NCT04321343

CLINICAL TRIAL PROTOCOL

Trial Protocol Number	PXL065-003
Study Full Title	A 36-week, randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL065 versus placebo in noncirrhotic, biopsy-proven Nonalcoholic Steatohepatitis (NASH) patients
Study Short Title	DESTINY 1
Program Acronym	**DESTINY** **D**euterium-stabilized R-pioglitazone (PXL065) **E**fficacy and **S**afety **T**rial **I**n **N**ASH
Phase	Phase 2
Authors	Corporate confidential information
IND Number	144089
EudraCT Number	N/A
Coordinating investigator	Stephen Harrison, MD Pinnacle Clinical Research 5109 Medical Dr Ste 200 San Antonio, TX 78229 United States
Sponsor	POXEL S.A. 259-261, avenue Jean Jaurès 69007 Lyon France
Sponsor's Legal Representative (EU)	N/A
Trial Protocol Version	Version 5.0 / 17th December 2020
Replaces Trial Protocol Version	Version 4.0 / 19th August 2020
Current Protocol Amendment	#4
Previous Protocol Amendments	#3

Signature Page

Corporate confidential information

Corporate confidential information

Investigator Signature

Study Full Title	A 36-week, randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL065 versus placebo in noncirrhotic, biopsy-proven Nonalcoholic Steatohepatitis (NASH) patients
Study Short Title	DESTINY 1
Program Acronym	DESTINY (**D**euterium-stabilized R-pioglitazone (PXL065) **E**fficacy and **S**afety **T**rial **I**n **N**ASH)
Protocol Version / Date	Version 5.0 / 17th December 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 Council for 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

List of Abbreviations

A2M	Alpha-2-macroglobulin
AASLD	American Association for the Study of Liver Diseases
Adipo-IR	Adipose tissue insulin resistance
ADL	Activities of daily living
ADR	Adverse Drug Reaction
AE	Adverse Event
AERP	Adverse Event Reporting Plan
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ALP	Alkaline Phosphatase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
AUC_{inf}	Area under the concentration time curve extrapolated to infinity
BA	Bone area
β-HCG	Human Chorionic Gonadotropin
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CD	Choline-deficient
CGM	Continuous Glucose Monitoring
CHI3L1	Chitinase-3-like protein 1
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease – Epidemiology Collaboration
C_{max}	Maximum concentration
C_{pre}	Predose concentration
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRN	Clinical Research Network
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DILI	Drug-Induced Liver Injury
DXA	Dual-energy X-ray absorptiometry
EC	Ethics Committee
ECG	Electrocardiogram

eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EDC	Electronic Data Capture
e.g.	*exempli gratia*
ELF	Enhanced Liver Fibrosis
EoS	End-of-Study Visit
EoT	End-of-Treatment Visit
ET	Early Termination Visit
FCS	Fully conditional specification
FDA	Food and Drug Administration
FFA	Free Fatty Acids
FIB-4	Fibrosis 4
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GLP1-RA	Glucagon-Like Peptide 1 – Receptor Agonist
GMP	Good Manufacturing Practice
HA	Hyaluronic acid
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HDL-c	High-Density Lipoprotein cholesterol
HF	Heart Failure
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
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
i.e.	*id est*
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ITT(S)	Intention-To-Treat (Set)
IWRS	Interactive Web Response System
LDL-c	Low-Density Lipoprotein cholesterol
LFC	Liver Fat Content

LSM	Least Square Mean
MATE	Multidrug and Toxin Extrusion
MCD	Methionine/choline-deficient
MedDRA	Medical Dictionary for Regulatory Activities
miR-34a	microRNA-34a
MPC	Mitochondrial pyruvate carrier
MR	Metabolite-to-parent ratio
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAFL	NonAlcoholic Fatty Liver
NAFLD	NonAlcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
NFS	NAFLD Fibrosis Score
NOAEL	No-observed-adverse-effect level
NYHA	New York Heart Association
OAT	Organic Anion Transporter
OCT	Organic Cation Transporter
PDFF	Proton Density Fat Fraction
PIIINP	Amino-terminal propeptide of type III procollagen
PK	Pharmacokinetic(s)
PPARγ	Peroxisome proliferator-activated receptor γ
PPS	Per Protocol Set
Pro-C3	N-terminal type III collagen propeptide
PTCA	Percutaneous Transluminal Coronary Angioplasty
QD	Once a day (*Quaque die)*
QUICKI	Quantitative Insulin Sensitivity Check Index
RNA	Ribonucleic Acid
RS	Randomized Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SD	Standard Deviation
SGLT2-I	Sodium-Glucose-Co-Transporter-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

TEAE	Treatment-Emergent Adverse Event
TIMP-1	Tissue inhibitor of metalloproteinases 1
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinediones
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

Table of Contents

1 SYNOPSIS 13

2 BACKGROUND INFORMATION 30

2.1 SCIENTIFIC RATIONALE 30
2.2 PXL065 31

Corporate confidential information

2.3 RESEARCH HYPOTHESIS 35

3 STUDY OBJECTIVES 36

3.1 PRIMARY OBJECTIVE 36
3.2 SECONDARY OBJECTIVES 36

4 STUDY DESIGN 37

4.1 STUDY DESIGN AND SCHEDULE 37
4.2 RATIONALE FOR STUDY DESIGN, DOSES AND CONTROL GROUP 37

5 STUDY POPULATION 39

5.1 INCLUSION CRITERIA 39
5.2 EXCLUSION CRITERIA 40
5.3 RESCREENING 43
5.4 RETESTING DURING THE SCREENING PERIOD 43
5.5 RESTRICTIONS DURING THE STUDY 43
5.6 PATIENTS INCORRECTLY RANDOMIZED 44
5.7 CRITERIA FOR SCREEN-FAILURE 44
5.8 CRITERIA FOR WITHDRAWAL FROM THE STUDY FOR RANDOMIZED PATIENTS DURING THE DOUBLE-BLIND TREATMENT PERIOD 45
5.8.1 Criteria for withdrawal from the study 45
5.8.2 Procedure for withdrawal from the study 46
5.9 DISCONTINUATION OF THE STUDY 46
5.10 REPLACEMENT POLICY 47

6 INVESTIGATIONAL MEDICINAL PRODUCT AND OTHER DRUGS USED IN THE TRIAL 48

6.1 DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCT 48
6.2 DOSAGE AND ADMINISTRATION 48
6.2.1 Double-blind Treatment Period 49
6.2.2 Follow-up Period 49
6.3 TREATMENT ASSIGNMENT AND BLINDING 50
6.3.1 Patient Numbering 50
6.3.2 Treatment Assignment or Randomization 50
6.3.3 Treatment Blinding 51
6.3.3.1 Method of Blinding 51
6.3.3.2 Emergency Unblinding 51
6.4 CONCOMITANT MEDICATIONS AND THERAPIES 52
6.5 NON-PERMITTED MEDICINES 53
6.6 PACKAGING AND LABELING 53
6.7 MANAGEMENT OF IMP 54
6.7.1 Shipment of IMP 54
6.7.2 Supply and Receipt of IMP 54
6.7.3 Storage of IMP 54
6.7.4 Dispensing, Accountability and Compliance of IMP 55
6.7.5 Return and Destruction of IMP 56
6.8 OVERDOSE PREVENTION 56

7 STUDY PROCEDURES 58
7.1 SCREENING PERIOD 58
7.2 DOUBLE-BLIND TREATMENT PERIOD 59
7.2.1 Visit 1: Randomization Visit (Day 1) 59
7.2.2 Visit 2: Week 3 60
7.2.3 Visit 3: Week 6 60
7.2.4 Visit 4: Week 12 61
7.2.5 Visit 5: Week 18 62
7.2.6 Visit 6: Week 24 62
7.2.7 Visit 7: Week 30 63
7.2.8 Visit 8: End-of-Treatment Visit (EoT-Week 36) 64
7.3 FOLLOW-UP PERIOD, VISIT 9: END-OF-STUDY VISIT (EOS) 65
7.4 EARLY TERMINATION VISIT (ET) 65
8 STUDY ASSESSMENTS 67
8.1 BLOOD VOLUME 67
8.2 EFFICACY ASSESSMENT 67
8.2.1 Liver fat mass content assessed by MRI-PDFF – Central imaging core laboratory 67
8.2.2 Liver biopsy 68
8.2.3 Other Efficacy Parameters 69
8.3 SAFETY 70
8.3.1 Physical Examination 70
8.3.2 Pitting edema assessment 70
8.3.3 Vital Signs and Body Measurements 71
8.3.4 Patient Diary 71
8.3.5 Supine 12-Lead electrocardiogram (ECG) 72
8.3.6 Laboratory Assessments 72
8.3.6.1 Standard Safety Laboratory Panel (Blood and Urine) 73
8.3.6.2 Viral Infection Screen Panel 73
8.3.6.3 eGFR 74
8.3.6.4 Serum and Urine Pregnancy Tests 74
8.3.7 Bone mineral density 74
8.3.8 Adverse Events 75
8.3.8.1 Adverse Event Definitions 75
8.3.8.1.1 Adverse Event (AE) 75
8.3.8.1.2 Adverse Drug Reaction (ADR) 76
8.3.8.1.3 Serious Adverse Event (SAE) 76
8.3.8.1.4 Adverse Event of Special Interest (AESI) 78
8.3.8.2 Definition of the AE Reporting Period 80
8.3.8.3 Methods of Recording and Assessing Adverse Events 80
8.3.8.4 Sponsor immediate notification and Regulatory Reporting 81
8.3.8.4.1 Sponsor Immediate Notification 81
8.3.8.4.2 Reporting to Regulatory Authorities (Expedited Reporting), Investigators and Independent Ethics Committees/Institutional Review Boards 82
8.3.8.5 Monitoring of Patients with Adverse Event 82
8.3.9 Overdose 83
8.3.10 Pregnancy and In Utero Drug Exposure 83
8.3.11 Special Recommendations for Hypoglycemia 84
8.4 PHARMACOKINETICS 85
8.5 BIOBANKING SAMPLES FOR POST-HOC ASSESSMENTS 85
9 STATISTICAL METHODS 86
9.1 GENERAL CONSIDERATIONS 86
9.2 SAMPLE SIZE DETERMINATION 86
9.3 RANDOMIZATION 87
9.4 ANALYSIS SETS 87
9.4.1 Screened Set 87
9.4.2 Safety Set 88
9.4.3 Efficacy Analyses 88
9.4.3.1 Randomized Set (RS) 88
9.4.3.2 Intention-to-treat Set (ITTS) 88

9.4.3.3 Per Protocol Set (PPS) ... 88
9.4.4 PK Population ... 88
9.5 EFFICACY ANALYSIS ... 88
9.5.1 Primary Endpoint: relative change in liver fat content (LFC) ... 88
9.5.2 Secondary Endpoints ... 90
9.5.2.1 Absolute Change in liver fat content (LFC) ... 90
9.5.2.2 Analysis of responders ... 90
9.5.2.3 Other Secondary Endpoints ... 91
9.5.3 Safety Analysis ... 91
9.5.3.1 Adverse Events ... 91
9.5.3.2 Concomitant Medications ... 91
9.5.3.3 Physical Examination, Pitting Edema, Vital signs and Body measurements, Bone mineral density and ECG ... 92
9.5.3.4 Clinical Laboratory Data ... 92
9.5.3.5 Withdrawals of study ... 92
9.5.4 Exploratory Endpoints ... 92
9.5.5 Analysis of Further Endpoints ... 93
9.6 INTERIM ANALYSIS ... 93

10 ETHICAL AND REGULATORY ASPECTS ... 94

10.1 ETHICS AND GOOD CLINICAL PRACTICE ... 94
10.2 PATIENT INFORMATION AND INFORMED CONSENT ... 94
10.3 PATIENT IDENTIFICATION AND PRIVACY ... 95
10.4 EMERGENCY MEDICAL SUPPORT AND PATIENT EMERGENCY CARD ... 95
10.5 PATIENT INSURANCE AND COMPENSATION TO PATIENTS ... 96
10.6 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE ... 96
10.7 REGULATORY AUTHORITIES ... 97

11 STUDY MANAGEMENT ... 98

11.1 DATA COLLECTION AND CRF MANAGEMENT ... 98
11.2 HANDLING OF PROTOCOL DEVIATIONS ... 99
11.3 SOURCE DATA AND PATIENT FILES ... 99
11.4 INVESTIGATOR SITE FILE AND ARCHIVING ... 100
11.5 MONITORING, QUALITY ASSURANCE AND INSPECTION BY AUTHORITIES ... 100
11.6 CHANGES TO THE PROTOCOL ... 101
11.7 CLINICAL STUDY REPORT AND PUBLICATION POLICY ... 101
11.7.1 Clinical Study Report ... 101
11.7.2 Publication ... 102
11.7.3 Disclosure and Confidentiality ... 102

