – Central imaging core lab

The primary evaluation of efficacy will be based on MRI-PDFF. This primary endpoint will be the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (End-of-treatment Visit, V7).

As key secondary efficacy endpoints, the (absolute) change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7) and the percentage of responders defined by the percentage of patients who achieve a clinically meaningful reduction of at least 5 % (≥ 5%) in absolute liver fat mass as measured by MRI-PDFF at Week 12 (V7) will be also compared between placebo and PXL770 groups.

Local MRI facilities in each study site will complete a qualification and quality assurance process prior to perform MRI acquisitions. MRI scans will be then performed on qualified and standardized devices at high field strength (either 3 or 1.5 Tesla) without enhanced contrast agents. MRI-PDFF acquisition protocols will include the acquisition guidelines for multi-echo PDFF sequence for most common manufacturers (GE, Siemens, Philips) and field strength (1.5T and 3.0T). All acquisitions images will be transferred to the Core Laboratories for central calculation and measurement of MRI-PDFF using a validated and established technique. The imaging submission manual will provide sites with information on data submission to Core Laboratories. Central readings will be performed by masking study sites, timepoints, clinical data and treatment groups information.

Fat mass results of MRI-PDFF at Randomization Visit (V3) and Week 12 (End-of-treatment Visit, V7) will be blinded for Investigators and POXEL until database hard lock.

MRI-PDFF technique will be exclusively used for assessment of liver fat mass. The image acquisition technique and programmable sequences used for MRI-PDFF in the study will restrict the obtainable diagnostic information to liver fat quantity and will not support its use for other clinical purposes.

Please refer to central imaging core lab manual for further details.

8.2.2 Other Efficacy Parameters

The following parameters will be also determined at various timepoints to further assess efficacy:

- Liver enzymes: ALT and AST
- Measured metabolic parameters: FPG, HbA1c, serum insulin, C-peptide, total cholesterol, HDL-c, LDL-c, triglycerides, Apo A1, Apo B, FFA, glycerol and adiponectin
- Calculated metabolic parameters: HOMA-IR, QUICKI, HOMA-β, Adipo-IR

  The homeostasis model assessment of insulin resistance (HOMA-IR), the quantitative insulin sensitivity check index (QUICKI) and the homeostasis model assessment of β-cell function (HOMA-ß) will be calculated using the fasting insulin and FPG values at visits specified in *Table 1*. The adipo-IR will be calculated using fasting insulin and fasting FFA.

  - The HOMA-IR is calculated as [11]:
    Fasting insulin (µIU/mL) × FPG (mg/dL) / 405
  - The QUICKI is calculated as [12]:
    1 / (log (FPG (mg/dL)) + log (Fasting insulin (µIU/mL)))
  - The HOMA-ß is calculated as [11]:
    (Fasting insulin (µIU/mL) × 360) / (FPG (mg/dL) – 63)
  - The Adipo-IR is calculated as [13]:

    Fasting FFA (mmol/L) x Fasting insulin (µIU/mL)

  To minimize the variability in insulin concentration, two blood samples should be collected at a 10-min interval at each timepoint these metabolic parameters are calculated. In the above formulas, the mean of the two insulin results will be used.
- hsCRP and other biomarkers of inflammation: fibrinogen and MCP-1
- Fibrosis biomarkers: NAFLD Fibrosis score (NFS) and Fib-4 score

  The NFS is based on a combination of clinical and laboratory measurements (i.e. age, glycemia, BMI, platelet, albumin and AST/ALT ratio). This score has been validated in a large cohort of patients with biopsy-proven NAFLD (> 700 patients) [14].

  - NFS is calculated as [14]:
    1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m²) + 1.13 x Impaired Fasting Glucose or Diabetes (yes =1; no=0) + 0.99 x AST/ALT ratio – 0.013 x platelet (10^9/L) – 0.66 x albumin (g/dL)

The Fib-4 score is based on a combination of clinical and laboratory (i.e. age, platelets, AST, ALT). This score has been created and validated in different cohorts of patients [15, 16].

- Fib-4 score is calculated as [15]:
  (Age (years) x AST (U/L))/ (platelet (10^9/L) x √(ALT (UI/L)))

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

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8.3 Safety

8.3.1 Physical Examination

Physical examination must be conducted by the Investigator.

A complete physical examination will include head, ears, eyes, nose, mouth, skin, heart 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.

Physical examinations (complete and limited) will also include height, weight, BMI, waist and hip circumferences for Screening Visit (V1) and weight, BMI, waist and hip circumferences for other visits as planned in *Table 1.*

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.

For weight measurement, a scale with appropriate resolution will be used and should be placed on a stable, flat surface. Patients should remove shoes, bulky layers of clothing, and jackets so that only light clothing remains.

8.3.2 Vital Signs

One HR measurement will be taken after the patient has been rest in supine position for at least 10 minutes and before blood samples are taken. The HR measurement will be followed by 3 BP measurements, using a standardized cuff adapted to the size of the patient's arm. BP readings will be taken with patients comfortably in a supine position with the arms raised to the level of the heart and in a supported position. All readings should be recorded as accurately as possible and the same BP device and the same patient's arm (preferentially the left arm) should be used for all assessments for a given patient.

All 3 readings have to be recorded in the source documents and reported in the eCRF. For analysis, the average of the 3 BP readings will be used.

8.3.3 Patient Diary

Patient diary will be dispensed according to *Table 1.*

Patients will be asked to report their IMP intakes (date + dose + time) and meal taken after IMP intakes (date + time). Any new AE or concomitant medications should be reported by the patient on the diary.

