PROTOCOL TITLE: **A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Followed by Open-Label Extension and Safety Follow-Up Phases to Evaluate the Activity of Seladelpar in Subjects with Nonalcoholic Steatohepatitis (NASH)**

PROTOCOL VERSION NUMBER: Version 3.0

DATE OF PROTOCOL: 20-DEC-2019

PROTOCOL NUMBER: CB8025-21730

STUDY PHASE: Phase 2

SPONSOR: CymaBay Therapeutics, Inc.
7575 Gateway Blvd, Suite 110
Newark, CA 94560
U.S.A.

IND Number: 133253

CONFIDENTIALITY STATEMENT

PROTOCOL CB8025-21730

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PREVIOUS PROTOCOL VERSION NUMBER: Version 1.2
PREVIOUS DATE OF PROTOCOL: 26-MAR-2018

PREVIOUS PROTOCOL VERSION NUMBER: Version 2.0
DATE OF PROTOCOL: 13-SEP-2019

VERSION NUMBER: Version 3.0
DATE OF PROTOCOL: 20-DEC-2019

SPONSOR: CymaBay Therapeutics, Inc.
7575 Gateway Blvd, Suite 110
Newark, CA 94560
U.S.A.

I have read the above-mentioned Protocol dated Day/Month/Year

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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LIST OF TERMS AND ABBREVIATIONS

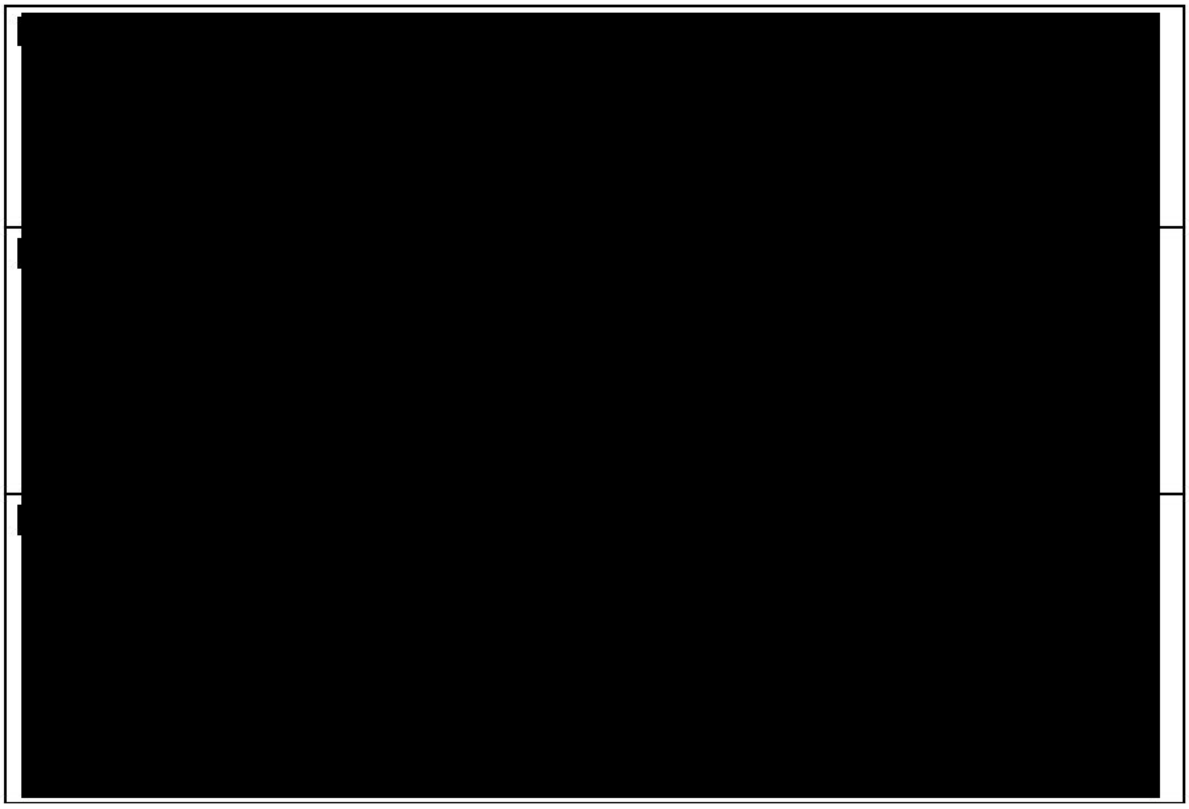
AB	Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APRI	AST/Platelet Ratio Index
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
C4	7- α -hydroxy-4-cholesten-3-one
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CK-BB	Creatine Kinase Brain Type
CK-MB	Creatine Kinase Heart Type
CK-MM	Creatine Kinase Muscle Type
CRO	Clinical Research Organization
DB	Double-Blind
DILI	Drug-Induced Liver Injury
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis Score
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FAO	Fatty Acid Oxidation
FIB-4	Fibrosis-4