12 REFERENCES ... 103

13 ANNEX 1. SPONSOR, COORDINATING INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE ... 106

14 ANNEX 2. SERIOUS ADVERSE EVENT CONTACT INFORMATION.. 110

Index of Tables

Table 1. Visit Schedule Chart 26

Table 2. Treatments to be administered in the 4 treatment groups 49

Table 3. Pitting edema scale..... 70

Index of Figures

Figure 1. Diagram of Study Design 25

Figure 2. Screening period examination flow 29

1 Synopsis

Protocol Number	PXL065-003
Study Full Title	A 36-week, randomized, double-blind, placebo-controlled, parallel group trial to assess the efficacy and safety of PXL065 versus placebo in noncirrhotic, biopsy-proven Nonalcoholic Steatohepatitis (NASH) patients
Study Short Title	DESTINY 1
Program Acronym	**DESTINY** **D**euterium-stabilized R-pio (PXL065) **E**fficacy and **S**afety **T**rial **I**n **N**ASH
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 patient screened-last patient out)	Study start: Q3 2020 Study end: Q1 2022
Trial Objectives	**Primary objective** • To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on liver fat content (LFC) in NASH patients after 36 weeks of treatment **Secondary objectives** • To assess the safety and tolerability of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo in NASH patients after 36 weeks of treatment • To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on metabolic and non-metabolic parameters in NASH patients after 36 weeks of treatment • To assess the effect of 3 doses of PXL065 (7.5 mg QD, 15 mg QD and 22.5 mg QD) versus placebo on histological changes in liver biopsy in NASH patients after 36 weeks of treatment • Corporate confidential information • To describe PXL065 pre-dose plasma concentrations during the course of the treatment and the pre- and

	post-dose concentrations in NASH patients after 36 weeks of treatment
Trial Design and Plan **(Design description in *Figure 1* and schedule of visits in *Table 1*)**	Phase 2, multi-center, double-blind, placebo-controlled, randomized study with 4 parallel groups in noncirrhotic, biopsy-proven NASH patients. There will be a total of 3 study periods, as follows: • Screening Period: maximum of 8 weeks • Double-blind treatment period: 36 weeks • Follow-up period: 2 weeks Patients will be randomized in a 1:1:1:1 ratio to receive either: • PXL065 7.5 mg oral QD • PXL065 15 mg oral QD • PXL065 22.5 mg oral QD • Placebo oral QD Randomization will be stratified according to type 2 diabetes mellitus (T2DM) status (T2DM patients versus non-T2DM patients) and the NASH Clinical Research Network (CRN) fibrosis score (F1 versus F2/F3).
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.
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) ≤ 50 kg/m² during Screening Period 4. Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73m² during Screening Period calculated by the Chronic Kidney Disease – Epidemiology collaboration (CKD-EPI) formulae 5. Either T2DM or non-T2DM patients (after 50% non-T2DM patients have been randomized, only T2DM patients will be eligible). If T2DM patients: a. Glycated hemoglobin (HbA1c) ≤ 9.5% during Screening Period

	b. If treatment-naïve: patients must be diagnosed and under diet and exercise for the last 6 months prior to Randomization Visit (V1) c. If currently treated: patients must be on stable mono- or bi-therapy (i.e. same doses and same drug(s)). Permitted antidiabetic drugs are: • Metformin, sitagliptin, alogliptin: stable for at least 3 months prior to Randomization Visit (V1) • Empagliflozin, canagliflozin, dapagliflozin: stable for at least 6 months prior to Randomization Visit (V1) All other antidiabetic drugs are not allowed 6. Liver fat content (LFC) ≥ 8% measured with magnetic resonance imaging-proton density fat fraction (MRI-PDFF) during the Screening Period 7. Noncirrhotic, biopsy-proven NASH patients with: - Histological evidence of NASH based on liver biopsy with a NonAlcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) ≥ 4 (at least 1 point in each histological feature: steatosis, lobular inflammation and hepatocellular ballooning) - Histological evidence of liver fibrosis defined as NASH CRN System fibrosis score F1, F2 or F3. F1 patients must have at least one of these risk factors: T2DM, BMI ≥ 30 kg/m², and/ or ALT > 1.5 x ULN. After 35% of patients with a fibrosis score of F1 have been randomized only patients with F2 and F3 will be eligible 8. Qualifying liver biopsy must be obtained within 6 months prior to Randomization Visit (V1). If there is no available liver biopsy within this period, a liver biopsy must be performed during the Screening Period 9. Women of child-bearing potential (e.g. not surgically sterile or not postmenopausal) must have a negative serum pregnancy test during Screening Period and a negative urine pregnancy test at Randomization Visit (V1) 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

	10. Male patients must have agreed on an effective method of 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 POXEL, and staff and/or the study site staff) 2. Participation in another clinical study with intake of an investigational product during the last 3 months prior to Screening Period 3. Participation in another NASH clinical study with intake of an active investigational product during the last 6 months prior to qualifying liver biopsy (i.e. screen-failure patients or patients treated with placebo do not meet this exclusion criterion) 4. Previous participation in any clinical study with PXL065 intake ***Target disease exclusions*** 5. Evidence of another form of active 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) 6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 200 IU/L during Screening Period 7. Evidence of hepatic impairment during Screening Period as defined by any of the following parameters: a. Total bilirubin (TBL) ≥ 1.3 mg/dL unless diagnosis of Gilbert's disease b. Serum albumin < 3.5 g/dL c. International Normalized Ratio (INR) ≥ 1.3, except for patients under anticoagulant treatment d. Platelets < 150 G/L e. Hemoglobin < 11 g/dL in females or < 12 g/dL in males f. Evidence of portal hypertension (e.g. ascites, esophageal varices) 8. Bariatric surgery of any kind at any time prior to Randomization Visit (V1)

	9. Change in body weight greater than 5% within the last 6 months prior to Randomization Visit (V1) 10. Positive serologic evidence of current infectious liver disease including hepatitis B surface antigen (HBsAg), and/or hepatitis C virus antibody (anti-HCV) with detected circulating ribonucleic acid (RNA) during Screening Period. 11. History of excessive alcohol intake defined by ≥ 21 units of alcohol/week in males and ≥ 14 units of alcohol/week in females for 2 years prior to Randomization Visit (V1), where a unit of alcohol is equal to 10 g pure alcohol. ***Medical History and Concurrent Disease Exclusions*** *Cardiovascular diseases* 12. Any of the following disease within 6 months prior to Randomization Visit (V1): - Myocardial infarction - Cardiac revascularization surgery (coronary artery bypass graft / percutaneous transluminal coronary angioplasty (CABG / PTCA)) - Unstable angina - Transient ischemic attack, stroke or cerebrovascular disease 13. Any history of heart failure (HF) 14. Unstable or undiagnosed arrhythmias, long QT syndrome, short QT syndrome, history of drug-induced Torsade de Pointe 15. Uncontrolled high blood pressure (BP): diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg with or without antihypertensive treatment during Screening Period and/or at Randomization Visit (V1). BP measurement is the mean of 3 measurements and can be repeated once. If currently treated for hypertension: patients must be on stable therapy (i.e. same doses and same drugs) for the last 1 month prior to Randomization Visit (V1) 16. Lipid-lowering drug treatment modified (doses and/or drugs) during the past month prior to Randomization Visit (V1) *Hematological and oncological diseases* 17. Active malignance or malignancy with a complete remission date within 2 years prior to Randomization Visit (V1) (with the exception of treated basal cell carcinoma or treated squamous cell carcinoma of the skin)

	18. Any history of bladder cancer or unexplored macroscopic hematuria 19. History of haemoglobinopathies (e.g., sickle cell anemia or thalassemia, sideroblastic anemia) *Endocrinological disease* 20. Diabetes other than T2DM 21. Uncontrolled hypothyroidism (thyroid stimulating hormone (TSH) > 2 x the upper limit of normal (ULN) during Screening Period) ***Other exclusion conditions*** 22. Any recent (<1 year prior to Randomization Visit (V1)) history of bone fracture 23. Postmenopausal women with a bone mineral density (BMD) T-score ≤ -2.5 SD (osteoporosis) measured by standard dual-energy X-ray absorptiometry (DXA) within 6 months prior to Randomization Visit (V1) or if not available, during the screening period. Postmenopausal women with a T-score between -1 and -2.5 SD can be included if they are treated according to standards of care for osteopenia 24. Immunocompromised patients such as patients that underwent organ transplantation or are diagnosed with human immunodeficiency virus (HIV) 25. 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 26. Any recent (< 5 years) or current drug addiction 27. 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 28. Anorexia or bulimia 29. Known hypersensitivity to any of the constituents or excipients of the investigational medicinal product (IMP) or pioglitazone, or history of relevant drug and/or food allergies (e.g. anaphylactic, anaphylactoid reactions) 30. Use of non-permitted concomitant medication within 6 months prior to Randomization Visit (V1) *(A transient intake < 2 weeks may be allowed with the approval of the Medical Monitor and the POXEL Medical Representative)*: a. Any medication containing pioglitazone (e.g. Actos®, Actoplus Met®, Duetact®, Oseni®) or

	other approved or experimental thiazolidinediones (TZDs) (e.g. rosiglitazone (Avandia®), leriglitazone (MIN-102), MSDC-0602K), or peroxisome proliferator-activated receptor γ (PPARγ) agonists b. Any other antidiabetic drug except those permitted in inclusion criterion #5 (metformin, sitagliptin, alogliptin, empagliflozin, canagliflozin, and dapagliflozin) c. Topiramate, amiodarone, bile salt chelators, methotrexate, equal or more than 800 U of vitamin E per day, chronic use (> 2 consecutive weeks) of corticosteroids with a systemic effect at doses ≥10 mg/day of oral prednisone (or equivalent), orlistat, obeticholic acid or any other medications (including vitamins, herbal and dietary supplements) known to affect liver function/steatosis at the Investigator's discretion 31. Use of non-permitted medications related to the risk of drug-drug interaction at randomization visit. Corporate confidential information Those medications should be stopped or switched if the patient is eligible for randomization based on all other inclusion/exclusion criteria. 32. 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 33. Pregnancy or lactation
Investigational Medicinal Product(s) (IMP): dose / dosing schedule / mode of administration	PXL065 tablets (7.5 mg or 15 mg) orally Placebo tablets (matched for each PXL065 dosage) orally One intake per day in the morning Treatments to be administered in the 4 treatment groups: • PXL065 7.5 mg + Placebo (*matching PXL065 15 mg tablet*)

	• Placebo (*matching PXL065 7.5 mg tablet*) + PXL065 15 mg • PXL065 7.5 mg + PXL065 15 mg • Placebo (*matching PXL065 7.5 mg tablet*) + Placebo (*matching PXL065 15 mg tablet*)
Planned Study Duration per Patient	Study duration per patient (from Screening Period up to End-of-Study Visit (V9)) • Minimum: 40 weeks • Maximum: 46 weeks
Assessments for Efficacy	Primary endpoint: Relative change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT) Secondary endpoints: • Absolute change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT) • Response defined as an absolute reduction in LFC ≥ 5% from baseline to Week 36 (V8-EoT) • Response defined as a relative reduction in LFC ≥ 30% from baseline to Week 36 (V8-EoT) • Response defined as a relative reduction in LFC ≥ 50% from baseline to Week 36 (V8-EoT) • Response defined as a LFC value at Week 36 (V8-EoT) that is normalized, i.e. ≤5% • Change in the following parameters from baseline to Week 36 (V8-EoT): - Liver enzymes: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) - Percentage of responders as defined by the percentage of patient with normalization of liver enzymes in the subset of patients with increased baseline value - Measured glycemic parameters: Fasting plasma glucose (FPG), HbA1c, serum insulin, C-peptide - Insulin resistance indexes: Homeostasis model assessment of insulin resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), Homeostasis model assessment of β-cell function (HOMA-β) and Adipose tissue insulin resistance (Adipo-IR) Exploratory endpoints Change from baseline in the following parameters at Week 36 (V8-EoT):

	• Adiponectin • Lipids: total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, free fatty acids (FFA) • Biomarker of inflammation: High-sensitivity C-reactive protein (hsCRP) • Biomarkers of fibrosis: N-terminal type III collagen propeptide (pro-C3), NAFLD Fibrosis score (NFS) and Fibrosis 4 (FIB-4) score and Enhanced Liver Fibrosis (ELF) score • Histological change in liver biopsy: - Change in NAS, in each component of NAS (steatosis, ballooning and inflammation) and in NASH CRN fibrosis score - Improvement in each component of NAS (steatosis, lobular inflammation and hepatocellular ballooning) by ≥ 1 point without worsening of fibrosis - Improvement in NAS by ≥ 2 points without worsening of fibrosis - Improvement in NASH CRN fibrosis score by ≥ 1 point - NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) - NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with improvement in NASH CRN fibrosis score by ≥ 1 point - NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with no worsening in NASH CRN fibrosis score - NASH resolution (NAS score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and improvement in NAS by ≥ 2 points with no worsening in NASH CRN fibrosis score • Corporate confidential information
Assessments for Safety	Safety and tolerability will be assessed on the following parameters: • Adverse events (AEs)

	• Physical examination • Weight, waist and hip circumferences, and BMI • Vital signs: systolic BP, diastolic BP, heart rate (HR) • Pitting edema assessment • 12-lead electrocardiogram (ECG) • Bone mineral density in postmenopausal women • Biological parameters: biochemistry, hematology, coagulation • eGFR (CKD-EPI formula) • Urinalysis
Pharmacokinetics (PK)	One pre-dose blood sample will be drawn just before the IMP daily intake at Week 12, Week 24 and Week 36 (visits V4, V6, and V8-EoT) and one sample between 1h and 4h post-dose at Week 36 (last IMP intake, V8-EoT).
Other Assessment	Blood samples will be drawn in all patients for extra-samples at Randomization Visit (V1) and Week 36 (V8-EoT) to allow post-hoc testing of any additional safety and efficacy parameters or any potential biomarkers related to liver, cardiovascular, or metabolic diseases in relation with the drug target. The blood samples will be frozen and 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 objective, i.e. to demonstrate that at least one dose of PXL065 is superior to placebo in terms of the primary endpoint, i.e. the relative percent change in LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT). 120 patients (30 per am) need to be randomized to achieve a 90% power for this primary objective, assuming an expected difference of 30% between at least one dose of PXL065 and placebo, a 1-sided nominal alpha level of 0.025 for each comparison vs placebo, a common standard deviation of 30% and an expected drop-out rate of about 20%. **Statistical methods** Analyses will be further detailed in the Statistical Analysis Plan (SAP), which will be finalized prior to the unblinding and locking of the clinical database. <u>Analyses sets</u> • Screened Set: all patients who were screened for inclusion into the study

- Randomized Set (RS): all patients randomized and considered as randomized regardless of the treatment actually received.
- Safety Set (SS): all randomized patients having received at least one dose of the IMP (either PXL065 or placebo) and considered as-treated. Primary set for safety analyses and tolerability will be analyzed on the Safety Set.
- Intention-to-treat Set (ITTS): all patients having received at least one dose of the IMP (either PXL065 or placebo) and considered as randomized. Primary set for efficacy analyses.
- Per Protocol Set (PPS): ITT patients without any major violations.
- PK population: all patients from the SS who have been treated with PXL065 according to the protocol and have provided at least one pre-dose assessment during the study with sufficient plasma to derive the C_{pre}.