At each visit, the Investigator will review the patient diary dispensed at the previous visit and will report in eCRF the appropriate data. To confirm the review, the Investigator will have to sign and date the previous patient diary and it will be kept in the patient file.

8.3.4 Supine 12-Lead ECG

A 12-lead ECG (I, II, III, aVR, aVL, aVF, V1-V6) will be performed at the visits shown in the Visit Schedule Chart in *Table 1* after the patient has been lying down resting for at least 10 minutes. Standard 12-lead digital ECGs will be recorded as single measurement at Screening Visit (V1) and in triplicate, at least 1 minute apart at all other visits. The ECG printout or electronic record will be evaluated by the Investigator and reported as "Normal" or "Abnormal" in the source documents and in the eCRF. If the ECG is evaluated as "Abnormal" the Investigator should document in the source documents as well as in the eCRF, the specific abnormality and if this abnormality is "clinically significant" or "not clinically significant". ECG printouts or electronic record will include date, time, patient number, and date/signature of the Investigator who reviewed the ECG. The ECG printouts or electronic records will be kept in the patient file.

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.

All 12-lead ECGs will be sent to for a centralized interpretation *a posteriori* by cardiologists.

8.3.5 Laboratory Assessments

All laboratory measurements will be performed at central laboratory using samples collected at the visits shown in the Visit Schedule Chart in *Table 1*. However, if judged necessary for the safety of the patients, the Investigator or POXEL may request unscheduled central laboratory assessments.

Blood samples will be collected, handled and stored according to the instructions described in the central laboratory manual.

A list of normal reference ranges will be provided by the central laboratory to POXEL and the Investigators before the study start. Any change in the normal reference ranges during the study will be forwarded by the central laboratory to POXEL and the Investigators, who will have to keep it in the Trial master file (TMF) and respectively, in the Investigator site file (ISF).

Central laboratory reports must be reviewed by the Investigator as soon as received. Each parameter must be assessed by the Investigator and the clinical significance of the abnormal parameters must be documented. To confirm the review, the Investigator will have to sign and date the report and keep it in the patient file.

The following panel will be evaluated.

8.3.5.1 Standard Safety Laboratory Panel (Blood and Urine)

Hematology	Biochemistry	Urinalysis
Erythrocytes Hemoglobin Hematocrit 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 Gamma-glutamyl transferase Total bilirubin Alkaline Phosphatase (ALP) Amylase Lipase TSH (at Screening Visit (V1) 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		
aPTT PT INR		

8.3.5.2 Viral Infection Screen Panel

Hepatitis screening	HIV screening
HBsAg Hepatitis C virus antibody (anti-HCV), in case of positive result, reflex test of HCV circulating RNA	Anti-HIV 1 and 2

8.3.5.3 eGFR

eGFR will be calculated using the CKD-EPI formula, as follows [18]:

$$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

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.

8.3.5.4 Serum and urine Pregnancy Test

For female patients of child-bearing potential only, a serum or urine β-HCG test will be performed at the visits shown in the Visit Schedule Chart in *Table 1.*

8.3.6 Adverse Events

Comprehensive assessment of AE experienced by the patient will be performed throughout the course of the study, from the time of the patient's ICF signature.

It is of the utmost importance that all staff involved in the study is familiar with the content of this section. The Investigator is responsible for ensuring this.

8.3.6.1 Adverse Event Definitions

8.3.6.1.1 Adverse Event

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 a medicinal, whether or not considered related to the medicinal product.

The official definition also extends to AEs occurring under placebo or in a reference group receiving drug or non-drug therapy. Because of regulatory requirements, events occurring during drug-free and pre- and post-treatment periods should also be designated as AEs.

Therefore, safety surveillance applies to the time when the patient is included into the study (date of ICF signature) until the End-of-study Visit (V8) performed one week after the End-of-treatment Visit (V7).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity/intensity of each AE.

8.3.6.1.2 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered ADR.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility e.g., the relationship cannot be ruled out.

8.3.6.1.3 Serious Adverse Event (SAE)

A SAE is an AE occurring during any study phase (i.e., Screening, Run-in, Treatment, Follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening

  NOTE: The term "life-threatening" in this definition refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of ICF. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AE and assessed for seriousness.

  Admission to the hospital for social or situational reasons (e.g. no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered as medically important

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include:

- allergic bronchospasm requiring intensive treatment in an emergency room or at home
- angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- blood dyscrasias (e.g. neutropenia or anemia requiring blood transfusion, or convulsions that do not result in inpatient hospitalization)
- development of drug dependency or drug abuse

Events that do not meet the definition of an SAE

Elective hospitalizations to simplify study treatment or study procedures are not considered as SAE. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g. undesirable effects of any administered treatment) must be documented and reported as SAE.

Events not to be considered as AE/SAE

Medical conditions present at the informed consent visit that do not worsen in severity or frequency during the study are defined as baseline medical conditions and are NOT to be considered as AEs.

Abnormal laboratory findings and other abnormal investigational findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG tracing) should not be reported as AE unless they are associated with clinical signs and symptoms, lead to IMP discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g. anemia, pancreatitis) must be reported as the AE rather than the abnormal value itself.

8.3.6.2 Methods of Recording and Assessing Adverse Events

All AEs will be collected from the time of ICF signature to the End-of-study Visit (V8). All AEs will be followed until the event has resolved or the condition has stabilized or until the database hard lock if not resolved or stabilized before.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the eCRF.