FSPGR	Fast Spoiled Gradient
GCP	Good Clinical Practice
GFR	Glomerular-Filtration Rate
GGT	Gamma-glutamyl Transferase
GLP-1	Glucagon-Like Peptide-1
HA	Hyaluronic Acid
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HCV AB	Hepatitis C Antibody
HDL-C	High-Density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HoFH	Homozygous Familial Hypercholesterolemia
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
hs-CRP	High Sensitivity C-Reactive Protein
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IXRS	Interactive X Response Technology
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
LFC	Liver Fat Content
LLN	Lower Limit of Normal
LMS	Liver*MultiScan*
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat (population)
mITTb	Modified Intent to Treat with Biopsy (population)
MRE	Magnetic Resonance Elastography

MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction
NAFLD	Nonalcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Nonalcoholic Steatohepatitis
Non-HDL	Non-High-Density Lipoprotein Cholesterol
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OLE	Open-Label Extension
PBC	Primary Biliary Cholangitis
PP	Per Protocol
PT	Prothrombin Time
PPAR	Peroxisome Proliferator-Activated Receptor
PPARα	Peroxisome Proliferator Receptor Alpha
PPAR-δ	Peroxisome Proliferator Receptor Delta
RBC	Red Blood Cells
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFU	Safety Follow-Up
SGLT-2	Sodium/Glucose Co-Transporter 2
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Total Cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TIMP-1	Tissue Inhibitor of Matrix Metaloproteinases-1
TQT	Thorough QT
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
UNS	Unscheduled
U.S.A.	United States of America
U.S. FDA	United States Food and Drug Administration

W	Week
WBC	White Blood Cells
WHO	World Health Organization
WHODrug	World Health Organization Drug Classification

STUDY IDENTIFICATION



The Sponsor will notify the Investigator(s) in writing of any change to the above information.

SYNOPSIS

Protocol Number	**CB8025-21730**
Title	**A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Followed by Open-Label Extension and Safety Follow-Up Phases to Evaluate the Activity of Seladelpar in Subjects with Nonalcoholic Steatohepatitis (NASH)**
Study Phase	Phase 2
Study Design	This is a 52-week double-blind (DB), randomized, placebo-controlled, dose-ranging study followed by a 52-week open-label extension (OLE). An additional Safety Follow-Up (SFU) phase will continue for up to 1 year after the Week 52/Early Termination (ET) liver biopsy in subjects with significant histologic findings.
Number of Investigational Sites	Up to 15 sites in the U.S.A.
Objectives	**Primary Objectives** 1. To evaluate the effect of seladelpar on hepatic fat fraction, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at Week 12 in the DB phase 2. To evaluate the safety and tolerability of seladelpar in the DB, OLE and SFU phases **Secondary Objectives** 1. To evaluate the effect of seladelpar on MRI-PDFF at Week 26 and Week 52 in the DB phase 2. To evaluate the effect of seladelpar on histological improvement of nonalcoholic fatty liver disease activity score (NAS) at Week 52 in the DB phase 3. To evaluate the effect of seladelpar on histological improvement of fibrosis at Week 52 in the DB phase 4. To evaluate the effect of seladelpar on metabolic biochemical markers and biochemical markers of inflammation in the DB and OLE phases **Exploratory Objectives** 1. To evaluate the effect of seladelpar on biochemical markers of fibrosis in the DB and OLE phases 2. To evaluate the effect of seladelpar on fibrosis and inflammation as assessed by magnetic resonance elastography (MRE) and Liver*MultiScan* (LMS) in the DB phase 3. To evaluate AST/platelet ratio index (APRI) and fibrosis-4 (FIB-4) in the DB and OLE phases 4. To assess markers of target engagement including 7-alpha-hydroxy-4-cholesten-3-one (C4), serum bile acids and fatty acid oxidation (FAO) tests in the DB and OLE phases