Efficacy analyses

Primary Endpoint:

The relative change in LFC from baseline to Week 36 (V8-EoT) will be analyzed on the ITTS in an analysis of covariance (ANCOVA) model adjusting for treatment (PXL065 doses of 7.5 mg QD, 15 mg QD and 22.5 mg QD, and placebo), for stratification factors, i.e. T2DM Status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline LFC as a continuous covariate. The Least Square Means (LSMs) of the primary endpoint for treatment groups and pairwise difference in LSMs will be estimated along with p-values and 95% confidence intervals.

Sensitivity analyses will be performed and detailed in the SAP.

Secondary Endpoints:

- *Absolute change in the percentage of LFC from baseline to Week 36 (V8-EoT)*: this will be analyzed in the same analysis of covariance (ANCOVA) model as for the primary endpoint.
- *Responders (as defined above)* will be analyzed with a stratified Cochran-Mantel-Haenszel-based approach. In addition, a logistic regression model adjusting for the same factors as for the primary analysis will be provided. Pairwise differences between PXL065 doses and placebo will be estimated in this model as odds ratio along with their p-values and 95% confidence intervals. A secondary approach described in Ge, *et al*., 2011 [1] will also be proposed.

	Other secondary and exploratory Endpoints: The analysis of these other secondary and exploratory endpoints will be fully detailed in the SAP. ***Safety Endpoints:*** Safety endpoints will be analyzed with usual descriptive methods. ***PK Endpoints:*** Pharmacokinetic data (PXL065 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

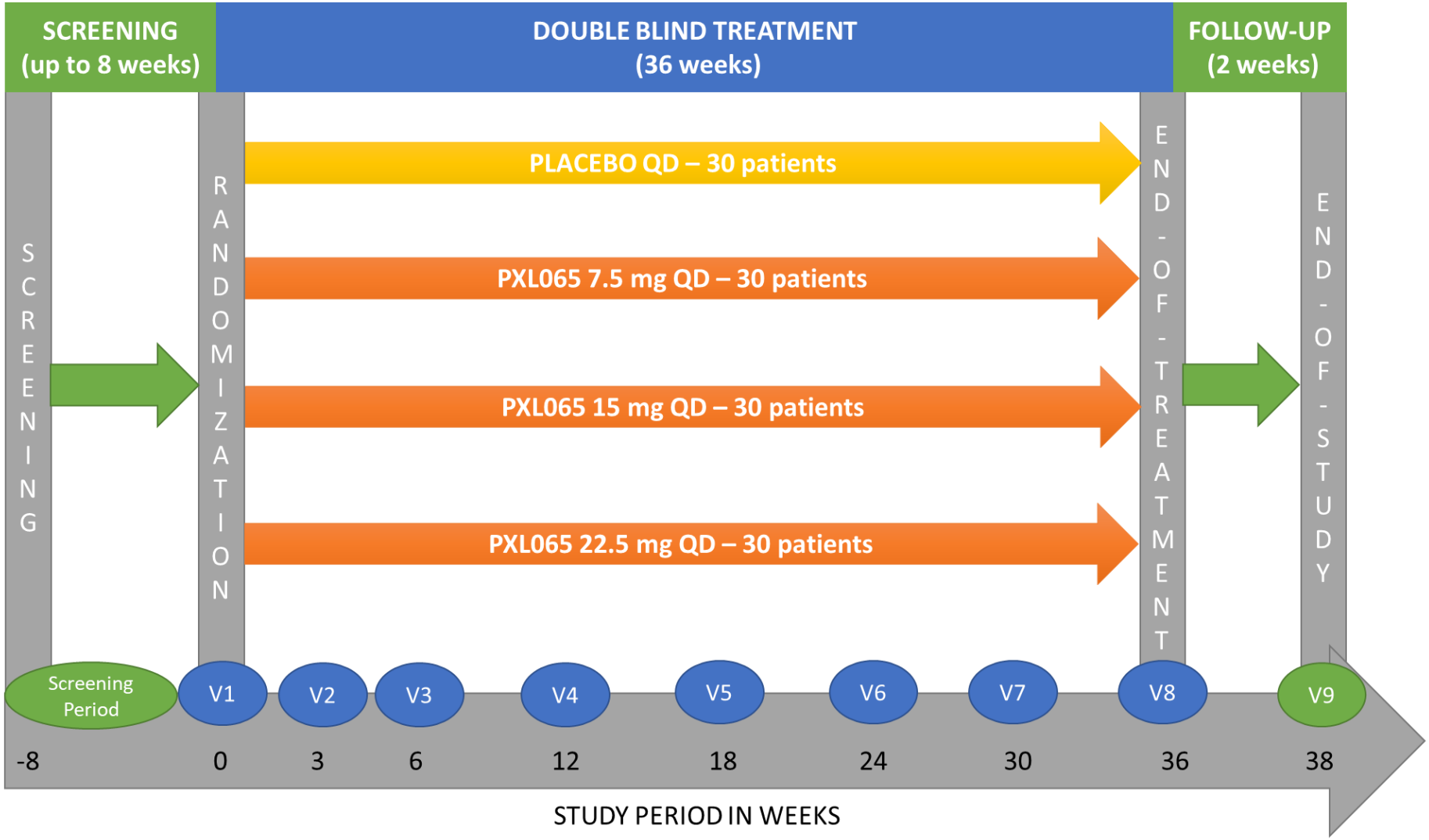


Table 1. Visit Schedule Chart

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.

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

AASLD: American Association for the Study of Liver Diseases; AE: adverse event; DXA: dual-energy X-ray absorptiometry; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; EoS: End-of-Study Visit; EoT: End-of-Treatment Visit; ET: Early Termination Visit; FPG: Fasting Plasma Glucose; HbA1c: glycated hemoglobin; hsCRP: High-sensitivity C-Reactive Protein; ICF: informed consent form; IMP: Investigational medicinal product; IWRS: Interactive Web Response System; lab: laboratory; MRI-PDFF: Magnetic Resonance Imaging - Proton Density Fat Fraction; param.: parameters; phys ex.: physical examination; PK: pharmacokinetics; SMBG: self-monitoring blood glucose;T2DM: Type 2 Diabetes mellitus V: visit; W: week(s)

[1]: The interval between two on-site visits must not exceed 48 days.

[2]: SMBG device dispensed to T2DM patients only. SMBG devices to be brought back to the study site at each visit for measurement review. SMBG device will be kept by the patient after the end of his/her study participation. Continuous Glucose Monitoring (CGM) is accepted and no SMBG device needs to be dispensed in this case.

[3]: Investigators will explain AASLD guidance regarding diet and exercise at Randomization Visit (V1). Investigators will collect the compliance to this guidance at each subsequent visit.

[4]: The complete physical examination will include head, ears, eyes, nose, mouth, skin, cardiovascular and lung examinations, lymph nodes, gastrointestinal, musculoskeletal and neurological systems. The limited physical examination will be focused on general appearance, the cardiovascular system as well as towards patient reported symptoms.

[5]: Vital signs and body measurements include: heart rate and 3 blood pressure measurements in supine or sitting position, and, height (during Screening Period only), body weight, BMI, waist and hip circumferences.

[6]: Postmenopausal women must have BMD T-score results assessed by standard DXA testing within 6 months prior to Randomization Visit (V1). If there is no available BMD T-score within this period, a DXA testing must be performed during the Screening Period only after receiving confirmation of eligibility on history, clinical examination and labs. DXA testing must also be performed before (within 8 days) or on the day of Week 36 (V8-EoT).

[7]: MRI-PDFF must be performed only after receiving confirmation of eligibility on history, clinical examination and labs during Screening Period. MRI-PDFF must also be performed before (within 8 days) or on the day of Week 36 (V8-EoT). MRI-PDFF must also be performed at Early termination Visit (ET) only for patients who withdraw from the study at or after Week 12 (V4) and only when the IMP was discontinued less than 14 days before the ET Visit.

[8]: Eligibility is to be confirmed based on all assessments before performing liver biopsy and/or sending material to histopathology central laboratory. A qualifying liver biopsy is required within 6 months prior to the Randomization Visit (V1). If no appropriate historical liver biopsy material is available, a liver biopsy must be performed during Screening Period. A second liver biopsy must be performed before (within 8 days) or on the day of Week 36 (V8-EoT).

[9]: The viral infection screen panel includes hepatitis screening (hepatitis B surface antigen (HBsAg), hepatitis C virus antibody (anti-HCV) and in case of positive result, reflex test of HCV circulating ribonucleic acid (RNA), anti-human immunodeficiency virus (HIV) 1 and 2)

[10]: The standard safety laboratory panel (blood and urine) includes hematology, biochemistry, coagulation and urinalysis. Refer to Section *8.3.6.1 Standard Safety Laboratory Panel (Blood and Urine)*

[11]: For female patients of child-bearing potential only. Serum pregnancy test (Human Chorionic Gonadotropin (β-HCG)) during Screening period, End-of-study Visit (V9) and Early termination Visit (ET) and urine pregnancy test at Randomization Visit (V1) and Week 18 (V5).

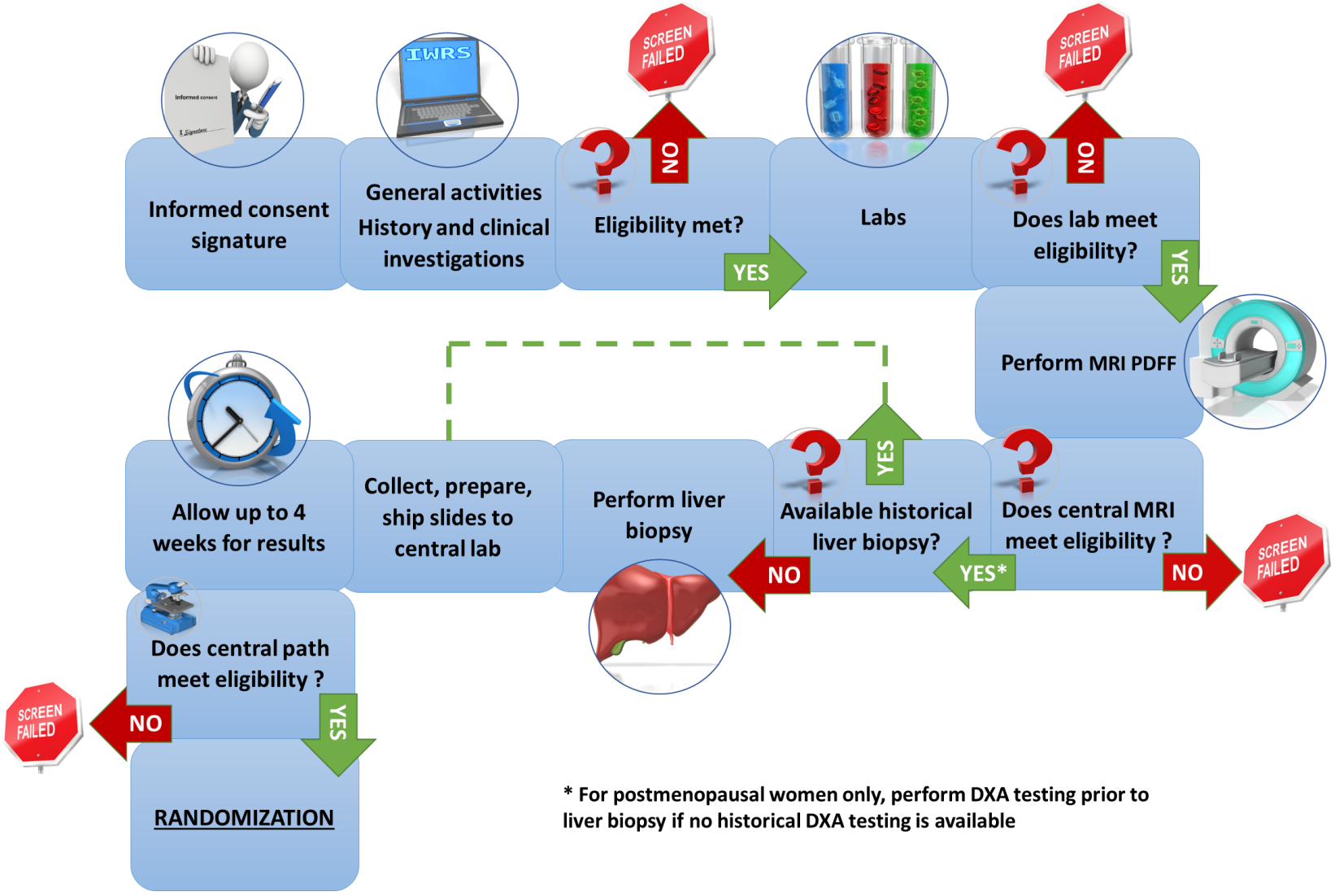
[12]: Measured metabolic parameters include serum insulin, C-peptide, adiponectin, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, free fatty acids (FFA)

[13]: Insulin resistance indexes include Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI), Homeostasis Model Assessment of β-cell function (HOMA-β) and Adipose tissue Insulin Resistance (Adipo-IR)

[14]: Fibrosis biomarkers include: N-terminal type III collagen propeptide (pro-C3), Nonalcoholic Fatty Liver Disease (NALFD) Fibrosis Score (NFS), Fibrosis 4 (FIB-4) score and Enhanced Liver Fibrosis (ELF) score

[15]: One pre-dose blood sample will be drawn just before the IMP daily intake at Week 12, Week 24 and Week 36 (visits V4, V6 and V8-EoT) and one sample between 1h and 4h post-dose at Week 36 (last IMP intake, V8- EoT).