The following aspects must be recorded for each event in the source documents and in the eCRF for AE:

- A description of the AE in medical terms, not as reported by patients (AE verbatim)
- The date and time of onset (start date and time)
- The date and time of recovery (stop date and time)
- The grade as assessed by the Investigator according to the following definitions:
    - Mild (awareness of event but easily tolerated)
    - Moderate (discomfort enough to cause interference with usual activity)
    - Severe (inability to carry out usual activity)
- Seriousness: yes or no
- The causal relationship to IMP as assessed by the Investigator; the decisive factor in the documentation is the temporal relation between the AE and the IMP. The following judgments of the causality to IMP or study procedures are to be used:

  - Unrelated: IMP cannot be reasonably suspected, a reasonable explanation must be given
  - Related: IMP can be reasonably suspected. AE could medically (pharmacologically/clinically) be attributed to the IMP
- Action taken on IMP (no change, temporary interruption, permanent discontinuation, not applicable)
- Other actions (none, corrective treatment, hospitalization or prolongation of hospitalization, other)
- The outcome and date of outcome according to the following definitions:
  - Recovered/resolved (AE disappeared)
  - Recovering/resolving (patient is recovering)
  - Not recovered/not resolved (AE remains without signs of improvement)
  - Recovered/resolved with sequelae
  - Fatal
  - Unknown (only applicable if patient has been lost to follow-up)

The following aspects must be recorded in the source documents and in the eCRF for SAE:

- A SAE medical term
- A description of the SAE in medical terms, not as reported by patient; only the term(s) that fulfills the seriousness criteria should be listed (including sequence of events, symptoms, diagnosis, treatment and any other relevant information)
- The seriousness criteria, according to Section *8.3.6.1, Adverse Event Definitions*
- The date of onset
- The outcome according to criteria already mentioned
- Causality assessed by the Investigator according to the criteria already mentioned
- Date and time of last IMP intake prior to SAE

If a patient experienced several times the same AE along his/her participation in the study, then this AE must be documented and assessed as a new AE each time.

Each AE will be classified using the Medical Dictionary for Regulatory Activities (MedDRA®).

8.3.6.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the patient is included into the study (date of first ICF signature) and continues through the end of the study's post-treatment Follow-up period, defined as the End-of-study Visit (V8). In case any AE occurs, the Investigator will follow

up the patient until the event has resolved or the condition has stabilized. All SAEs that the Investigator considers related to IMP occurring after the post-treatment Follow-up period must be reported to POXEL.

AE will be recorded on an ongoing basis from date of ICF signature up to the End-of-study Visit (V8).

Only events that occur after the first dose intake of IMP of the Double-blind treatment period (V3) or if they were present prior to the first intake of IMP of the Double-blind treatment period and increased in severity or relationship to IMP after the first intake of IMP of the Double-blind treatment period will be considered as TEAEs.

8.3.6.4 Procedure for Reporting Immediately Reportable Events (IREs= SAEs and Pregnancy)

The Investigator must report immediately (within 24 hours of the Investigator's awareness) to all SAEs/Pregnancy occurring from the date of ICF signature to the End-of-study Visit (V8) or to the last study visit performed in case of premature discontinuation.

An AE eCRF page must be completed with as much available information within 24 hours of knowledge of the SAEs.

For pregnancy the study site will be required to complete the appropriate eCRF page within 24 hours of knowledge of the event and also complete the Manual Exposure in Utero Form once received from

Manual Back-Up Reporting Procedures

This study is utilizing an Electronic Data Capture (EDC) system for data entry. In the event that the EDC system is unavailable for electronic reporting, the manual back-up reporting procedures below should be followed.

- Complete a SAE or Exposure in Utero Form
- Email (preferred) or Fax the form to Clinical Safety

When the EDC system becomes available, the EDC system should be updated with all previously reported information.

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8.3.6.4.1 Safety Reporting to Regulatory Authorities, Investigators and Independent Ethics Committees/Institutional Review Boards

SUSARs and other safety information requiring expedited reporting will be reported to Investigators, Ethics Committees and/or Competent Authorities in agreement with applicable guidelines and US regulations.

In accordance with ICH GCP guidelines, POXEL will inform the Investigator of "findings that could adversely affect the safety of patients, impact the conduct of the study or alter the IRB/EC's approval/favorable opinion to continue the study." In particular, and in line with respective US regulations, POXEL will inform the Investigator of AE that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of these safety reports in the ISF. National regulations with regard to safety report notifications to Investigators will be considered.

8.3.6.5 Monitoring of Patients with Adverse Event

Any AE that occurs during the course of a clinical trial and is possibly related to IMP must be monitored and followed up until the outcome is known, unless patients are documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

8.3.7 Pregnancy and In Utero Drug Exposure

All pregnancies with an estimated conception date after the date of ICF signature until the End-of-study Visit (V8) must be reported. Upon immediate notification, the Investigator (or designee) will complete the Pregnancy eCRF page. Clinical Safety will send the Exposure In Utero form to the study site for completion within 24 hours. POXEL must be notified by Clinical Safety within 24 hours of being notified.

In case of pregnancy, patients will discontinue the IMP and withdraw from the study. The Investigator must actively follow up, document and report on the outcome of these pregnancies.

Any abnormal outcome:

1. Spontaneous abortion includes abortion or missed abortion
2. Induced abortion
3. Stillbirth

4. Death of newborn
5. Congenital anomaly
6. Delivery within appropriate pregnancy terms, but congenital abnormalities in the newborn

should be reported first to Clinical Safety with 24 hours of the Investigator's awareness. The Exposure In Utero form should be used for the reporting of the outcome.