	5. To evaluate histology, biochemical markers and FibroScan® during the SFU phase in subjects with significant histologic findings on the Week 52/ET liver biopsy
Study Outcome Measures	**Primary Outcome Measures** 1. Relative change in MRI-PDFF at Week 12 in the DB phase Adverse events (AEs) and/or treatment emergent adverse events (TEAEs), physical exams, vital signs, electrocardiograms (ECGs), biochemistry, hematology, and urinalysis as determined by investigator assessment for causality and grading by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0 in the DB, OLE and SFU phases **Secondary Outcome Measures** 1. Absolute change in MRI-PDFF at Week 12, 26, and 52 in the DB phase 2. Relative change in MRI-PDFF at Week 26 and 52 in the DB phase 3. Proportion of subjects with a relative decrease in MRI-PDFF ≥ 30% at Week 12, 26, and 52 in the DB phase 4. Proportion of subjects with normalization of MRI-PDFF (defined as a fat fraction of < 5%) at Week 12, 26, and 52 in the DB phase 5. Proportion of subjects with an absolute MRI-PDFF change > 5% at Weeks 12, 26, and 52 in the DB phase 6. Proportion of subjects with reversal of nonalcoholic steatohepatitis (NASH) and no worsening of hepatic fibrosis (centrally scored histology at Week 52) in the DB phase. The reversal of NASH is defined as the absence of hepatocellular ballooning (score of 0) and no or minimal inflammation (score of 0 or 1) 7. Proportion of subjects with improvement by at least one stage in fibrosis without worsening of NASH in the DB phase 8. Proportion of subjects with a 2-point improvement in NAS in the DB phase 9. Percent and absolute change in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) in the DB and OLE phases 10. Percent and absolute change in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL), homeostatic model assessment of insulin resistance (HOMA-IR) in the DB and OLE phases 11. Percent and absolute change in high-sensitivity C-reactive protein (Hs-CRP) and fibrinogen in the DB and OLE phases **Exploratory Outcome Measures** 1. AST/platelet ratio index (APRI), FIB-4 in the DB and OLE phases 2. Enhanced Liver Fibrosis (ELF) score and its components (hyaluronic acid, procollagen III N-terminal peptide, tissue inhibitor of matrix metalloproteinases) in the DB and OLE phases

	3. MRE changes at Week 52 in the DB phase 4. LMS (iron corrected T1 – cT1) changes at Week 12, 26, and 52 in the DB phase 5. FibroScan® changes (kPa and CAP) at Week 52 and at SFU visits 6. C4, serum bile acids and FAO tests in DB and OLE phases **Safety Outcome Measures** In those subjects with significant histological findings, other than NASH, in the end of treatment biopsy (Week 52 or Early Termination), resolution or stabilization of the findings at the SFU visits.
Investigational Product and Control	Seladelpar (and matching placebo) will be supplied as 5 mg, 10 mg, and 25 mg capsules.
Study Drug Administration	The study drug (seladelpar or matched placebo capsules) will be administered orally, once daily with or without food.
Treatment Groups and Number of Subjects	The DB phase will enroll approximately 175 subjects at the following dose levels: • Placebo (n=25) • Seladelpar 10 mg (n=50) • Seladelpar 20 mg (n=50) • Seladelpar 50 mg (n=50) The OLE phase will enroll up to approximately 175 subjects. All subjects will receive seladelpar 50 mg regardless of dose received during the DB phase. There is no study drug administered during the SFU Phase.
Randomization and Stratification	**DB Phase** Randomization: 1:2:2:2 (placebo: seladelpar 10 mg:20 mg:50 mg) Stratification: By diabetic status (yes/no) and fibrosis stage (F1 versus F2-3) **OLE Phase** No randomization or stratification criteria for the OLE phase **SFU Phase** No randomization or stratification criteria for the SFU phase
Study Duration	**DB Phase** Screening: Up to 10 weeks Treatment: Up to 52 weeks Follow-up: approximately 4 weeks **OLE Phase**: Treatment: Up to 52 weeks Follow-up: approximately 4 weeks

	SFU Phase Up to 1 year from the Week 52 or ET liver biopsy
Eligibility	**DB Inclusion Criteria** 1. Must be able to provide written informed consent (signed and dated) and any authorizations required by local law 2. 18 to 75 years old (inclusive) 3. Histological evidence of definite NASH on a liver biopsy (obtained during the screening period or historical liver biopsy obtained no more than 90 days prior to the initial screening visit) 4. NAS of 4 points or greater with a score of at least 1 point in each component (steatosis, lobular inflammation, and ballooning) 5. Fibrosis stage 1, 2, or 3 on liver biopsy 6. MRI-PDFF ≥ 10% 7. Females of reproductive potential must use at least one barrier contraceptive and a second effective birth control method during the study and for at least 30 days after the last dose of study drug. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose of study drug. **DB Exclusion Criteria** 1. Significant alcohol consumption, defined as more than 2 drink units per day (equivalent to 20 g) in women and 3 drink units per day (equivalent to 30 g) in men, or inability to reliably quantify alcohol intake 2. Treatment with drugs associated with nonalcoholic fatty liver disease (NAFLD) (amiodarone, methotrexate, oral glucocorticoids at doses greater than 5 mg/day, tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids (such as testosterone) and valproic acid for more than 4 weeks within the last 2 months prior to the initial screening 3. Treatment with pioglitazone or high-dose vitamin E (>400 IU/day) within the last 2 months prior to the initial screening 4. Initiation of treatment with a glucagon-like peptide-1 (GLP-1) agonist or a dose change within the last 2 months prior to the initial screening 5. Prior or planned bariatric surgery (a prior reversed sleeve gastrectomy is permitted) 6. Poorly controlled type 2 diabetes mellitus as defined by hemoglobin A1c [HbA1c]9.5% or higher or type 1 diabetes mellitus 7. Diabetic patients who are taking sodium/glucose cotransporter 2 (SGLT-2) inhibitors must be on a stable dose within 2 months prior to the initial screening and throughout the study 8. Significant weight loss within the last 6 months (e.g., > 10%) 9. Use of any weight-loss medication for 3 months prior to and during the study period 10. Body mass index (BMI) < 18.5 kg/m^2 11. Hepatic decompensation defined as the presence of any of the following: • Serum albumin less than 3.5 g/dL • International normalized ratio (INR) greater than 1.4 (unless due to therapeutic anticoagulants)