Figure 2. Screening period examination flow



2 Background Information

2.1 Scientific Rationale

Nonalcoholic fatty liver disease (NAFLD) is one of the most prominent forms of chronic liver disease worldwide and is defined as the presence of ≥ 5% of hepatic steatosis in the absence of competing liver disease etiologies, use of medications that induce steatosis, and other chronic liver diseases. Within the general population, the overall global prevalence of NAFLD is estimated to be 25% [2]. NASH is a subset of NAFLD which is associated with inflammation and hepatocyte injury (with or without accompanying fibrosis). The prevalence of NASH in the general population is approximately 1.5% to 6.5% [2]. Multiple comorbidities are associated with NAFLD and/or NASH, including obesity, insulin resistance and/or T2DM, dyslipidemia, hypertriglyceridemia, hypertension, liver cirrhosis, hepatic impairment, and hepatocellular carcinoma [2]. Both cardiovascular and liver mortality are significantly elevated in patients with NAFLD, and these mortalities rise dramatically as the disease progresses to more advanced stages of fibrosis and scarring. In fact, NASH cirrhosis is currently the primary etiology for dual liver kidney transplantation and is estimated to become the number one indication for liver transplant by 2020 [3]. The striking prevalence of NAFLD and NASH paired with their profound complications underscore the critical need for safe and effective therapies [3]. However, there are no medications currently approved by the Food and Drug Administration (FDA) for the treatment of NASH.

Pioglitazone was first approved in the United States in 1999 and has been prescribed extensively for the treatment of T2DM. As of 2014, it was estimated that there were over 29 million patient years of exposure data available for pioglitazone [4]. Pioglitazone has been studied in humans as well as animal models for indications other than T2DM, including NASH. The safety profile of pioglitazone has been established via numerous animal toxicology studies, human clinical studies, and through its extensive use as an active ingredient in approved drugs. The efficacy of pioglitazone in both nondiabetic and diabetic NASH patients has been demonstrated in randomized controlled studies [5] and the use of pioglitazone in nondiabetic or diabetic biopsy-proven NASH patients is recommended by the practice guidance of the American Association for the Study of Liver Diseases (AASLD) [6] and of the European Association for the Study of the Liver [7]. However, in the United States, pioglitazone is prescribed by only about 14% of gastroenterologists and hepatologists to their biopsy-proven NASH patients, due primarily to its propensity to induce weight gain [8, 9].

Pioglitazone is a member of the class of compounds known as thiazolidinediones (TZDs). TZDs are known to be PPARγ activators. However, while PPARγ activation has been shown to result in positive pharmacological effects, PPARγ activation can also explain many of the side-effects observed in patients treated with TZDs. Specifically, PPARγ activation has been linked to weight gain [10], fluid retention [11], and bone loss [12, 13]. Recently, pioglitazone and other TZDs have been reported to exert pharmacological activity through additional, non-PPARγ-related mechanisms of action including

inhibition of mitochondrial pyruvate carrier (MPC) [14]. MPC inhibition, as opposed to PPARγ activation, is predicted to provide the treatment benefits for NASH patients [15].

All TZDs, including pioglitazone, are mixtures of stereoisomers with at least one chiral center at the 5-position of the TZD moiety. However, these stereoisomers chemically interconvert in solution and *in vivo* due to the chemical instability of the 5-position. Because of this chemical interconversion, information on the potential contribution of each enantiomer of pioglitazone to the overall pharmacological effects of the racemic mixture (1:1 mixture of *(R)*- and *(S)*-enantiomers) has not been previously reported. Replacement of hydrogen with deuterium at the chiral center of pioglitazone stabilized the chiral center and enabled characterization of each enantiomer. Deuterium is a naturally occurring, non-radioactive isotope of hydrogen broadly used in medicine to facilitate the tracing of compounds *in vivo* or to alter metabolism. Humans can tolerate high exposure to deuterium in body fluids, as no evident toxicity was observed upon acute exposure to levels of 15% to 23% deuterium replacement in whole body plasma [16]. Deuterated compounds that exemplify metabolic switches, i.e. stabilization against metabolism, have been extensively studied in nonclinical and clinical settings and the first deuterated drug, Austedo®, was approved by the FDA in 2017. Several applications of deuterium labeling in therapeutic research and development have been or are being pursued [17].

PXL065 is the deuterium-stabilized (*R*)-enantiomer of pioglitazone. PXL065 is stabilized against inversion of configuration by deuterium substitution at the chiral center of pioglitazone. This minor chemical change stabilizes the enantiomer by slowing, through a deuterium kinetic isotope effect, the formation of a planar intermediate, which leads to the formation of a mixture of the (*R*)- and (*S*)-enantiomers of pioglitazone. PLX065 is anticipated to have similar or better efficacy with less side effects than pioglitazone.

2.2 PXL065

2.2.1 Non-clinical Information

Corporate confidential information

Corporate confidential information

Corporate confidential information

Corporate confidential information

Corporate confidential information

2.3 Research Hypothesis

After 36 weeks of double-blind treatment, we aim to show superiority in LFC reduction, assessed by MRI-PDFF, achieved with PXL065 compared to placebo in noncirrhotic biopsy-proven NASH patients.

3 Study Objectives

3.1 Primary Objective

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

3.2 Secondary Objectives

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

Corporate confidential information

- To describe PXL065 pre-dose plasma concentrations during the course of the treatment and the pre- and post-dose concentrations in NASH patients after 36 weeks of treatment

4 Study Design

4.1 Study Design and Schedule

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

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

- Screening Period: maximum of 8 weeks

The screening period can be exceptionally extended after approval of the medical monitor and the POXEL medical representative, if there is no more than 10 weeks between MRI-PDFF and Randomization Visit (V1).

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

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

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

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients) and the NASH Clinical Research Network (CRN) fibrosis scoring system (F1 versus F2/F3). This study will have to include at least 50% of T2DM patients and a maximum 35% of F1 patients.

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

The duration of study for each patient from the first visit for the informed consent signature (ICF) up to the end of the Follow-up period will be between 40 and 46 weeks.

The end of study (EoS) 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 2, multicenter, double-blind, placebo-controlled, randomized, parallel group, dose-ranging trial in noncirrhotic, biopsy-proven NASH patients to assess the efficacy, safety and tolerability of PXL065 administered as monotherapy.

The design of the study is based upon the known safety and efficacy of pioglitazone in clinical practice and in NASH patients (assessed by liver biopsy) [18-20]. PXL065 is the deuterium-stabilized (*R*)-enantiomer of pioglitazone and is anticipated to have similar or better efficacy with less side effects than pioglitazone. The goal of this phase 2 study is to evaluate the dose(s) to be used for the confirmatory Phase 3 study, using a surrogate marker for LFC (MRI-PDFF) (primary endpoint), with histologic evaluation of the liver (secondary endpoints) to support the effect on NASH and to guide the SAP for the Phase 3 study. The patient population will include both non-T2DM and T2DM patients. The duration of the study is 36 weeks to assess the primary efficacy endpoint (MRI-PDFF) and secondary and exploratory endpoints based on liver histology with sufficient time between liver biopsies. The primary efficacy endpoint is based on emerging data that supports the use of MRI-PDFF as a noninvasive, quantitative, and accurate measure of LFC to assess treatment response in Phase 2 NASH trials [21] and reduction in LFC observed with pioglitazone by MRI or magnetic resonance spectroscopy (MRS) in biopsy-proven NASH patients [19, 22]. The assessment of weight as a secondary safety endpoint will seek to confirm the reduction in PPARγ activity and related weight gain seen with pioglitazone. The three doses of PXL065 (7.5 mg, 15 mg and 22.5 mg) were selected based on preclinical and Phase 1 studies combined with the product label of the listed drug, Actos. Since the highest approved dose of Actos is 45 mg QD and the Phase 1b Study of PXL065 demonstrated dose proportionality up to 30 mg QD, 22.5 mg PXL065 is the highest dose to be tested. The 15 mg dose of PXL065 is predicted to have efficacy similar to Actos 45 mg with little or no weight gain. The 7.5 mg dose of PXL065 is predicted to be the minimally efficacious dose without weight gain.

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. Rescreening will be allowed once (see Section 5.3)

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. Body mass index (BMI) ≤ 50 kg/m² during Screening Period
4. Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73m² during Screening Period calculated by the Chronic Kidney Disease – Epidemiology collaboration (CKD-EPI) formulae
5. Either T2DM or non-T2DM patients (after 50% non-T2DM patients have been randomized, only T2DM patients will be eligible).
   If T2DM patients:
   a. Glycated hemoglobin (HbA1c) ≤ 9.5% during Screening Period
   b. If treatment-naïve: patients must be diagnosed and under diet and exercise for the last 6 months prior to Randomization Visit (V1)
   c. If currently treated: patients must be on stable mono- or bi-therapy (i.e. same doses and same drug(s)).
      Permitted antidiabetic drugs are:
      - Metformin, sitagliptin, alogliptin: stable for at least 3 months prior to Randomization Visit (V1)
      - Empagliflozin, canagliflozin, dapagliflozin: stable for at least 6 months prior to Randomization Visit (V1)

      All other antidiabetic drugs are not allowed
6. Liver fat content (LFC) ≥ 8% measured with magnetic resonance imaging-proton density fat fraction (MRI-PDFF) during the Screening Period
7. Noncirrhotic, biopsy-proven NASH patients with:
   - Histological evidence of NASH based on liver biopsy with a NonAlcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS) ≥ 4 (at least 1 point in each histological feature: steatosis, lobular inflammation and hepatocellular ballooning)
   - Histological evidence of liver fibrosis defined as NASH CRN System fibrosis score F1, F2 or F3. F1 patients must have at least one of these risk factors: T2DM, BMI ≥ 30 kg/m², and/ or ALT > 1.5 x ULN. After 35% of patients with a fibrosis score of F1 have been randomized only patients with F2 and F3 will be eligible
8. Qualifying liver biopsy must be obtained within 6 months prior to Randomization Visit (V1). If there is no available liver biopsy within this period, a liver biopsy must be performed during the Screening Period

9. Women of child-bearing potential (e.g. not surgically sterile or not postmenopausal) must have a negative serum pregnancy test during Screening Period and a negative urine pregnancy test at Randomization Visit (V1) 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
10. Male patients must have agreed on an effective method of contraception with their female partner

5.2 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 POXEL, and staff and/or the study site staff)
2. Participation in another clinical study with intake of an investigational product during the last 3 months prior to Screening Period
3. Participation in another NASH clinical study with intake of an active investigational product during the last 6 months prior to qualifying liver biopsy (i.e. screen-failure patients or patients treated with placebo do not meet this exclusion criterion)
4. Previous participation in any clinical study with PXL065 intake

Target disease exclusions

5. Evidence of another form of active 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)
6. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 200 IU/L during Screening Period
7. Evidence of hepatic impairment during Screening Period as defined by any of the following parameters:
   a. Total bilirubin (TBL) ≥ 1.3 mg/dL unless diagnosis of Gilbert's disease
   b. Serum albumin < 3.5 g/dL
   c. International Normalized Ratio (INR) ≥ 1.3, except for patients under anticoagulant treatment
   d. Platelets < 150 G/L
   e. Hemoglobin < 11 g/dL in females or < 12 g/dL in males
   f. Evidence of portal hypertension (e.g. ascites, esophageal varices)
8. Bariatric surgery of any kind at any time prior to Randomization Visit (V1)
9. Change in body weight greater than 5% within the last 6 months prior to Randomization Visit (V1)

10. Positive serologic evidence of current infectious liver disease including hepatitis B surface antigen (HBsAg), and/or hepatitis C virus antibody (anti-HCV) with detected circulating ribonucleic acid (RNA) during Screening Period.
11. History of excessive alcohol intake defined by ≥ 21 units of alcohol/week in males and ≥ 14 units of alcohol/week in females for 2 years prior to Randomization Visit (V1), where a unit of alcohol is equal to 10 g pure alcohol.