The Clinical Safety will forward pregnancy reports to POXEL the next business day. If the pregnancy outcome occurs following the end of the study; the Investigator will report the pregnancy outcome directly to POXEL.

Newborns should be followed up for at least 8 weeks for any potential congenital anomalies.

Pregnancy and pregnancy outcome of female partners of male trial patients need to be reported in the same way. The Exposure In Utero form can be used to report the pregnancy information for the partner of a male patient.

8.3.8 Special Precautions

8.3.8.1 Hypoglycemia

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Patients with T2DM should be reminded of symptoms of hypoglycemia i.e. increased sweating, palpitation, trembling, shaky feeling, headaches, anxiety, poor concentration, confusion, dizziness, irritability, hunger or pale skin.

Patients are requested to immediately perform a finger stick glucose measurement with the SMBG device provided for this study if any symptoms occur that may be related to hypoglycemia but 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 in the eCRF. Hypoglycemia will be reported as recommended by the FDA guidance [19]:

- Hypoglycemia evidenced only by symptoms without blood glucose measurement will be reported as probable symptomatic hypoglycemia.

- Hypoglycemia evidenced only by plasma glucose concentration of less than 70 mg/dL (3.9 mmol/L) will be reported as asymptomatic hypoglycemia. In case of asymptomatic hypoglycemia observed on SMBG, it should be reported using the verbatim of asymptomatic hypoglycemia (with the glucose value) reported from SMBG.

- Hypoglycemia evidenced both by typical symptoms and plasma glucose concentration of less than 70 mg/dL (3.9 mmol/L) will be reported as documented symptomatic hypoglycemia.

- Hypoglycemia requiring assistance of another person to administer carbohydrate or glucagon or other procedure will be reported as severe hypoglycemia.

Therefore, there might be values coming from the SMBG device under the threshold for hypoglycemia without any associated symptoms. In such case, it is important for the Investigator to judge whether this has to be reported or not as an AE of hypoglycemia, depending on the clinical context and the overall glycemic control.

In case 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 IMP intake and SMBG…).

8.3.8.2 DILI

To detect and monitor a possible DILI, the following evaluations should be performed in the presence of significant elevations of liver indices.

- **For patients with normal liver transaminases and total bilirubin at baseline (Randomization Visit (V3)):**

If patients with normal baseline (Randomization Visit (V3)) liver indices develop new elevations of AST or ALT or ALP >3 × ULN or TBL >2 × ULN values during the study, repeat testing should be performed within 48 to 72 hours. Investigators should also ask the patient if he/she has symptoms.

If there are persistent elevations (ALT or AST >3 × ULN or TBL >2 × ULN) upon repeat testing, then close observation (as described below) should be implemented and discontinuation of drug should be considered.

Drug should be discontinued, and the patient followed until resolution of symptoms or signs in the following situations:

- ALT or AST >8 × ULN
- ALT or AST >5 × ULN for more than 2 weeks.
- ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5)
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

- **For patients with elevations in liver transaminases or total bilirubin at baseline (Randomization Visit (V3)):**

If patients with abnormal baseline liver indices develop elevations of AST or ALT >2 × baseline or TBL >2 × baseline values during the study, repeat testing should be performed within 48 to 72 hours. Investigators should also ask to the patient if he/she has symptoms.

If there are persistent elevations (ALT or AST >2 × baseline or TBL >2 × baseline values) upon repeat testing, then close observation (as described below) should be implemented and discontinuation of drug should be considered.

Drug should be discontinued, and the patient followed until resolution of symptoms or signs in the following situations:

- If baseline measurements were <2 × ULN, discontinue if ALT or AST increases to >5 × baseline measurements.
- If baseline measurements ≥2 × ULN (<200 IU/L as per eligibility requirements), discontinue if ALT or AST increases to >3 × baseline measurements.
- If baseline measurements ≥5 × ULN (<200 IU/L as per eligibility requirements), discontinue if ALT or AST increases to >2 × baseline measurements.
- Discontinue if ALT or AST increase >2 × baseline measurements AND the increase is accompanied by a concomitant increase in TBL to >2 × baseline measurements or the INR concomitantly increases by >0.2.
- For any patients who present with a constellation of syndromes indicative of liver disease as per the Investigator's overall assessment (i.e. fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]).

- **Close observation for suspected drug-induced liver injury includes the following:**
  - Repeating liver enzyme (ALT, AST, and ALP) and TBL tests 2 or 3 times weekly. The frequency of repeat testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the patient is asymptomatic.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
  - Obtaining a history of exposure to environmental chemical agents.
  - Obtaining additional tests to evaluate liver function, as appropriate (e.g. INR, direct bilirubin, lactate, liver ultrasound).
  - Considering gastroenterology or hepatology consultations.

If a DILI is confirmed or suspected by the Investigator, or in case of liver function parameters (ALT, AST, ALT, TBL) above the threshold defined in this section, the Investigator will complete

an Expedited Liver Assessment Report page (ELAR) in the eCRF within 24 hours of knowledge of the case. If the DILI is confirmed, it should be reported in addition as an AE (see *Section 8.3.6.2 Methods of Recording and Assessing Adverse Events*).

8.4 Pharmacokinetics

During this study, pre-dose and post-dose plasma concentration of PXL770 will be assessed as indicated in *Table 1*.

The assays of PXL770 will only be carried out in patients who have received the active drug. Thus, the laboratory responsible for PK bioanalysis will be provided with a randomization list. Under no circumstances will this list be brought to the attention of the Investigators, or to the project team members.

Pre-dose and post-dose plasma samples for PK bioanalysis will be collected at study sites and forwarded to central laboratory. For the determination of PXL770, blood samples will be taken by an indwelling catheter or direct venipuncture, as appropriate.