	• Total bilirubin greater than 2 mg/dL with the exception of Gilbert syndrome • History of esophageal varices, ascites, or hepatic encephalopathy 12. Other chronic liver diseases: • Active hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg) • Active hepatitis C as defined by presence of hepatitis C virus antibody (HCV AB) plus a positive hepatitis C virus (HCV) ribonucleic acid (RNA) • History or evidence of current active autoimmune hepatitis • History or evidence of primary sclerosing cholangitis (PSC) • History or evidence of primary biliary cholangitis (PBC) • History or evidence of Wilson's disease • History or evidence of alpha-1-antitrypsin deficiency • History or evidence of hemochromatosis • History or evidence of drug-induced liver disease, as defined exposure and history • Known bile duct obstruction • Suspected or proven liver cancer 13. ALT > 200 U/L 14. AST < 20 U/L 15. Creatine kinase (CK) > upper limit of normal (ULN) 16. Serum creatinine > ULN 17. Platelet < lower limit of normal (LLN) 18. Inability to obtain a liver biopsy 19. History of biliary diversion 20. Known history of human immunodeficiency virus (HIV) infection 21. History of malignancy diagnosed or treated within 2 years • Recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted • Cervical carcinoma in-situ is allowed if appropriately treated prior to Screening • Participants under active evaluation for malignancy are not eligible 22. Active substance abuse, based on Investigator judgment, including inhaled or injected drugs, within 1 year prior to the initial screening 23. Females who are pregnant or breastfeeding 24. Patients unable to undergo MRI-PDFF due to: • Contraindication to magnetic resonance imaging (MRI) examination • Severe claustrophobia impacting ability to perform MRI during the study, despite mild sedation/treatment with an anxiolytic • Weight or girth exceeds the scanner capacities 25. Treatment with any other investigational therapy or device within 30 days or within five half-lives, whichever is longer, prior to the initial screening 26. Active, serious medical disease with likely life expectancy < 5 years 27. Any other condition(s) that would compromise the safety of the subject or compromise study quality as judged by the Investigator

	OLE Phase Enrollment Criteria Subjects must fulfill the following before allowing to start OLE dosing: 1. Provide informed consent on or before Day 1 and prior to any OLE-related study procedures. 2. Completed through the Week 52 biopsy and Week 56 lab assessments in the DB phase 3. Meet the above DB phase Inclusion and Exclusion Criteria before Day 1 of the OLE phase, with the exception of the following: • AST < 20 U/L • Inability to obtain a liver biopsy (no new biopsy required for OLE) • Unable to undergo MRI-PDFF (no imaging performed in OLE) Week 56 labs from the DB phase may be used for eligibility assessment if less than 45 days from OLE Day 1. If greater than 45 days, an Unscheduled visit must be performed to collect safety and eligibility labs. **SFU Phase Enrollment Criteria** Subjects entering the SFU phase of the study must fulfill the following criteria: 1. Presence of significant histologic findings other than NASH on the Week 52 or Early Termination liver biopsy 2. Received seladelpar during the DB phase for at least 6 months.
Study Design and Procedures	**DB Phase** This phase of the study is designed as a dosing ranging proof-of-concept study to evaluate the safety and potential efficacy effects of seladelpar on hepatic fat fraction (MRI-PDFF). The study includes liver biopsies to confirm that subjects have histological evidence of NASH at screening and to evaluate histological improvement in NASH and fibrosis after 52 weeks of treatment. Approximately 175 subjects will be randomly assigned to receive placebo, seladelpar 10 mg/day, seladelpar 20 mg/day or seladelpar 50 mg/day at a 1:2:2:2 ratio. Subjects will be stratified by diabetic status (yes/no) and fibrosis stage (F1 versus F2-3). Study drug (placebo or seladelpar) will be taken in a blinded manner orally once a day for a period of 52 weeks. The screening period will be up to 10 weeks, the blinded treatment period will be up to 52 weeks, and a follow-up period of 4 weeks after the last dose of study drug. During the treatment period, the first on-treatment visit will occur 4 weeks after initiation of the study drug. Subjects will then be evaluated in clinic every 4 weeks until Week 12. After Week 12, visits will be 6-7 weeks apart. Subjects will also be contacted by phone or email at Weeks 19, 32 and 45. The amount of fat in the liver will be evaluated by MRI-PDFF at baseline, Weeks 12, 26, and 52. A liver biopsy will be performed twice during the study: at baseline and at Week 52. The primary efficacy analysis will be the change from baseline to Week 12 in MRI-PDFF. The study will continue in a blinded fashion until the Week 52 biopsy is collected.