Medical History and Concurrent Disease Exclusions

Cardiovascular diseases

12. Any of the following disease within 6 months prior to Randomization Visit (V1):
    - Myocardial infarction
    - Cardiac revascularization surgery (coronary artery bypass graft / percutaneous transluminal coronary angioplasty (CABG / PTCA))
    - Unstable angina
    - Transient ischemic attack, stroke or cerebrovascular disease
13. Any history of heart failure (HF)
14. Unstable or undiagnosed arrhythmias, long QT syndrome, short QT syndrome, history of drug-induced Torsade de Pointe
15. Uncontrolled high blood pressure (BP): diastolic BP ≥ 100 mmHg or systolic BP ≥ 160 mmHg with or without antihypertensive treatment during Screening Period and/or at Randomization Visit (V1). BP measurement is the mean of 3 measurements and can be repeated once. If currently treated for hypertension: patients must be on stable therapy (i.e. same doses and same drugs) for the last 1 month prior to Randomization Visit (V1)
16. Lipid-lowering drug treatment modified (doses and/or drugs) during the past month prior to Randomization Visit (V1)

Hematological and oncological diseases

17. Active malignance or malignancy with a complete remission date within 2 years prior to Randomization Visit (V1) (with the exception of treated basal cell carcinoma or treated squamous cell carcinoma of the skin)
18. Any history of bladder cancer or unexplored macroscopic hematuria
19. History of haemoglobinopathies (e.g., sickle cell anemia or thalassemia, sideroblastic anemia)

Endocrinological disease

20. Diabetes other than T2DM
21. Uncontrolled hypothyroidism (thyroid stimulating hormone (TSH) > 2 x the upper limit of normal (ULN) during Screening Period)

Other exclusion conditions

22. Any recent (<1 year prior to Randomization Visit (V1)) history of bone fracture
23. Postmenopausal women with a bone mineral density (BMD) T-score ≤ -2.5 SD (osteoporosis) measured by standard dual-energy X-ray absorptiometry (DXA) within 6 months prior to Randomization Visit (V1) or if not available, during the screening period. Postmenopausal

women with a T-score between -1 and -2.5 SD can be included if they are treated according to standards of care for osteopenia

24. Immunocompromised patients such as patients that underwent organ transplantation or are diagnosed with human immunodeficiency virus (HIV)
25. 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
26. Any recent (< 5 years) or current drug addiction
27. 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
28. Anorexia or bulimia
29. Known hypersensitivity to any of the constituents or excipients of the investigational medicinal product (IMP) or pioglitazone, or history of relevant drug and/or food allergies (e.g. anaphylactic, anaphylactoid reactions)
30. Use of non-permitted concomitant medication within 6 months prior to Randomization Visit (V1) *(A transient intake < 2 weeks may be allowed with the approval of the Medical Monitor and the POXEL Medical Representative)*:
    a. Any medication containing pioglitazone (e.g. Actos®, Actoplus Met®, Duetact®, Oseni®) or other approved or experimental thiazolidinediones (TZDs) (e.g. rosiglitazone (Avandia®), leriglitazone (MIN-102), MSDC-0602K), or peroxisome proliferator-activated receptor γ (PPARγ) agonists
    b. Any other antidiabetic drug except those permitted in inclusion criterion #5 (metformin, sitagliptin, alogliptin, empagliflozin, canagliflozin, and dapagliflozin)
    c. Topiramate, amiodarone, bile salt chelators, methotrexate, equal or more than 800 U of vitamin E per day, chronic use (> 2 consecutive weeks) of corticosteroids with a systemic effect at doses ≥10 mg/day of oral prednisone (or equivalent), orlistat, obeticholic acid or any other medications (including vitamins, herbal and dietary supplements) known to affect liver function/steatosis at the Investigator's discretion
31. Use of non-permitted medications related to the risk of drug-drug interaction at randomization visit.

Those medications should be stopped or switched if the patient is eligible for randomization based on all other inclusion/exclusion criteria.

32. 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

33. Pregnancy or lactation

5.3 Rescreening

Re-screening is permitted once with the approval of the Medical Monitor and the POXEL Medical Representative if a subject has not met the eligibility criteria within the screening period with the following exception:

- If a subject fails screening due to Inclusion Criterion #7 in Section 5.1, re-screening is not permitted.

Patients are only allowed to be re-screened once; the entire screening process (including informed consent signature) must be repeated except MRI-PDFF only if the investigator can ensure that there will be maximum 10 weeks between MRI-PDFF and Randomization Visit (V1).

5.4 Retesting during the Screening Period

If the investigator is not able to assess patient's eligibility for any of the laboratory or imaging eligibility criteria in cases of technical malfunction (e.g. loss of laboratory specimen) or an indeterminate result (e.g. out of stability sample, breathing motion artifact during the MRI) should be retested.

If there is reason to believe the assessment result may be inconsistent (i.e. contradicts recent result for the same parameter), the test may be repeated once within the screening period only with the approval of the Medical Monitor and the POXEL Medical Representative. If the original result was exclusionary and is confirmed by repeat testing, then the patient is to be considered a screen failure; these subjects may be rescreened as described in Section 5.3.

5.5 Restrictions during the Study

Investigators will explain to the patients at Randomization Visit (V1) the AASLD guidance [6] regarding diet and exercise. Investigators will collect the compliance to this guidance at each subsequent visit. Patients must make every effort to maintain the same diet/exercise treatment through the study. They will be asked about their compliance to this guidance at every visit. Answers will be documented in source documents and reported in the electronic Case Report Form (eCRF).

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

To respect *Inclusion criteria* #9, 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.

Effective contraception (as detailed in the *Inclusion criterion #9*) or abstinence should be used during the study and for at least 7 days after the last dose of study drug for both males and females of child-bearing potential.

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.

5.6 Patients Incorrectly Randomized

Patients who fail to meet the inclusion/exclusion criteria must not, under any circumstances, enter the double-blind treatment period.

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.

5.7 Criteria for Screen-failure

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

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

1. Target LFC (MRI-PDFF) not met (as defined in Section *5.1 Inclusion Criteria, Inclusion Criteria #6*)
2. Target liver histology criteria not met (as defined in Section *5.1 Inclusion Criteria, Inclusion Criteria #7*)
3. Cap reached for patients with NASH CRN fibrosis F1 (see Section *4.1 Study Design and Schedule*)
4. Other Inclusion criteria not met (as defined in Section *5.1 Inclusion 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. Occurrence of any other Exclusion criteria (as defined in Section *5.2 Exclusion Criteria*)
10. Withdrawal of patient informed consent
11. Lost to follow-up

The reason for screen failure must be documented in source documents and reported in the 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.

The Investigator will verify AE and concomitant medications. This information will be recorded in the patient file and in the eCRF, including screen-failure reason and date.

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

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

5.8.1 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 (Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher AE related to the drug **OR** CTCAE grade 4 or higher regardless of attribution to the study drug), if discontinuation of the IMP is considered necessary by the Investigator or POXEL Medical Representative
2. Occurrence of pregnancy
3. Important protocol deviation if discontinuation of IMP is considered necessary by the Investigator or POXEL Medical Representative/designee
4. 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
5. Requirement of an emergency unblinding (as described in Section *6.3.3.2 Emergency Unblinding)*
6. Withdrawal of patient informed consent

7. Lost to follow-up
8. Sponsor decision (as defined in Section *5.9 Discontinuation of the Study*)

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

5.8.2 Procedure for withdrawal from the study

In the case of discontinuation of IMP for any reason listed in Section *5.8.1 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 8 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 kits (used and unused), his/her patient diary and the self-monitoring blood glucose (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. The reason and date for withdrawal from the study must be documented in source documents, and reported in the eCRF and 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 resolution or stabilization of the medical condition. The Investigator must make every effort to collect the information related to the outcome of the event, as described in Section *8.3.8.5*. This information is recorded in the part of eCRF dedicated to AEs. If the IMP is discontinued as a result of a SAE/AESI/Overdose/Pregnancy, the procedure described in Section *8.3.8.4* 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; last contact date will be reported in the eCRF.

Any withdrawal from the study, irrespective of the reason, is to be notified immediately to the Medical Monitor and POXEL Medical Representative.

5.9 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 severity 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

The study will be paused if any of the following occurs:

- Three patients develop the same Grade 3 CTCAE classified as related to study drug
- Two patients develop the same Grade 4 CTCAE classified as related to study drug
- One patient develops a grade 5 CTCAE classified as related to study drug

In case the study is paused, the Sponsor will organize an *ad hoc* global safety board according to Sponsor's Standard Operating Procedures. This global safety board will assess the benefit/risk ratio in order to decide whether the study should be stopped or can be continued. This assessment/conclusion will be sent to Competent Authorities.

Competent Authorities and Institutional Review Boards/Ethics Committees (IRB/EC) 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.

5.10 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" [23].

In this study, the terminology IMP refers both to PXL065 (any dosage) or placebo.

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

PXL065 tablets contain 7.5 mg or 15 mg of PXL065 plus the excipients. The active pharmaceutical ingredient is the single, mono-deuterated *(R)*-enantiomer of pioglitazone, which is isolated as a Placebo tablets will contain excipients alone. PXL065 tablet of each dosage strength has the same shape, size and appearance (including the same color, smell and taste) as its respective placebo tablet.

Corporate confidential information

. The tablets are packaged in blisters. The qualitative composition of PXL065 tablets is given in the IB [24].

6.2 Dosage and Administration

PXL065 and/or placebo tablets will be taken once daily (QD) in the morning with a glass of water. Patients will take 2 tablets at each administration. For one administration, tablets should be taken together or one after the other. An optimal interval between the daily IMP intakes would be 24 ± 2 hours.

No IMP should be taken in the morning at home before each visit. IMP will be taken at study site after all visit assessments are performed as specified in *Table 1* and intake date/time will be recorded in the patient file by delegated staff.

Patients will be provided with the patient diary (paper format) as specified in *Table 1*. All IMP intakes (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). This also applies to Week 3 (V2), where the patient diary and IMP kits dispensed at Randomization Visit (V1) will be used until Week 6 (V3).

6.2.1 Double-blind Treatment Period

The double-blind treatment period starts at the time the first IMP dose is taken by the patient, on the day of the Randomization Visit (V1), in the morning, following randomization to one of the 4 double-blind treatment groups in this study.

To ensure a double-blind design, regardless of the treatment group, all patients will take an oral dose of 2 tablets QD of either placebo and/or PXL065 7.5 mg or 15 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 Tablets (Total = 2 Tablets/Day)
PXL065 7.5 mg QD (7.5 mg/day)	1 tablet of PXL065 7.5 mg + 1 tablet of placebo (*matching PXL065 15 mg tablet*)
PXL065 15 mg QD (15 mg/day)	1 tablet of placebo (*matching PXL065 7.5 mg tablet*) + 1 tablet of PXL065 15 mg
PXL065 22.5 mg QD (22.5 mg/day)	1 tablet of PXL065 7.5 mg + 1 tablet of PXL065 15 mg
Placebo	1 tablet of placebo (*matching PXL065 7.5 mg tablet*) + 1 tablet of placebo (*matching PXL065 15 mg tablet*)

The double-blind treatment period will last for 36 weeks after Randomization Visit (V1).

The first dose from the new IMP kit dispensed during the visit should be taken on-site during the visit, as detailed in Section *7.2 Double-blind Treatment Period*.

The last IMP intake will be at study site on the day of End-of-Treatment Visit (V8-EoT) (morning time; after completion of all pre-dose assessments).

6.2.2 Follow-up Period

The Follow-up period starts at the end of the 36-week double-blind treatment period. At the End-of-Treatment Visit (V8-EoT), 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 2 weeks.

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 (Screening Period to V9) by a patient number assigned upon ICF signature at the start of Screening Period.

The patient number consists of a unique 9-digit number using the schema AAA-XYY-ZZZ. The first 3 digits (AAA) indicate the study number (065). The 3 digits (XYY) indicate the pre-defined site number that consists of one-alphabetic letter and 2-digit number. The last 3 digits (ZZZ) identify the patient within the site. The first patient entered in a site will be assigned the number 001, the second will be assigned the number 002, and so on. For example, patient 065-S04-001 will be the first patient screened at site S04.

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. In case of rescreening, the Investigator (or designee) will register the patient again in the IWRS (as he/she was a new patient). A new patient number will be created and allocated automatically by the IWRS.

6.3.2 Treatment Assignment or Randomization

Double-blind treatment period

At Randomization Visit (V1), after confirming the eligibility criteria, the Investigator (or designee) will log on to the IWRS to 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 PXL065 doses of 7.5 mg QD, 15 mg QD and 22.5 mg QD or placebo for 36 weeks.

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3).

Patients will be assigned a unique randomization number at the Randomization Visit (V1) 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 the CRO in charge of medication packaging and logistics, and to the bioanalytical laboratory in charge of the PK assessments on samples from patients receiving PXL065.

During the double-blind treatment period, at each visit (except at Week 3 (V2)), 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 placebo tablets that have the same shape, size and appearance (including the same color, smell and taste) as the corresponding PXL065 tablets. Whatever the dose group they will be assigned to, patients will receive the same number of tablets (PXL065 and/or placebo) in order to keep the blind during the double-blind treatment period.

PXL065 and placebo tablets 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 and 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 designee Safety Provider) will also receive an authorization to access IWRS 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 *8.3.8.4*).

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 (Screening Period) to the End-of-Study Visit (V9-EoS). This is of particular importance for all concomitant medications which may affect the assessment of the efficacy endpoints (e.g. antidiabetic drugs, lipid lowering drugs); the dose(s) and drug(s) must remain stable during the whole study. Patients must not take any unlicensed medication, i.e. other investigational drugs except PXL065 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 (V9-EoS) will be considered as new medication.

Any prior, concomitant and new 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 medications from the Randomization Visit (V1) up to Week 38 (V9-EoS):

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

Corporate confidential information

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

PXL065 and placebo tablets will be packaged in appropriate blister and will be labeled in English with respect to the regulatory requirements in the United States.

Two tablets, one of each size for the two dosages of PXL065 (15 mg and 7.5 mg, or their respective placebo), should be taken at each intake. The patient must strictly follow these indications.

IMP kit: An IMP kit contains 96 tablets (48 days), corresponding to 6 weeks of treatment with 6 additional daily doses to cover time-window between visits; and will be dispensed at each dispensing visit during the double-blind treatment period.

IMP kit numbering: The IMP kit number will identify medication packs.

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 remaining 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, data logger temperature records and any damage to the IMP. The Investigator (or designee) will then 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 Site Drug Inventory Log throughout the whole duration of the study.

IMP resupply will be managed automatically through the IWRS.

6.7.3 Storage of IMP

The Investigator (or designee) will ensure that all IMPs are stored under recommended storage conditions in accordance with applicable US regulatory requirements and the pharmacy manual. IMP must be carefully and safely stored at the study site, 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) before the first dispensation of the day, at least on every working day (i.e. manually) 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 is the Investigator 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 visit. The IMP expiry date might be extended after the drug stability has been re-analyzed.