Please refer to the lab manual for further explanations.

8.5 Biobanking Samples for Post-hoc Assessments

Blood samples for supplementary tests will be collected at visits shown in *Table 1* 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 frozen and stored until further use. All the biobanking samples will be destroyed within 2 years after the final study report is issued.

Please refer to the lab manual for further explanations.

8.6 Pharmacogenetics

Blood samples for genotyping purposes will be collected at visits shown in *Table 1* to enable post-hoc genetic and pharmacogenetic research on the DNA/RNA samples from patients who sign an optional, additional informed consent. The samples will be frozen and stored until further use. All samples will be destroyed within 2 years after the final study report is issued.

Please refer to the lab manual for further explanations.

8.7 Acceptable deviation times

The following will **not** be regarded as protocol deviations:

Table 3. Acceptable deviation times

Procedure	Timepoint	Acceptable deviation
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Blood sampling for PK	Predose	Up to 30 min before IMP intake
	Up to and including 3h post-dose	±2 min of the scheduled time
	After 3h to 8h post-dose	±5 min of the scheduled time
Blood sampling for insulin	Second sample performed 10 min after the first sample	±2 min of the scheduled time
ECG	Predose	Up to 180 min before IMP intake
	2h post-dose	±10 min of the scheduled time
All other procedures	Predose	Up to 180 min before IMP intake

9 Statistical methods

Statistical analysis will be performed by under the supervision of POXEL. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Full details of analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to the unblinding and locking of the database.

9.1 General considerations

In general, summary tabulations will be presented by treatment arm and will display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent per category for categorical data.

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

Given the early stage of development (i.e. a Phase II trial for internal decision), no adjustment for multiplicity will be considered. Hence, pairwise comparisons between PXL770 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.

The primary endpoint will be the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7).

The primary set for efficacy analysis will be the Intention-to-treat Set.

No interim analysis is planned for this study.

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

9.2 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 (Randomization Visit (V3)) to Week 12 (V7) and the following assumptions:

- Superiority design of PXL770 compared to placebo
- 2-sided alpha (Type 1) error = 0.05
- Beta (Type 2) error = 0.10 (Power = 90%)
- Expected difference (percentage change in liver fat mass): 30%

- 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

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%, 30 patients are to be randomized per treatment group (120 patients in total).

9.3 Randomization

A statistician independent of POXEL will prepare the randomization list. Each patient will be assigned to one of four treatments in a 1:1:1:1 ratio:

- Group 1: Placebo
- Group 2: PLX770 250 mg QD
- Group 3: PXL770 250 mg BID
- Group 4: PXL770 500 mg QD

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients) Corporate confidential information

See Section *6.3.2 Treatment Assignment or Randomization* for further details of the randomization procedures to be applied.

9.4 Analysis Sets

9.4.1 Screened Analyses Set

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

9.4.2 Safety analyses and Safety Set

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.

The Safety Analysis Set (SS) comprises all randomized patients having received at least one dose of the study drug (either PXL770 or placebo) and considered as-treated. Safety and tolerability will be analyzed on the safety set.

9.4.3 Efficacy Analyses

All primary and secondary efficacy endpoints will be analyzed using the intention-to-treat set (ITTS). The per protocol (PP) set will be used only for the analysis of the primary endpoint to assess the robustness of the primary analysis.

9.4.3.1 Randomized Set (RS):

All patients considered as-randomized regardless of the treatment actually received.

9.4.3.2 Intention-to-treat Set

The ITTS consists of all as-randomized patients having received at least one dose of the IMP (either PXL770 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.

9.4.3.3 Per Protocol Set (PPS)

The PPS consists of all ITTS patients without any major violations of study procedures. Major protocol violations will be identified prior to breaking the blind. Protocol deviations will be reviewed and classified as minor or major during a data review meeting that will be held before database lock and breaking the blind.

9.4.4 PK Population

The PK population corresponds to the Safety Set and includes all randomized patients who have been treated with PXL770 according to the protocol and have provided at least one pre-dose PK assessment during the study.

9.5 Efficacy analysis

9.5.1 Primary Endpoint: relative change in the percentage of liver fat mass

The primary analysis of efficacy will be performed on the ITTS.

Primary analysis:

The primary endpoint, i.e. expressed as the relative change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7), will be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo) and for stratification factors, i.e. T2DM

status (T2DM patients versus non-T2DM patients)

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Least square means (LSMs) of the primary endpoint for treatment groups and pairwise differences in LSMs will be estimated along with their p-values and 95% confidence intervals.

Missing MRI-PDFF at Week 12 (V7) will be estimated using a multiple imputation method (fully conditional specification method) assuming missing at random (MAR) mechanism which will be detailed in the SAP. Missing baseline MRI-PDFF will not be estimated.

Validity of the ANCOVA model will be checked (studentized residuals will be plotted against predicted values, etc.).

Sensitivity analyses:

Pairwise Wilcoxon tests stratified according to T2DM status and Site will be performed. Hodges-Lehmann estimates along with their 95% confidence intervals will also be provided.

The primary and sensitivity analyses will be repeated on the PPS.

Subgroup analyses:

Subgroup analyses will be performed:

- within each T2DM status (T2DM patients versus non-T2DM patients). The treatment by T2DM status interaction will be tested.