	OLE Phase All subjects who participate in the DB phase, complete the 52-week biopsy and the 56-week follow-up labs, and meet the specified enrollment criteria will be offered participation in the OLE phase of the study. Subjects will not be required to have any additional liver histology, imaging or elastography assessments for enrollment or on-treatment assessments of treatment effect. The OLE Day 1 visit may be combined with the Week 56 visit in the DB phase. Informed Consent may occur at Week 52 or Week 56 in the DB phase for subjects still active in the DB phase or any time prior to any OLE procedures in patients who have completed the DB phase. Eligibility assessment may occur on or after the Week 56 in the DB phase. Laboratory assessments from the DB phase Week 52 visit should be used to determine OLE eligibility if the DB phase Week 56 visit and OLE phase Day 1 visit are planned to be completed on the same day. Lab assessments from the DB Week 56 visit may be used for OLE eligibility assessment if less than 45 days from that visit. If greater than 45 days have elapsed from DB phase Week 56 visit, subjects should complete an unscheduled visit where all lab assessments required for DB phase Week 56 are retested. The results from the re-test must be available and assessed for eligibility prior to the Day 1 visit. Subjects must also be clinically stable based on the investigator's medical judgement and key enrollment criteria to enter the OLE. Clinic visits during the 52-week OLE phase will occur at Day 1 and Weeks 2, 13, 26, 39 and 52 with a final end of study (EOS) visit approximately at Week 56. The primary objective of the OLE phase is to assess long-term safety and treatment effect as measured by biochemical tests after an additional 52 weeks of treatment. **SFU Phase** All subjects who participated in the DB phase that have significant histologic findings other than NASH on the Week 52 or ET liver biopsy **and** received active seladelpar for at least 6 months will be asked to enroll in the SFU phase. Subjects in the placebo dosing group will not be enrolled into the SFU phase. After informed consent is obtained, an SFU visit will be performed at 6 months ± 4 weeks, after the Week 52 or ET liver biopsy. A liver biopsy will be obtained to reassess the status of the original significant histologic findings. Other study procedures performed during the visit include a physical exam, vital signs, safety laboratory assessments, exploratory liver injury biomarker assessments, and FibroScan®. Subjects with resolution or stabilization of the observed histologic findings will have completed the SFU phase, and no further visits or assessments will be required. Subjects with worsening of the observed histologic findings will be followed up by phone at 3-month intervals and may be requested to have additional SFU visits with a repeat of some or all of the above procedures.

Statistics	**Populations for Analysis:** Safety: Any subject who receives at least one dose of study drug. Intent-to-Treat (ITT): Any subject who is randomized and receives at least one dose of study drug. Modified Intent-to-Treat (mITT): Any subject who is randomized, receives at least one dose of study drug, and has Baseline and Week 12 MRI-PDFF. Modified Intent-to-Treat with Biopsy (mITTb): Any subject who is randomized, receives at least one dose of study drug and has Baseline and Week 52/early termination (ET) liver biopsies. Per-Protocol (PP): Any subject who is randomized and receives at least one dose of study drug, has Baseline and Week 52/ET liver biopsies and does not have a protocol violation that is deemed to impact the efficacy analysis. **Population Analyses:** The safety analysis will be conducted on the Safety population. Efficacy analyses will be conducted on the ITT, mITT, mITTb, and the PP populations. The mITT population will be used for the primary efficacy analysis. **Statistical Methods:** All statistical comparisons will be made at a two-sided alpha of 0.05. Treatment comparisons of the primary efficacy endpoint will be tested using a hierarchical "fixed-sequence" approach to assess clinical benefit of each of the seladelpar dose levels versus placebo, starting first with the 50 mg dose at a 5% alpha level. If positive, the seladelpar 20 mg dose will be compared to placebo at a 5% alpha level. If both seladelpar 20 mg and 50 mg doses are statistically superior to placebo then the testing will continue to the 10 mg dose vs placebo. Additional consideration for the testing procedures for alpha control will be discussed in the statistical analysis plan (SAP). **Sample Size:** A sample size of 175 subjects (50 subjects per each dose of seladelpar and 25 subjects for placebo) provides at least 80% power to detect a pairwise treatment difference of at least 20% between the active and placebo groups with respect to a relative change from baseline in hepatic fat fraction, as assessed by MRI-PDFF at Week 12. Power calculations were performed using a standard t-test, allowed for a 12% dropout rate (6 subjects per seladelpar arm, 3 subjects for the placebo arm), and a pooled standard deviation of 26 for the relative change endpoint. **Primary Efficacy Analysis:** Pairwise comparisons between each dose of seladelpar versus placebo with respect to the relative change in hepatic fat fraction as assessed by MRI-PDFF at Week 12 will be conducted using analysis of covariance (ANCOVA). The LS means, standard errors, 95% confidence intervals (CIs), and p-values will be provided from an ANCOVA model with percent change from baseline in MRI-PDFF as the

dependent variable, treatment group, diabetic status, and fibrosis stage as factors and baseline MRI-PDFF as a covariate.