Instructions in case of expiration date extension and 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 .

IMP accountability

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

- Site Drug Inventory 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 Dispensing Log recording IMP dispensing and IMP return by patient detailed in terms of number of tablets.

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) at each visit except Week 3 (V2), from Randomization Visit (V1) to End-of-Treatment Visit (V8-EoT), 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. 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:

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

The acceptable compliance will be within 80% - 120% (≥80 % - ≤120%). If at any visit the compliance does not fall within this range, unless due to temporary interruption requested by the Investigator (e.g. due to AE), it must be reported as a protocol deviation and the Investigator must remind the patient to follow the IMP instructions.

Though no IMP compliance calculation is recorded at Week 3 (V2), the Investigator will still ensure that the patient takes IMP according to instructions.

6.7.5 Return and Destruction of IMP

The Investigator (or designee) will reconcile tablets returned by the patients with the Subject Dispensing Log. 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 clinical database hard 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 prevention

The packaging has been designed to prevent any overdose with a clear indication on the blisters of the 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, 6 extra daily doses are provided between 2 visits (6 weeks). For Week 3 (V2, 3 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 (V1) until Week 6 (V3, 6 weeks after randomization).

In the event of an overdose, please refer to Section *8.3.9 Overdose*.

7 Study Procedures

At each visit, it will be recommended to perform the assessments in the following order: Body measurements, ECGs, vital signs, blood samplings and IMP intakes (when applicable). Patients must be in a fasting condition for at least 10 hours (during which only water is permitted) prior to all study visits to allow for PK assessments and other labs.

7.1 Screening Period

Patients will be informed about the study in detail and sign the ICF prior to any study-related procedure. Rescreening will be allowed once (see Section 5.3)

The Screening Period starts from the date of ICF signature. Screening evaluations to determine patient eligibility will be conducted within 8 weeks prior to Randomization Visit (V1). The screening period can be exceptionally extended after approval of the medical monitor and the POXEL medical representative, if there is no more than 10 weeks between MRI-PDFF and Randomization Visit (V1).

The following procedures should be performed:

- Obtain ICF signature
- Register the patient in the IWRS to retrieve his/her patient study number
- Dispense patient emergency card
- Review Inclusion and Exclusion criteria
- Obtain demography
- 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 to ICF signature
- Conduct complete physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- 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:
    - Viral infection screen panel
    - Standard safety laboratory panel (blood and urine)

- eGFR calculation using CKD-EPI formula
- Serum pregnancy test (if applicable)
- FPG
- HbA1c

- Perform MRI-PDFF
- If no available historical BMD T-scores, perform standard DXA for postmenopausal women only
- Check if a qualifying liver biopsy is available and send the slides to the histopathology central laboratory to confirm eligibility
- If no available historical liver biopsy material, perform liver biopsy and send the slides to the histopathology central laboratory to confirm eligibility

The Screening Period can last up to 8 weeks in order to organize procedures and receive results to assess patient's eligibility. The screening period can be exceptionally extended after approval of the medical monitor and the POXEL medical representative, if there is no more than 10 weeks between MRI-PDFF and Randomization Visit (V1).

Procedures should follow the sequence as shown in *Figure 2. Screening period examination flow*, to avoid unnecessary examinations for screen-failure patients.

7.2 Double-blind Treatment Period

7.2.1 Visit 1: Randomization Visit (Day 1)

Randomization Visit (V1) will take place within a maximum of 8 weeks after ICF signature.

The following procedures will be completed:

- Review Inclusion and Exclusion criteria (**including MRI-PDFF and liver biopsy criteria**)
- Log on to IWRS to confirm patient eligibility and retrieve IMP kit number assigned by the system
- Dispense IMP kit for 6 weeks of treatment
- Dispense patient's diary
- Dispense SMBG device only for T2DM patients
- Provide AASLD lifestyle guidance
- Collect AE
- Collect concomitant medications
- Conduct complete physical examination
- Complete pitting edema assessment

- Record vital signs and body measurements
- 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:
    - Standard safety laboratory panel (blood and urine)
    - eGFR calculation using CKD-EPI formula
    - Urine pregnancy test (if applicable)
    - FPG
    - HbA1c
    - Measured metabolic parameters
    - Insulin resistance indexes
    - Fibrosis biomarkers
    - Biobanking sampling
- Ensure patient takes IMP daily dose on site

7.2.2 Visit 2: Week 3

Week 3 (V2) will take place 3 weeks (± 4 days) after Randomization Visit (V1).

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- Ensure appropriate IMP intakes and review patient diary (no data to record at this visit, no new dispensation)
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Ensure patient takes IMP daily dose on site

7.2.3 Visit 3: Week 6

Week 6 (V3) will take place 6 weeks (± 4 days) after Randomization Visit (V1).

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Calculate and record IMP compliance from Randomization Visit (V1) to Week 6 (V3) and review corresponding patient diary
- Dispense IMP kit for 6 weeks, according to IWRS, and patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Ensure patient takes IMP daily dose on site

7.2.4 Visit 4: Week 12

Week 12 (V4) will take place 12 weeks (± 6 days) after Randomization Visit (V1). The interval between V3 and V4 must not exceed 48 days.

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary
- Dispense IMP kit for 6 weeks, according to IWRS, and patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - Standard safety laboratory panel (blood and urine)

- FPG
- HbA1c
- Measured metabolic parameters
- Insulin resistance indexes
- PK sampling (before IMP intake)

- Ensure patient takes IMP daily dose on site

7.2.5 Visit 5: Week 18

Week 18 (V5) will take place 18 weeks (± 6 days) after Randomization Visit (V1). The interval between V4 and V5 must not exceed 48 days.

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary
- Dispense IMP kit for 6 weeks, according to IWRS, and patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Perform standard supine single 12-lead ECG
- If applicable, collect urine specimens for urine pregnancy test
- Ensure patient takes IMP daily dose on site

7.2.6 Visit 6: Week 24

Week 24 (V6) will take place 24 weeks (± 6 days) after Randomization Visit (V1). The interval between V5 and V6 must not exceed 48 days.

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system

- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary
- Dispense IMP kit for 6 weeks, according to IWRS, and patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Following at least a 10-hour fast (food and drink, except water), collect blood and urine specimens for the following:
    - Standard safety laboratory panel (blood and urine)
    - FPG
    - HbA1c
    - Measured metabolic parameters
    - Insulin resistance indexes
    - PK sampling (before IMP intake)
- Ensure patient takes IMP daily dose on site

7.2.7 Visit 7: Week 30

Week 30 (V7) will take place 30 weeks (± 6 days) after Randomization Visit (V1). The interval between V6 and V7 must not exceed 48 days.

The following procedures will be completed:

- Log on to IWRS to retrieve IMP kit number assigned by the system
- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary
- Dispense IMP kit for 6 weeks, according to IWRS, and patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications

- Conduct limited physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- Ensure patient takes IMP daily dose on site

7.2.8 Visit 8: End-of-Treatment Visit (EoT-Week 36)

End-of-Treatment Visit (V8-EoT) will take place 36 weeks (± 6 days) after Randomization Visit (V1). The interval between V7 and V8-EoT must not exceed 48 days.

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct complete physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- 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:
    - Standard safety laboratory panel (blood and urine)
    - eGFR calculation using CKD-EPI formula
    - FPG
    - HbA1c
    - Measured metabolic parameters
    - Insulin resistance indexes
    - Fibrosis biomarkers
    - Biobanking sampling
    - PK sampling (before IMP intake and between 1h and 4h after IMP intake). The morning meal time after IMP intake should be collected.

- Ensure patient takes the last IMP daily dose on site, in accordance with PK sampling schedule
- Perform MRI-PDFF, before (within 8 days) or on the day of Week 36 (V8-EoT)
- For postmenopausal women only, perform standard DXA testing, before (within 8 days) or on the day of Week 36 (V8-EoT)
- Perform liver biopsy, before (within 8 days) or on the day of Week 36 (V8-EoT),

7.3 Follow-up Period, Visit 9: End-of-Study Visit (EoS)

End-of-Study Visit (V9-EoS) will take place 2 weeks (± 3 days) after End-of-Treatment Visit (V8-EoT).

The following procedures will be completed:

- Log on to IWRS to register patient visit date
- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct complete physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- 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:
    - Standard safety laboratory panel (blood and urine)
    - Serum pregnancy test (if applicable)
    - FPG
- Refer patient to his/her previous physician for the pursuit of his/her routine medical care

7.4 Early Termination Visit (ET)

The following procedures will be completed during a visit within 8 days after the IMP discontinuation:

- Log on to IWRS to register patient withdrawal date
- Calculate and record IMP compliance from previous to current visit and review corresponding patient diary

- For T2DM patients, review SMBG measurements (or CGM recording) according to the Investigator (or designee) recommendation
- Record AASLD lifestyle guidance compliance as reported by patient
- Collect AE
- Collect concomitant medications
- Conduct complete physical examination
- Complete pitting edema assessment
- Record vital signs and body measurements
- 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:
    - Standard safety laboratory panel (blood and urine)
    - Serum pregnancy test (if applicable)
    - FPG
    - HbA1c
    - Measured metabolic parameters
    - Insulin resistance indexes
- Perform MRI-PDFF, before or on the day of Early Termination Visit, if study withdrawal occurs at or after Week 12 (V4) and only when the IMP was discontinued less than 14 days before the ET Visit
- 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 content assessed by MRI-PDFF – Central imaging core laboratory

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

MRI-PDFF is deemed a non-invasive, quantitative, and accurate measure of LFC to identify the study population and assess the treatment response in subjects with NASH. MRI-PDFF will be performed using a standardized imaging protocol and the results will be analyzed by a central reader. The central reader for this study will train the local imaging centers for this study and will provide imaging manual.

MRI-PDFF reports for Screening Period received by the central core imaging laboratory will be source data to confirm eligibility based on Inclusion criterion #6.

MRI-PDFF will be performed as planned in *Table 1*. MRI-PDFF must be performed only after receiving confirmation of eligibility on history, clinical examination and labs during Screening Period. MRI-PDFF must also be performed before (within 8 days) or on the day on the day of Week 36 (V8-EoT). MRI-PDFF must also be performed at Early termination Visit (ET) only for patients who withdraw from the study at or after Week 12 (V4) and only when the IMP was discontinued less than 14 days before the ET Visit.

MRI-PDFF will be exclusively used for assessment of LFC. 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 laboratory manual for further details.

8.2.2 Liver biopsy

All patients must have a qualifying liver biopsy within 6 months prior to Randomization Visit (V1). If no available liver biopsy at screening, a liver biopsy must be performed during Screening Period (see Inclusion criterion #7). All patients will have a liver biopsy at Week 36 (V8-EoT).

Histopathological examination of the liver biopsy specimen by a central reader will confirm the diagnosis and provide the staging for the disease. Scores for total NAS, steatosis, ballooning, lobular inflammation, and portal inflammation, as well as fibrosis stage will be evaluated.

Before performing a percutaneous liver biopsy, there must be a clearly defined indication for the biopsy, and the risks to the patient should not outweigh the potential benefits.

The platelet count and INR (or additional blood test) of the patient may be checked at a local clinical laboratory prior to the percutaneous liver biopsy according to local guidelines. If the conditions are not all respected, a safer option would be to perform the liver biopsy by trans-jugular route, when available.

Anticoagulants should be suspended around the time of liver biopsies to reduce hemorrhagic risk, according to local practices.

Sedation is recommended to be given for percutaneous liver biopsy and should be given with caution in liver disease.

The recommended biopsy procedure is as following:

- Needle core biopsy
- 16 or lower gauge needle
- Tissue core ≥ 2 cm long (≥ 10 portal tracts) represents optimal biopsy length
- Preferably obtain biopsy from the right lobe. If left lobe biopsy is used for the qualifying biopsy, a left lobe biopsy should be used for future biopsy at Week 36 (V8-EoT).

If the liver biopsy fragment is too small or of bad quality, precluding adequate reading, other available slides or new slides to be prepared from an available block of tissue may be requested of the site.

It is recommended that the patient should remain in the hospital consistent with the standard of care of that institution after the percutaneous biopsy.

Liver biopsy report for Screening Period received by the histopathology central laboratory will be source data to confirm eligibility based on Inclusion criterion #7.

Liver biopsies will be performed as planned in *Table 1*, please refer to Liver biopsy manual for further details.

Corporate confidential information

Results from central assessment of liver biopsy should be exclusively used for the purpose of this clinical trial and should not be used for the purpose of patient standard of care.

8.2.3 Other Efficacy Parameters

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

- Liver enzymes: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP)
- Measured metabolic parameters: fasting plasma glucose (FPG), HbA1c, serum insulin, C-peptide, adiponectin, total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides and free fatty acids (FFA)
- Insulin resistance indexes: Homeostasis model assessment of insulin resistance (HOMA-IR), Quantitative insulin sensitivity check index (QUICKI), Homeostasis model assessment of β-cell function (HOMA-β) and Adipose tissue insulin resistance (Adipo-IR)

HOMA-IR, QUICKI, and HOMA-ß will be calculated using the fasting C-peptide and FPG values at visits specified in *Table 1.* Adipo-IR will be calculated using the fasting insulin and FFA values at visits specified in *Table 1.*

The HOMA-IR is calculated as [25]:

Serum C-peptide (ng/mL) × FPG (mg/dL) / 405

The QUICKI is calculated as [26]:

1 / (log (FPG (mg/dL)) + log (C-peptide (ng/mL)))

The HOMA-ß is calculated as [25]:

(Serum C-peptide (ng/mL) × 360) / (FPG (mg/dL) – 63)

The Adipo-IR is calculated as [27]:

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

- Biomarker of inflammation: hsCRP (assessed as part of Section *8.3.6.1 Standard Safety Laboratory Panel (Blood and Urine)*
- Biomarkers of fibrosis: N-terminal type III collagen propeptide (pro-C3), NAFLD Fibrosis score (NFS), Fibrosis 4 (FIB-4) score and Enhanced Liver Fibrosis (ELF) 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) [28].