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9.5.2 Key Secondary Endpoints

9.5.2.1 Absolute Change in the percentage of liver fat mass

The (absolute) change in the percentage of liver fat mass (assessed by MRI-PDFF) from baseline (Randomization Visit (V3)) to Week 12 (V7) will be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment, T2DM status (T2DM patients versus non-T2DM patients), Corporate confidential information and baseline liver fat mass. Least square means of the change in the percentage of liver fat mass for treatment groups (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo) and pairwise differences in LSMs will be estimated along with their p-values and 95% confidence intervals.

Missing MRI-PDFF at Week 12 (V7) will be estimated using a multiple imputation method (fully conditional specification method) assuming missing at random (MAR) mechanism which will be detailed in the SAP. Missing baseline MRI-PDFF will not be estimated.

Validity of the ANCOVA model will be checked (studentized residuals will be plotted against predicted values, etc.).

The same sensitivity analyses proposed for the primary endpoint will be performed.

9.5.2.2 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)) 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)) 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)) higher than or equal to 50% (≥ 50 %).
- Response defined as a liver fat mass value at Week 12 (V7)) that is normalized, i.e. lower than or equal to 5% (≤ 5 %).

Percentages of response will be estimated within each treatment group.

The response will be analyzed in a logistic regression model adjusting for treatment (PXL770 doses of 250 mg QD, 250 mg BID and 500 mg QD and placebo), T2DM status (T2DM patients versus non-T2DM patients), Corporate confidential information and baseline liver fat mass. Pairwise differences in treatment groups will be estimated in this model as odds ratios along with their p-values and 95% confidence intervals.

Methods handling missing MRI-PDFF at Week 12 (V7) and therefore missing responder status at Week 12 (V7) will be detailed in the SAP.

9.5.3 Other Secondary Endpoints

The analysis of these secondary endpoints will be provided and fully detailed in the SAP.

Other efficacy secondary endpoints are as follows:

- Liver enzymes: ALT and AST
- Measured metabolic parameters: FPG, HbA1c, insulin, C-peptide, Total cholesterol, HDL-c, LDL-c, triglycerides, Apo A1, Apo B, FFA, glycerol and adiponectin
- Calculated metabolic parameters: HOMA-IR, QUICKI, HOMA-β and Adipo-IR
- hsCRP and other markers of inflammation: fibrinogen and MCP-1
- Fibrosis markers: NFS and Fib-4 score
- Body weight, waist circumference and waist-to-hip ratio

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The timepoints for collection of each of these are given in detail in Section *7 Study Procedures* and in *Table 1*.

9.5.5 Safety Analysis

The analysis of safety parameters will be based on the safety analysis set. In general, missing safety data will not be replaced. Standard safety analysis will be performed and fully detailed in the SAP.

Safety parameters are as follows:

9.5.5.1 Adverse Events

AE will be coded using MedDRA®. The frequency and incidence of TEAE will be presented by System Organ Class (SOC) and preferred term for PXL770 treatment groups and placebo (number and percentage of patients experiencing at least one AE per preferred term as well as the number of observed events per preferred term). Separate tables will be presented by severity and by relationship. All AE will be presented in a full and comprehensive listing including patient number, treatment, severity, seriousness, action taken, outcome, relationship to treatment, onset/stop and duration. Details of SAE and AE leading to permanent discontinuation of IMP or to death will be listed separately.

9.5.5.2 Concomitant Medications

Previous, concomitant and new medications will be coded using the World Health Organization (WHO) Dictionary.

Previous, concomitant and new medication will be tabulated and summarized by treatment groups.

9.5.5.3 Vital Signs, ECG, Body Weight, Waist Circumference, waist to hip ratio, BMI and Physical Examination

Vital signs, ECG parameters, body weight, waist circumference, waist to hip ratio and BMI will be summarized descriptively by treatment and timepoint. Similarly, changes from baseline (Randomization Visit (V3)) will be summarized.

Physical examination results will be listed by patients and body system.

9.5.5.4 Clinical Laboratory Data

Laboratory findings will be evaluated using central laboratory's normal reference ranges. Clinically relevant values will be flagged (please refer to central laboratory manual). Descriptive statistics

will be derived for quantitative laboratory parameters for each treatment group and timepoint. Similarly, changes from the baseline will be summarized.

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 at each post-baseline visit showing the number of patients per treatment group with N, H or L.

9.5.5.5 Withdrawals of study

Patients who withdraw from the study will be summarized by treatment group according to their reason of withdrawal.

9.5.6 Analysis of Further Endpoints

Pharmacokinetic parameters assessment will include pre- and post-dose concentrations of PXL770 in blood at visits and timepoints specified in *Table 1*.

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Post-hoc testing of any additional safety parameters or any potential biomarkers related to liver, cardiovascular diseases or metabolic diseases in relation with the drug target evaluation will be assessed using the Safety Set.

9.6 Interim Analysis

No interim analysis is planned.

10 Ethical and Regulatory Aspects

10.1 Ethics and Good Clinical Practice

The Investigator will ensure that this study is conducted in full compliance with the principles of the 'Declaration of Helsinki' (as amended in Tokyo, Venice, Hong Kong, Somerset West, Edinburgh and Seoul), and with the laws and regulations of the country in which the clinical research is conducted. A copy of the Declaration of Helsinki will be provided to each study site.

All studies must follow ICH GCP Guidelines and local regulations. Investigators will strictly ensure adherence to the stated provisions.

For any study site staff member responsible for performing a critical task, ICH GCP experience and training must be documented on the Curriculum Vitae. Any study site staff member not familiar with or having conducted an ICH GCP training more than 2 years prior to the study initiation or start of involvement in the study will have to be trained before the start of the study.

10.2 Patient Information and Informed Consent

It is the responsibility of the Investigator to obtain informed consent according to GCP and local regulations from each individual participating in this study.