Relative change will be calculated as:

$[\text{MRI-PDFF}_{\text{WEEK12}} - \text{MRI-PDFF}_{\text{BASELINE}}] \times 100 / \text{MRI-PDFF}_{\text{BASELINE}}$.

Top-Line Results

The 12-week Primary Analysis, including top-line results for efficacy and safety, will be provided and communicated when it becomes available and before study completion. These results will be provided by treatment group, but individual patient data will remain blinded and the study will continue as a double-blind study until its completion. Details of the conduct of the Primary Analysis will be provided in the SAP.

Secondary Efficacy Analyses:

Comparisons between each seladelpar dose versus placebo with respect to the absolute change in hepatic fat fraction as assessed by MRI-PDFF at Week 12, 26 and 52 will be conducted using mixed model repeated measures analyses, with factors for scheduled time point, treatment, time point by treatment interaction, baseline diabetic status, and fibrosis stage, with the baseline hepatic fat fraction as a covariate. Supportive analyses will be conducted using Wilcoxon rank-sum tests, stratified by diabetic status and fibrosis stage.

Comparisons between each seladelpar dose versus placebo with respect to the relative change in hepatic fat fraction as assessed by MRI-PDFF at Week 26 and 52 will be conducted using mixed model repeated measures analyses with factors for scheduled time point, treatment, time point by treatment interaction, baseline diabetic status, and fibrosis stage, with the baseline hepatic fat fraction as a covariate. Supportive analyses will be conducted using Wilcoxon rank-sum tests, stratified by diabetic status and fibrosis stage.

Each seladelpar dose will be compared versus placebo for the number and percent of subjects with normalization of hepatic fat content (<5%) at Week 12, 26, and 52 using Cochran-Mantel-Haenszel tests, stratified by diabetic status and fibrosis stage. Similar analyses will be performed for:

- number and percent of subjects with an absolute change > 5% on MRI-PDFF at Week 12, 26, and 52
- number and percent of subjects with a relative decrease in hepatic steatosis of > 30% on MRI-PDFF at Week 12, 26, and 52
- number and percent of subjects with reversal of NASH with no worsening of fibrosis as defined by centrally scored histology assessment at 52 weeks of treatment
- number and percent of subjects with improvement by at least one stage in fibrosis (NASH Clinical Research Network Classification) without worsening of NASH
- number and percent of subjects with a 2-point decrease in NAS

Efficacy-related laboratory data will be summarized by laboratory parameter, treatment group and study visit for the DB and OLE phases.

	Safety data, including AEs, safety laboratory results, significant histologic findings, physical examination results, vital signs, and ECG will be summarized by treatment group and/or listed for the DB, OLE and SFU phases. Full details on the statistical methodology to be used will be included in an SAP to be developed prior to study unblinding.

Table 1: Schedule of Assessments - Double-Blind (DB) Phase

Study Periods	**Screen**	**Baseline**	**Treatment**								**Follow-up**			
Visits (±7 days)	Week -10 to Day -1	Day 1	W4	W8	W12	W19	W26	W32	W39	W45	W52[11]	W56[11]	ET	UNS
Informed Consent	X													
Eligibility Evaluation	X													
Randomization		X												
Subject Contact[1]						X		X		X				
Medical History	X	X												
AE/TEAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X	X	X	X		X		X		X	X	X	X[2]
Vital Signs, Weight, Height[3]	X	X	X	X	X		X		X		X	X	X	X
ECG	X	X					X				X	X	X	X[4]
Hematology[5]	X	X	X	X	X		X		X		X	X	X	X
Biochemistry[5]	X	X	X	X	X		X		X		X	X	X	X
Exploratory Biochemistry[5]		X	X	X	X		X		X		X	X	X	
Hep B and Hep C Tests[5]	X													
Serum Pregnancy Test[6]	X	X			X		X		X		X	X	X	
Back-up Blood Sample[5]	X	X	X	X	X		X		X		X	X	X	
FibroScan®	X										X[9]		X[9]	
MRI-PDFF	X				X		X				X[9]		X[9]	
Liver*MultiScan*	X				X		X				X[9]		X[9]	
MRE (where available)	X										X[9]		X[9]	
Liver Biopsy[7]	X[8]										X[9]		X[9]	
Study Drug Compliance			X	X	X	X	X	X	X	X	X		X	X
Study Drug Accountability			X	X	X		X		X		X		X	
Study Drug Dispensing		X[10]	X	X	X		X		X					