NFS is calculated as [28]:

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 [29, 30].

FIB-4 score is calculated as [29]:

(Age (years) x AST (IU/L))/ (platelet (10^9/L) x √(ALT (IU/L)))

ELF score is an extracellular matrix marker set consisting of tissue inhibitor of metalloproteinases 1 (TIMP-1), amino-terminal propeptide of type III procollagen (PIIINP) and hyaluronic acid (HA) showing good correlations with fibrosis stages in chronic liver disease [31].

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, cardiovascular and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, and neurological systems. The limited physical examination will be focused on general appearance, the cardiovascular system as well as towards patient reported symptoms.

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.

8.3.2 Pitting edema assessment

At each visit, an assessment of pitting edema will be performed.

The pitting edema will be assessed following this procedure:

- Place your index finger over the patient's tibia, 10 cm above the lateral malleolus
- Exert pressure for 5 seconds
- Any depression that does not resume its original contour almost immediately is a sign of pitting edema

If the presence of pitting edema is confirmed, the following scale should be used to grade it.

Table 3. Pitting edema scale

Grade	Physical Characteristics
1+	No visible change in shape of the extremity

	Pitting ≤ 2 mm Pit disappears rapidly
2+	No marked change in the shape of the extremity 2 mm < pitting ≤ 5 mm Pit usually disappears in 10-15 seconds
3+	Noticeable swollen extremity 5 mm < pitting ≤ 10 mm Pit may persist for about a minute
4+	Very swollen and distorted extremity Very deep pit > 10 mm Pit may persist 2 – 5 minutes

The presence or absence of edema will be recorded at each visit (Yes/No). If there is a pitting edema, a grade will be recorded for the edema according to the pitting edema scale.

8.3.3 Vital Signs and Body Measurements

Body measurements will be taken, before vital signs measurement. Weight should be measured with a scale having an appropriate resolution. The scale should be placed on a stable and flat surface. Patients are to be weighed in similar attire (only light clothing) and without shoes at each visit. Height will be recorded only during Screening Period. Waist and hip circumferences will be measured at each visit as planned in *Table 1.* All these data have to be recorded in the source documents and reported in the eCRF

One HR measurement will be taken after the patient has been resting in supine or sitting 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 or sitting 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.

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.

8.3.4 Patient Diary

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

Patients will be asked to report their IMP intakes (date + dose + 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. The review will be documented in the source documents and the Investigator will have to sign and date the previous patient diary and keep it in the patient file. At each visit, except Week 3 (V2) where no IMP/patient diary dispensation occurs, the appropriate data have to be reported in the eCRF.

8.3.5 Supine 12-Lead electrocardiogram (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. 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.

8.3.6 Laboratory Assessments

All laboratory measurements will be performed by a 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.

Any new clinically significant findings or worsening of laboratory abnormalities previously recorded as Medical History will be reported as AEs, and followed up and/or treated locally until the AE has resolved or the condition has stabilized. The CTCAE criteria, version 5.0, will be used to determine severity.

The following panel will be evaluated.

8.3.6.1 Standard Safety Laboratory Panel (Blood and Urine)

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

8.3.6.2 Viral Infection Screen Panel

Hepatitis screening	HIV screening
HBsAg	Anti-HIV 1 and 2

anti-HCV, and in case of positive result, reflex test of HCV circulating RNA

8.3.6.3 eGFR

eGFR will be calculated using the CKD-EPI formula, as follows [32]:

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

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.

8.3.6.4 Serum and Urine Pregnancy Tests

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

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

All pregnancy tests performed should be recorded in the source documents and reported in the eCRF.

If a pregnancy occurs during the study, refer to Section *8.3.10 Pregnancy and In Utero Drug Exposure*.

8.3.7 Bone mineral density

For postmenopausal women only, a standard DXA testing will be performed at the visits shown in the Visit Schedule Chart in *Table 1.*

If possible, all DXA testing for a given patient (historical testing or testing performed during Screening Period and Week 36 (V8-EoT)) should be performed at the same facility and using the same procedure.

DXA reports must be reviewed by the Investigator as soon as received. To confirm the review, the Investigator will need to sign and date the report and retain it in the patient file.

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

8.3.8 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 till the EoS (V9).

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.

8.3.8.1 Adverse Event Definitions

8.3.8.1.1 Adverse Event (AE)

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 (V9-EoS) performed two weeks after the End-of-Treatment Visit (V8-EoT).

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.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The Investigator is required to grade the severity/intensity of each AE according to CTCAE:

- CTCAE Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- CTCAE Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- CTCAE Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
- CTCAE Grade 4 (Life threatening): life-threatening consequences; urgent intervention indicated

- CTCAE Grade 5 (Death): death related to AE

8.3.8.1.2 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.

The following judgments of the causality to IMP or study procedures will 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.

8.3.8.1.3 Serious Adverse Event (SAE)

A SAE is an AE occurring during any study phase (i.e., Screening, 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 prior to ICF signature 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.

NOTE: To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3.8.1.4 Adverse Event of Special Interest (AESI)

An AE of Special Interest (AESI, serious or non-serious) is one of scientific and/or medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., regulators) might also be warranted.

Even if non-serious, AESI are managed with the same process than SAE:

- notification to the Sponsor within 24h following investigator awareness
- case to be created and processed in the safety database (including narrative writing) by Safety Provider.

In this study, the following AEs are considered as AESI:

- Heart failure. In case of any event of heart failure, whatever the cause, patients should be referred to a cardiology specialist.
- Pitting edema. In case of occurrence of pitting edema with presence of other suspected signs and/or symptoms of heart failure, patients should be referred to a cardiology specialist.
- Bladder cancer
- Bone fracture
- Drug-induced liver injury (DILI)

Below are specific recommendations for the management of elevated liver transaminases and/ or total bilirubin to detect and monitor a possible DILI, following FDA guidelines:

- **For patients with normal liver transaminases and total bilirubin at baseline (Randomization Visit (V1)):**

If patients with normal baseline (Randomization Visit (V1)) liver indices develop new elevations of AST or ALT >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, except for patients on anticoagulant treatment)
- 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 (V1)):**

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, except for patients on anticoagulant treatment.
- 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 DILI 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 IMP 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).
- Considering gastroenterology or hepatology consultations.

Only confirmed DILI should be reported as AESI.

8.3.8.2 Definition of the AE Reporting Period

The AE reporting period for safety surveillance begins when the patient is included into the study (ICF signature date) and continues through the end of the study's post-treatment follow-up period, defined as EoS (V9). AEs will be recorded on an ongoing basis in EDC. In case any AE occurs, the Investigator will follow up the patient within the AE reporting period until the event has resolved or the condition has stabilized. For SAEs, regardless of their relatedness to the IMP, the follow-up period might be extended, see Section *8.3.8.5*.

All SAEs that the Investigator considers related to IMP occurring after the post-treatment follow-up period (V9-EoS, or Early Termination Visit) must be reported to POXEL as well as to Safety Provider (see contact details in Section *14. Annex 2. Serious Adverse Event Contact Information)*.

Only events that occur after the first intake of IMP of the double-blind treatment period (Randomization Visit (V1)) 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 treatment-emergent AEs (TEAEs).

8.3.8.3 Methods of Recording and Assessing Adverse Events

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above in Section *8.3.8.2*) 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 severity grade (CTCAE Grade 1-5)
- 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:

- All the above information listed for AEs
- Additional information:
  - 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 (as described in Section *8.3.8.1.3*)

If a patient experienced the same AE several times during 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 version of the Medical Dictionary for Regulatory Activities (MedDRA®) available at the start of the study.

8.3.8.4 Sponsor immediate notification and Regulatory Reporting

8.3.8.4.1 Sponsor Immediate Notification

The Investigator must report immediately (within 24 hours of the Investigator's awareness) to POXEL as well as to Safety Provider all SAE/AESI/Overdose/Pregnancy occurring from

the date of ICF signature to the End-of-study Visit (V9-EoS) or to the last study visit performed in case of premature discontinuation.

For SAE, AESI, overdose and pregnancy, the study site must complete the corresponding eCRF page with as much available information within 24 hours of knowledge of the event.

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 Pregnancy/Overdose Form
- Email the form to POXEL as well as to Safety Provider (fax can be used as second option), contact details in Section *14. Annex 2. Serious Aaverse Event Contact Information*.

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

8.3.8.4.2 Reporting to Regulatory Authorities (Expedited Reporting), Investigators and Independent Ethics Committees/Institutional Review Boards

SUSARs and other safety information requiring expedited reporting will be reported to Investigators, Ethics Committees as well as 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 AEs that are both serious and unexpected and are considered to be related to the administered product (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.

8.3.8.5 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 event is resolved or stabilized, 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.

For SAEs, regardless of their relatedness to the IMP, follow-up of the outcome might be extended until the clinical database hard lock if not resolved or stabilized before, in agreement by the Investigator, POXEL Medical Representative and Medical Monitor.

8.3.9 Overdose

Preclinical data showed that daily administration of PXL065 was well tolerated in the dog for 13 weeks at doses up to 15 mg/kg/day.

Clinical data available so far with PXL065 showed a good safety and tolerability profile in healthy subjects after single and repeated administrations of PXL065 up to 30 mg QD. The dose of 30 mg QD is the maximal dose tested in humans.

Overdose is defined as any dose greater than the daily dose prescribed, equivalent to the intake of 3 or more capsules per day, in any of the cohorts.

Any suspicion of overdose, whether or not associated with a AE must be reported to POXEL and Safety Provider immediately (within 24 hours of the Investigator's awareness) (contact details in Section *14. Annex 2. Serious Adverse Event Contact Information*). Details of overdose and any AE associated with this will be reported by the Investigator in the eCRF system also.

These events will be managed, followed up and reported as any other SAE.

No specific antidote is currently available for PXL065 and only symptomatic therapy is possible.

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

8.3.10 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 (V9-EoS) must be reported to POXEL and Safety Provider immediately (within 24 hours of the Investigator's awareness) (contact details in Section *14. Annex 2. Serious Adverse Event Contact Information*).

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 Safety Provider with 24 hours of the Investigator's awareness.

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 after obtaining written consent from the pregnant partner.

8.3.11 Special Recommendations for Hypoglycemia

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 with T2DM should check their glucose levels, using SMBG devices at least twice a week (unless CGM is used). The investigator will be responsible to ensure the clinical assessment of hypoglycemic events. The investigator might decide to reduce the dose and / or to discontinue the background glucose lowering therapy in order to reduce recurrence of hypoglycemia.

Patients are requested to immediately perform a finger stick glucose measurement with the SMBG device provided for this study (unless CGM is used) if any symptoms occur that may be related to hypoglycemia and to avoid any delay in treating these symptoms. After the recovery of the symptoms, patients may report all the symptoms, date and time, dietary intake states, time of the recovery in the patient diary as well as blood glucose values if available. Only symptoms and / or plasma glucose concentration values deemed by the Investigator to meet the definition of hypoglycemia should be reported in the eCRF. Hypoglycemia will be reported as recommended by the FDA guidance [33]:

- 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 (or CGM) 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…).

8.4 Pharmacokinetics

During this study, pre-dose and post-dose plasma concentration of PXL065 will be assessed as indicated in *Table 1*.

The assays of PXL065 will only be carried out in patients who have received the active drugs. 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 PXL065, blood samples will be taken by an indwelling catheter or direct venipuncture, as appropriate.

Please refer to the central laboratory manual for further explanations.

8.5 Biobanking Samples for Post-hoc Assessments

Blood (total, plasma and serum) 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 stored until further use. All the biobanking samples will be destroyed within 2 years after the final study report is issued.

No genetic testing will be performed.

Please refer to the central laboratory manual for further explanations.

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 SAP, which will be finalized prior to the unblinding and locking of the clinical database.

9.1 General considerations

In general, summary tabulations will be presented by treatment arm and will display the number of patients/observations, mean, standard deviation, median, 25% and 75% percentiles, 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 2 trial for internal decision), no adjustment for multiplicity will be considered. Hence, pairwise comparisons between PXL065 doses (PXL065 doses of 7.5 mg QD, 15 mg QD and 22.5 mg QD) vs placebo and pairwise comparisons between PXL065 active doses will be tested at the two-sided nominal level of significance of 0.05.

The primary endpoint will be the relative change LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT).

The primary set for efficacy analysis will be the ITTS.

No interim analysis is planned for this study.

Sensitivity methods to handle missing data will be further detailed in the SAP.

9.2 Sample Size Determination

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

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

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

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

- No adjustment for multiple comparisons between PXL065 doses and placebo will considered and the usual nominal 1-sided alpha level of 0.025 (or equivalently the 2-sided level of 0.05) will be considered for each PXL065 dose vs placebo comparison
- A power of 90%
- An expected difference μ_{PXL065} - $\mu_{placebo}$ of -30% for **at least one PXL065 dose** vs placebo comparison
- A standard deviation (SD) of the primary endpoint equal to 30%, as estimated from previous published data [34]
- With these assumptions, a sample size of 23 patients per arm is needed to achieve 90% power for at least one PXL065 dose vs placebo comparison.

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

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: PLX065 7.5 mg QD
- Group 2: PXL065 15 mg QD
- Group 3: PXL065 22.5 mg QD
- Group 4: Placebo

Randomization will be stratified according to T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3).