An unconditional prerequisite for patients' participation in the study is their written informed consent. The patient's written informed consent to participate in the study must be given before any study-related activities are carried out.

Adequate information must therefore be given to the patient by the Investigator before informed consent is obtained. A patient information sheet prepared in accordance with the Note for Guidance on GCP (ICH E6) will be provided by and validated by POXEL for the purpose of obtaining informed consent. In addition to providing this written information to a potential patient, the Investigator (or his/her designate) will inform the patient verbally of all pertinent aspects of the study. The Investigator (or his/her designate) must provide adequate explanation of the methods, objectives and potential hazards of the study. The language used in doing so must be chosen so that the information can be fully and readily understood by laypersons. The Investigator (or his/her designate) must explain to patients that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

The ICF must be signed and dated by the patient in person at study site and the Investigator in person at study site. The signed and dated declaration of informed consent will remain at the Investigator's site and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated ICF

should be provided to patients prior to participation. The whole consenting process must be clearly documented in the patient file.

The information Leaflet and ICF will be provided in the local language.

Whenever important new information become available that may be relevant to the patient's consent, the written patient information sheet and any other written information provided to patients will be revised by POXEL and be submitted again to the IRB/EC for review and favorable opinion. The agreed, revised information will be forwarded to each patient in the study. The Investigator (or his/her designate) will explain the changes to the previous version and patient will be asked to sign the new version.

The patient identification log must be maintained for all patients who consented to participate in the study, whether or not they were randomized.

10.3 Patient Identification and Privacy

A unique patient number (see Section *6.3.1 Patient Numbering*) will be assigned to each patient at Screening Visit (V1). This number will serve as the patient's identifier in the study as well as in the clinical study database.

The patient's data collected in the study (including genetic tests) will be stored under this number. Only the Investigator will be able to link the patient's study data to the patient via an identification list kept at the study site. The patient's original medical data that are reviewed versus eCRF data (source data verification process) at the study site during routine monitoring, audits and authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. Patients will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with US regulations.

10.4 Emergency Medical Support and Patient Emergency Card

Patients included in this study will be provided with a Patient Emergency Card at Screening Visit (V1). The Patient Emergency Card is based on the need to provide patients with a way of identifying themselves as participating in this study, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the patient's medical treatment.

This card is designed to provide information to health care providers who are not part of the clinical study; this may include the possibility of emergency unblinding if needed, in case of blinded studies. The Investigators, who are already aware of the protocol and treatment, have other means

of accessing necessary medical information for the management of emergencies occurring in their patients.

The first point of contact for all emergencies will be the Investigator caring for the affected patient. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, he/she will answer any questions. Any subsequent action (e.g. unblinding) will follow the standard processes established for the Investigators.

10.5 Patient Insurance and Compensation to Patients

Insurance coverage shall be provided in line with the regulations. Coverage will be provided from the time a patient has been screened in the study, i.e. from the time the patient has given written informed consent.

In the event that a patient is injured as a direct result of study participation, POXEL will reimburse for treatment of such injuries, as long as those costs are not covered by the patient's health care payer. However, if the patient has not complied with the study procedures, has not followed the instructions of the Principal Investigator or if the injury is a result of a medical condition not related to the IMP, the patient's health care payer will be responsible for the costs of diagnosing and treating the condition.

10.6 Institutional Review Board/Ethics committee

Prior to commencement of the study at a given study site, the study protocol will be submitted together with its associated documents (Patient Information and Consent Form, IB) and any other relevant information (e.g. patient diary) to the responsible IRB/EC for its favorable opinion/approval. The written favorable opinion/approval of the IRB/EC will be filed in the ISF, and a copy will be filed in the TMF at

The study must not start at a study site before POXEL has obtained written confirmation of favorable opinion/approval from the concerned IRB/EC. The IRB/EC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the protocol version and the Patient Information and Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained. Amendments to the protocol will also be submitted to the concerned IRB/EC, before implementation in case of substantial changes (see Section *11.6 Changes to the Protocol*). Relevant safety information will be submitted to the IRB/EC during the course of the trial in accordance with national regulations and requirements.

10.7 Regulatory Authorities

The protocol and any applicable documentation will be notified to the Food and Drug Administration (FDA) in US.

11 Study Management

11.1 Data collection and CRF management

In this study, an eCRF will be used. CRF data will be captured via EDC using , a web-based tool. An eCRF will be completed for each screened patient.

Patient diary, specifically designed for the clinical trial by POXEL and provided to the study sites will be given to the patients. Data collected in this patient diary are detailed in Section *8.3.3 Patient Diary*.

The data in the eCRF should be consistent with the relevant source documents as verified by CRA during monitoring visits. The data will be processed, evaluated, and stored in pseudonymous form in accordance with the data-protection regulations.

The Investigator must ensure that any document associated with an eCRF forwarded to POXEL contains no mention of any patient names.

The eCRFs will be reviewed by the Investigator for completeness and accuracy. Each patient's eCRF must be signed electronically by the Investigator to document correctness and accuracy of data contained. Any amendments and corrections necessary must be undertaken and countersigned electronically by the Investigator, stating the date of the amendment/correction. The Investigator must state his/her reasons for the correction of important data. Electronic errors will be captured by the audit trail within the collection system. Details on eCRF completion will be given in the eCRF completion guidelines.

The eCRFs are regulatory documents and must be suitable for submission to authorities.

The Investigator or designee will be responsible for entering study data in the eCRF provided by It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs. The eCRF information need to be completed as soon as possible after each patient's visit (but no later than 5 business days after the patient's visit).