1. Subject contact will be performed over phone contact or email communication. A follow-up Unscheduled Visit may be scheduled if deemed necessary by investigator.
2. Symptoms-directed (brief) physical examination is only allowed at an Unscheduled Visit.
3. Height will be measured only at the initial screening visit.
4. ECG will be performed at the Unscheduled visit only if the subject has cardiac-related symptoms.
5. Blood will be collected after at least an 8-hour overnight fast and prior to dosing. If the subject forgets to fast, the site will continue to draw labs. Subjects should not be dosed with study drug until blood is collected.
6. Applicable for women of childbearing potential only.
7. PT, INR, and platelets must be performed with results available prior to performing any new liver biopsy.
8. A new liver biopsy should only be performed on a potentially eligible subjects, based on screening labs and imagining (per Appendix A). If a potential subject had a liver biopsy 90 days prior to the initial screening visit, and the pathology slides are available for review, the Baseline liver biopsy can be waived.
9 The end of treatment (EOT) liver biopsy, MRI-PDFF, MRE, Liver*MultiScan* and FibroScan® should be performed 52 weeks (±1 week) from the Day 1 visit.
10. The first dose of study drug will be administered onsite.
11 Informed consent for the OLE may be obtained at either Week 52 or Week 56 for subjects still in the DB phase. The Week 56 visit may also serve as the Day 1 visit for the OLE if consent has been obtained and the OLE eligibility criteria are met.

Table 2: Schedule of Assessments – Open-Label Extension (OLE) Phase

Visits (±7 days)	Day 1	OLE-W2	OLE-W13	OLE-W26	OLE-W39	OLE-W52 (EOT)	OLE-W56 (EOS)	OLE-ET	OLE-UNS
Informed Consent [1]	X[1]								
Eligibility Assessment[2]	X[1]								
AE/TEAE	X	X	X	X	X	X	X	X	X
Weight and vital signs	X	X	X	X	X	X	X	X	X
ECG	X					X		X	X[5]
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Brief Physical Exam	X	X	X	X	X	X	X	X	X
Hematology [3]	X	X	X	X	X	X	X	X	X
Biochemistry [3]	X	X	X	X	X	X	X	X	X
Exploratory Biochemistr[3]	X	X	X	X	X	X	X	X	
Back-up Blood Sample [3]	X	X	X	X	X	X	X	X	
Urine Pregnancy Test [4]	X			X		X		X	
Study Drug Compliance			X	X	X	X		X	X
Study Drug Accountability			X	X	X	X		X	
Study Drug Dispensing	X		X	X	X				

1. Informed Consent may occur at Week 52 or Week 56 in the DB phase if subject is still active in the DB phase.
2. Eligibility Assessment may occur on or any time after the Week 56 visit in the DB phase and after informed consent.
3. An Unscheduled Visit for laboratory assessment for OLE eligibility if more than 45 days have elapsed from the Week 56 laboratory results from the DB phase. The results must be available prior to the Day 1 visit
4. Applicable for women of childbearing potential only.
5. ECG will be performed at the Unscheduled visit only if the subject has cardiac-related symptoms.

Table 3: Schedule of Assessments – Safety Follow Up Extension (SFU) Phase

Study Periods	SFU Visit(s)	Phone Contact	UNS
Informed Consent[1]	X		
Subject Contact[2]	X	X[2]	
Medical History	X		X
AE/TEAE	X	X	X
Prior and Concomitant Medications	X	X	X
Complete Physical Exam	X		X
Vital Signs, Weight	X		X
Hematology[3]	X		X
Biochemistry[3]	X		X
Exploratory Biochemistry[3]	X		X
Back-up Blood Sample[3]	X		X
FibroScan®	X[4]		X[5]
Liver Biopsy[6]	X[4]		X[5]

1. Informed consent for the Safety Follow Up (SFU) must be obtained before doing any of the procedures but may occur on or after the Week 52 or Early Termination visit.
2. Subject contact will be performed over phone contact, approximately every 12 weeks. A follow-up Unscheduled Visit may be scheduled if deemed necessary by investigator
3. Blood will be collected after at least an 8-hour overnight fast. If the subject forgets to fast, the site will continue to draw labs.
4. The SFU FibroScan® and liver biopsy should be performed 6 months (±4 week) from the Week 52 or Early Termination visit.
5. An additional FibroScan® and/or liver biopsy may be considered if subject's histological findings, other than NASH, have not resolved or stabilized.
6. Prothrombin time (PT), International Normalized Ratio (INR), and platelets must be performed with results available prior to performing any new liver biopsy.