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 Set

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

9.4.2 Safety Set

The Safety Set (SS) comprises all randomized patients having received at least one dose of the IMP (either PXL065 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 ITTS. The PPS 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 (ITTS)

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

9.4.3.3 Per Protocol Set (PPS)

The PPS consists of all ITTS patients without any important violations of study procedures. Important protocol violations will be identified prior to breaking the blind. Protocol deviations will be reviewed and classified as important and non-important during a data review meeting that will be held before clinical database hard lock and breaking the blind.

9.4.4 PK Population

The PK population corresponds to the SS and includes all randomized patients who have been treated with PXL065 according to the protocol and have provided at least one pre-dose assessment during the study with sufficient plasma to derive the C_{pre}.

9.5 Efficacy analysis

9.5.1 Primary Endpoint: relative change in liver fat content (LFC)

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

No adjustment for multiplicity will be considered.

Primary method to handle missing data: the LFC will be assessed at baseline and Week 36 (V8-EoT) only. For patients who withdraw from the study at or after Week 12 (V4), the LFC will be assessed at Early Termination Visit (ET) as far as possible. With the assumption that the LFC assessed at or after Week 12 (V4) reflects what could have been observed at Week 36 (V8-EoT), the missing LFCs at Week 36 (V8-EoT) will be estimated by this value. For patients who withdraw before Week 12 (V4) or withdraw at or after Week 12 (V4) but without any LFC assessment on treatment, LFC missing values at Week 36 (V8-EoT) will be imputed using a multivariate imputation approach by fully conditional specification (FCS) regression method assuming Missing At Random Mechanism. The set of variables included in the multiple imputation model will be further specified in the SAP.

Primary analysis:

The primary endpoint, i.e. expressed as the relative change in the percentage of LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT), will be analyzed in an analysis of covariance (ANCOVA) model adjusting for treatment (PXL065 doses of 7.5 mg QD, 15 mg QD and 22.5 mg QD and placebo) and for stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients) and NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline LFC as a continuous covariate.

The LSMs of the primary endpoint for treatment groups and pairwise differences in LSMs will be estimated along with p-values and 95% confidence intervals.

The 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 NASH CRN fibrosis scoring system 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.

Other sensitivity analyses to handle missing data will be further detailed in the SAP.

Subgroup analyses:

Subgroup if interest will be analyzed for the primary endpoint.

Subgroup analyses will be displayed with a forest plot to check consistency of the treatment effect across subgroups. Tests for subgroup by treatment interaction at the nominal alpha level of 0.10 will be provided and further detailed in the SAP:

- baseline age group (<65 years, ≥65 years)
- BMI (<median and ≥ median)
- Sex (female and male)

- T2DM status (T2DM patients versus non-T2DM patients)
- NASH CRN fibrosis scoring system (F1 versus F2/F3)
- Baseline LFC (assessed by MRI-PDFF) (<median and ≥ median)
- Pooling site. Before unblinding, the rule of pooling site according to geographical area or other rationale shall be discussed by study team and documented in SAP.

9.5.2 Secondary Endpoints

9.5.2.1 Absolute Change in liver fat content (LFC)

The absolute change in LFC (assessed by MRI-PDFF) from baseline to Week 36 (V8-EoT) will be analyzed in ANCOVA model adjusting for treatment, T2DM status (T2DM patients versus non-T2DM patients), and NASH Fibrosis CRN histological scoring system (F1 versus F2/F3) and for baseline LFC as a continuous covariate. Least square means of the primary endpoint for treatment groups (PXL065 doses of 7.5 mg QD, 15 mg QD, 22.5 mg QD and placebo) and pairwise differences in LSMs will be estimated along with their p-values and 95% confidence intervals.

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

For each type of response, responder rate will be provided within each treatment group.

Binary endpoints will be primarily analyzed with a stratified Cochran-Mantel-Haenszel approach and further detailed in the SAP.

Additional analyses will be proposed:

- The binary response will be analyzed in a logistic regression model adjusting for treatment (PXL065 doses of 7.5 mg QD, 15 mg QD, 22.5 mg QD and placebo), stratification factors, i.e. T2DM status (T2DM patients versus non-T2DM patients),

NASH CRN fibrosis scoring system (F1 versus F2/F3), and for the baseline LFC as a continuous covariate. Pairwise differences in treatment groups will be estimated in this model as odds ratios along with their p-values and 95% confidence intervals.

- The binary response will be analyzed based on the approach proposed by Ge, *et al.*, 2011 [1] and further detailed in the SAP.

9.5.2.3 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, AST, GGT, ALP
- Percentage of responders as defined by the percentage of patient with normalization of liver enzymes in the subset of patients with increased baseline value
- Measured glycemic parameters: FPG, HbA1c, serum insulin, C-peptide
- Insulin resistance indexes: HOMA-IR, QUICKI, HOMA-β, Adipo-IR

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

9.5.3 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:

9.5.3.1 Adverse Events

AEs will be coded using the most recent version available of the MedDRA at the start of the study. The frequency and incidence of TEAEs will be presented by System Organ Class (SOC) and preferred term for PXL065 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 AEs 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 SAEs and AEs leading to permanent discontinuation of IMP or to death will be listed separately.

9.5.3.2 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.

9.5.3.3 Physical Examination, Pitting Edema, Vital signs and Body measurements, Bone mineral density and ECG

Physical examination, pitting edema assessment, vital signs and body measurements, bone mineral density and ECG parameters will be summarized descriptively by treatment and timepoint. Similarly, changes from baseline will be summarized.

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

9.5.3.4 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.

9.5.3.5 Withdrawals of study

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

9.5.4 Exploratory Endpoints

Efficacy exploratory endpoints are as follows:

- Adiponectin
- Lipids: total cholesterol, LDL-c, HDL-c, triglycerides, FFA
- Biomarker of inflammation: hsCRP
- Biomarkers of fibrosis: pro-C3, NFS, FIB-4 and ELF score
- Histological change in liver biopsy:
  - Change in NAS, in each component of NAS (steatosis, ballooning and inflammation) and in NASH CRN fibrosis score
  - Improvement in each component of NAS (steatosis, lobular inflammation and hepatocellular ballooning) by ≥ 1 point without worsening of fibrosis
  - Improvement in NAS ≥ 2 points without worsening of fibrosis
  - Improvement in NASH CRN fibrosis score by ≥ 1 point

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

Corporate confidential information

9.5.5 Analysis of Further Endpoints

Pharmacokinetic data (PXL065 concentrations) will be analyzed using a Population PK model. PK parameters will be listed and summarized by treatment groups and by visits/timepoints.

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.

Study staff 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 training must be documented on the Curriculum Vitae and/or evidence of training provided. 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 person obtaining consent 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 patient 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 upon ICF signature, at the start of Screening Period. 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 will be stored under this number. The identification list, to link the patient's study data to the patient, will be kept at the study site with restricted access under the Investigator's responsibility. 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 upon ICF signature at the start of Screening Period. 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. 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, patient emergency card) 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 for favorable opinion/approval 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 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 *8.3.4*.

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 anonymous 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.
- A portion of the slides prepared from liver biopsies collected during the study will be sent to a centralized pathologist. Results will be communicated to the centralized laboratory for data entry into the laboratory database and data will then be electronically transferred to the Data Management Department.

- Laboratory blood and urine samplings will be sent to the centralized laboratory and results will be transferred electronically to Data Management Department.
- 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 final transfers and clinical database hard lock.

All the data collected during the trial will be integrated into a validated clinical database. will be responsible for data processing, in accordance with data management procedures. Clinical 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.

During the study, SAE/Overdose/Pregnancy/AESI (reported on the respective forms in eCRFs) will be shared with POXEL and the Safety Provider within 24h following Investigator awareness. Each SAE will be processed into the POXEL global safety database hold by and according to Adverse Event Reporting Plan (AERP). Each case will be assigned a safety database case identification number. Each case will be reviewed by POXEL before being reported to the relevant Competent Authorities as required. SAE/Overdose/Pregnancy/AESI from the safety database will be reconciled with those of the clinical database.

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 (or his/her designee).

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 ICFs. 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
- 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 entirety 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.

12 References

1. Ge, M., et al., *Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences.* Drug Information Journal, 2011. **45**: p. 481-493.

2. Younossi, Z.M., et al., *Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes.* Hepatology, 2016. **64**(1): p. 73-84.

3. Konerman, M.A., J.C. Jones, and S.A. Harrison, *Pharmacotherapy for NASH: Current and emerging.* J Hepatol, 2018. **68**(2): p. 362-375.

4. Takeda, *Takeda announces completion of the postmarketing commitment to submit data to the FDA, the EMA, and the PMDA for pioglitazone-containing medicines including ACTOS.* 2014.

5. Musso, G., et al., *Thiazolidinediones and Advanced Liver Fibrosis in Nonalcoholic Steatohepatitis: A Meta-analysis.* JAMA Intern Med, 2017. **177**(5): p. 633-640.

6. Chalasani, N., et al., *The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases.* Hepatology, 2018. **67**(1): p. 328-357.

7. EASL-EASD-EASO, *EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease.* J Hepatol, 2016. **64**(6): p. 1388-402.

8. Rinella, M.E., et al., *Practice patterns in NAFLD and NASH: real life differs from published guidelines.* Therap Adv Gastroenterol, 2016. **9**(1): p. 4-12.

9. Sanyal, A.J., et al., *Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis.* N Engl J Med, 2010. **362**(18): p. 1675-85.

10. Shah, P. and S. Mudaliar, *Pioglitazone: side effect and safety profile.* Expert Opin Drug Saf, 2010. **9**(2): p. 347-54.

11. Guan, Y., et al., *Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption.* Nat Med, 2005. **11**(8): p. 861-6.

12. Wan, Y., *PPARgamma in bone homeostasis.* Trends Endocrinol Metab, 2010. **21**(12): p. 722-8.

13. Fukunaga, T., et al., *An insulin-sensitizing thiazolidinedione, which minimally activates PPARgamma, does not cause bone loss.* J Bone Miner Res, 2015. **30**(3): p. 481-8.

14. Divakaruni, A.S., et al., *Thiazolidinediones are acute, specific inhibitors of the mitochondrial pyruvate carrier.* Proc Natl Acad Sci U S A, 2013. **110**(14): p. 5422-7.

15. McCommis, K.S. and B.N. Finck, *Treating Hepatic Steatosis and Fibrosis by Modulating Mitochondrial Pyruvate Metabolism.* Cell Mol Gastroenterol Hepatol, 2019. **7**(2): p. 275-284.

16. Harbeson, S. and R. Tung, *Deuterium in drug discovery and development.* Annual Reports in Medicinal Chemistry, 2011. **46**: p. 403-417.

17. Pirali, T., et al., *Applications of Deuterium in Medicinal Chemistry.* J Med Chem, 2019. **62**(11): p. 5276-5297.

18. Promrat, K., et al., *A pilot study of pioglitazone treatment for nonalcoholic steatohepatitis.* Hepatology, 2004. **39**(1): p. 188-96.

19. Belfort, R., et al., *A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis.* N Engl J Med, 2006. **355**(22): p. 2297-307.

20. Cusi, K., et al., *Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial.* Ann Intern Med, 2016. **165**(5): p. 305-15.

21. Caussy, C., et al., *Noninvasive, Quantitative Assessment of Liver Fat by MRI-PDFF as an Endpoint in NASH Trials.* Hepatology, 2018. **68**(2): p. 763-772.

22. Kim, C.W., et al., *Acetyl CoA Carboxylase Inhibition Reduces Hepatic Steatosis but Elevates Plasma Triglycerides in Mice and Humans: A Bedside to Bench Investigation.* Cell Metab, 2017. **26**(2): p. 394-406.e6.

23. Council, E.P.a.o.t., *Official Journal Of the European Communities. Directive 2001/20/EC of the Europea Parliament and of the Council of 4 april 2001*, in *Article 2(d)*. 2001.

24. *POXEL Investigator's Brochure Version 4. 0 / 31 Mar 2020.*

25. Wallace, T.M., J.C. Levy, and D.R. Matthews, *Use and Abuse of HOMA Modeling.* Diabetes Care, 2004. **27**(6): p. 1487-1495.

26. Katz, A., et al., *Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans.* J Clin Endocrinol Metab, 2000. **85**(7): p. 2402-10.

27. Lomonaco, R., et al., *Effect of adipose tissue insulin resistance on metabolic parameters and liver histology in obese patients with nonalcoholic fatty liver disease.* Hepatology, 2012. **55**(5): p. 1389-97.

28. Angulo, P., et al., *The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD.* Hepatology, 2007. **45**(4): p. 846-54.

29. Sterling, R.K., et al., *Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection.* Hepatology, 2006. **43**(6): p. 1317-25.

30. Verlinden, W., et al., *Validation of APRI and FIB-4 score in an Antwerp cohort of chronic hepatitis C patients.* Acta Gastroenterol Belg, 2015. **78**(4): p. 373-80.

31. Lichtinghagen, R., et al., *The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values.* J Hepatol, 2013. **59**(2): p. 236-42.

32. Levey, A.S., et al., *A new equation to estimate glomerular filtration rate.* Ann Intern Med, 2009. **150**(9): p. 604-12.

33. FDA, *Guidance for Industry. Diabetes mellitus: developping drugs and therapeutic biologics for treatment and prevention*. 2008.

34. Harrison, S.A., et al., *NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial.* Lancet, 2018. **391**(10126): p. 1174-1185.

13 Annex 1. Sponsor, Coordinating Investigators and Study Administrative Structure

Corporate confidential information

Corporate confidential information

Corporate confidential information

Corporate confidential information

14 Annex 2. Serious Adverse Event Contact Information

In case of a SAE/AESI/Overdose/Pregnancy (see Section *8.3.8.4.1*), the Investigator will share the information immediately and no later than within 24 hours of awareness to below email addresses:

Corporate confidential information