In addition to eCRF, other external data are collected:

- MRIs performed during the study will be sent to a centralized imaging core laboratory. Results will be electronically transferred to the Data Management Department.
- ECGs performed during the study will be sent to a centralized ECG core laboratory. Results will be electronically transferred to the Data Management Department.
- Laboratory blood and urine samplings will be sent to centralized laboratory and results will be transferred electronically to Data Management Department.

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- PK samplings will be sent to for analysis and results will be transferred electronically to Data Management Department.

Reconciliation of all centralized data will be done by before database lock and final data transfer received.

During the study, SAE data (reported on the AE form in eCRFs) will be integrated into the centralized pharmacovigilance database upon receipt of these forms and after a duplicate check. Each case will be assigned a case identification number. Each case will be assessed by POXEL before being reported to the relevant authorities as necessary.

The information from the pharmacovigilance database cases will be reconciled with that in the clinical database.

All these data will be integrated into a validated database. will be responsible for data processing, in accordance with data management procedures. Database lock will occur once quality assurance procedures have been completed. Patient Data Reports, recorded on CD or DVD, will be provided to the Investigators at the completion of the study. Each patient data report will contain all the data for a particular patient in the same format as the eCRF pages as well as audit trails and indexed comments.

11.2 Handling of Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (e.g. violation of informed consent process, IMP dispensing or patient dosing error, treatment assignment error, patient enrolled in violation of eligibility criteria, or concomitant medication criteria), the Investigator (or designee) will contact POXEL (or its designee) at the earliest possible time by telephone or by email. The Investigator and POXEL (or its designee) will come as quickly as possible to a joint decision regarding the patient's continuation in the trial. This decision will be documented by the Investigator and POXEL (or its designee) and reviewed by the CRA.

11.3 Source Data and Patient Files

The Investigator must keep a patient file (medical file, original medical records) on paper or electronically for every patient included in the study. This file will contain the available demographic and medical information for the patient and should be as complete as possible.

It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.

It must be possible to identify each patient by using this patient file.

Printouts of electronic patient file documents as stated above must be signed and dated by the Investigator and kept with the Investigator's copy of the document.

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment or printouts have to be filed in the patient files. This includes e.g. ECG recordings, BP monitoring, laboratory value listings, patient diary, etc. All these documents have to bear at least the patient number, study number, scheduled time and the printing date printed by the recording device to indicate to which patient and to which study procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the Investigator.

11.4 Investigator Site File and Archiving

The Investigator will be provided with an ISF upon initiation of the study. This file will contain all documents necessary for the conduct of the study and will be updated and completed throughout the study. It must be available for review by the CRA, must be ready for inspection by Competent Authorities during and after the study, and must be safely archived for at least 15 years after the end of the study. The documents to be thus archived include the Patient Identification List and the signed patient ICF. If archiving of the Investigator Site File is no longer possible at the study site, the Investigator must notify POXEL.

All original patient files (medical records) must be stored at the study site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of POXEL.

11.5 Monitoring, Quality Assurance and Inspection by Authorities

This study will be monitored in accordance with the ICH Note for Guidance on GCP (ICH E6). The CRA will perform visits to study site at regular intervals.

During monitoring visits, the CRAs will review:

- the conformity of ICFs with the applicable regulation
- the compliance of patient inclusion with protocol Inclusion/Exclusion criteria
- that the data management is adequate: source data verification, queries resolution, SAEs/ AEs reporting, protocol deviations reporting
- Investigator Site File (ISF) (e.g. Protocol & Amendments and Regulatory sections, delegation list and training records)
- that IMP handling is compliant with the protocol requirements
- the compliance of centralized procedures management (e.g. central laboratory and central imaging) by study site staff
- the adequacy of facilities, equipment and material management

In line with ICH GCP guidelines, monitoring will include verification of data entered in the eCRF against original patient's records. This verification will be performed by direct access to the original patient records, and POXEL guarantees that patient confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification.

Representatives of appropriate POXEL personnel or its designee(s), as well as Competent Regulatory Authorities, must be permitted to inspect all study-related documents and other materials at study site, including the ISF, the completed eCRFs, IMP and the patients' original medical records/files.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the eventual clinical study report, will be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

11.6 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the competent authorities and to the relevant IRB/EC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be submitted to the relevant IRB/EC or to competent authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the patient's agreement to participate in the study requires the patient's informed consent prior to implementation (see Section *10.2 Patient Information and Informed Consent)*

11.7 Clinical Study Report and Publication Policy

11.7.1 Clinical Study Report

After completion of the study, a clinical study report according to ICH E3 will be written by under the direction of POXEL.

11.7.2 Publication

In accordance with standard editorial and ethical practice, the results of the study will be published. Results from multi-center studies must be published or presented at congress only in their entirely and not as individual study site data, except for ancillary studies.

The coordinating Investigator will have the opportunity to review the analysis of data and to discuss with POXEL the interpretation of the study prior to publication.

Any study-related article or abstract written independently by Investigators must be submitted to POXEL for review at least 60 days prior to submission for publication or presentation. POXEL is entitled to delay publication in order to protect intellectual property rights.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of POXEL, and will be determined by mutual agreement.

11.7.3 Disclosure and Confidentiality

By signing this protocol, the Investigator agrees to keep all information provided by POXEL in strict confidence, and to request similar confidentiality from his or her staff and the IRB/EC. Study documents (including IB, protocol, eCRF and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by POXEL to the Investigator may not be disclosed to others without direct written authorization from POXEL, except to the extent necessary to obtain ICF patients who wish to participate in the study.

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