1 INTRODUCTION

1.1 NASH

Nonalcoholic steatohepatitis (NASH) defines a subgroup of nonalcoholic fatty liver disease where steatosis coexists with hepatic cell injury (apoptosis and hepatocyte ballooning), and inflammation (Chalasani et al., 2012). NASH is closely associated with overweight/obesity, type 2 diabetes mellitus, and cardiometabolic conditions that define the metabolic syndrome (Ratziu et al., 2010). Because of the prevalence of these comorbidities, NASH is emerging as the most common chronic liver disease.

NASH promotes liver fibrosis and some patients progress to cirrhosis, liver failure, hepatocellular carcinoma, or require liver transplantation (Vernon et al., 2011). Compared with the general population, liver-related mortality is increased 10-fold in NASH patients (Ekstedt et al., 2006).

NASH is also a multisystem disease that could worsen insulin resistance, the metabolic syndrome, and systemic inflammation (Yki-Jarvinen et al., 2014). Consequently, NASH patients also have an increased rate of cardiovascular events. and the leading cause of death is cardiovascular events (Vernon et al., 2011).

There are currently no approved therapies for NASH.

1.2 Seladelpar

1.2.1 Overview

Seladelpar is a potent and selective PPAR-δ agonist. Seladelpar is being developed for the treatment of primary biliary cholangitis (PBC) in subjects with inadequate response to ursodeoxycholic acid (UDCA) or who are intolerant to UDCA, for the treatment of homozygous familial hypercholesterolemia (HoFH), and NASH. Seladelpar could also be developed for other disorders of lipid metabolism or disorders characterized by chronic intra-hepatic cholestasis.

1.2.2 Mechanism of Action

Seladelpar is a potent and selective peroxisome proliferator receptor delta (PPAR-δ) agonist, and is a key regulator of lipid metabolism, cholesterol transport, bile acid synthesis, and inflammation/fibrosis. Ligand binding to PPAR-δ results in activation and repression of its target genes by which it regulates the above processes. In the liver, PPAR-δ is expressed in hepatocytes, cholangiocytes, Kupffer and stellate cells (Iwaisako et al., 2012; Xia et al., 2012).

The activity of seladelpar in NASH was studied in a diabetic, dyslipidemic obese mouse model (the *foz*/*foz* mouse model; Haczeyni et al., 2017). Seladelpar reversed NASH pathology and reduced fibrosis while improving insulin sensitivity and decreasing inflammation. These effects appear to be a consequence of its effects on lipid metabolism including reduction of lipotoxic species, which are key pathological drivers of NASH and fibrosis.

For more detailed information, see the Seladelpar Investigator's Brochure.

1.2.3 Seladelpar in NASH

In a preclinical diabetic obese mouse model of nonalcoholic steatohepatitis (NASH), the *foz*/*foz* mouse model (Haczeyni et al., 2017), seladelpar reversed NASH in all treated mice, and completely

eliminated ballooning while reducing inflammation and steatosis. The activities observed with seladelpar treatment in mice included reduction in hepatic fat (including lipotoxic lipids, free and total cholesterol), reduction in staining for Kupffer cell and macrophage infiltrates, decreased collagen deposition, decreased serum levels of alanine aminotransferase (ALT), and reversal of hyperglycemia, hyperinsulinemia, and insulin resistance.

In a phase 2 study of seladelpar in obese patients with mixed dyslipidemia, a population that is presumed to include patients with fatty liver disease, seladelpar treatment for 8 weeks decreased TG and LDL-C levels. Additionally, seladelpar decreased small dense pro-atherogenic LDL lipoproteins, increased HDL-C concentrations, and HOMA-IR, hs-CRP, ALP, and GGT (Bays et al., 2011; Choi et al., 2012). Thus, the cardiovascular, metabolic and anti-inflammatory activities observed in patients further justify the evaluation of seladelpar as a candidate for the treatment of NASH.

The interim analysis of the 12-week primary endpoint for the DB phase of this ongoing study provided initial clinical experience with seladelpar in NASH patients. A total of 181 subjects, with biopsy-confirmed NASH and a liver fat content (LFC) greater than 10%, were randomized into the trial to receive either placebo or seladelpar 10 mg, 20 mg, or 50 mg once-daily. The enrolled subjects had established NASH with a mean NAFLD Activity Score (NAS) of 5.2 at baseline, with 83% of subjects having stage 2 or stage 3 fibrosis and mean LFC by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) of 21%. The primary endpoint was the relative change in LFC from baseline to 12 weeks. The study remains blinded and will continue to 52 weeks with assessments including a liver biopsy, non-invasive imaging evaluations, and biomarker assessments of inflammation and fibrosis. Changes in LFC as measured by MRI-PDFF at week 12 demonstrated minimal reductions in liver fat that were not significant when compared to placebo. However, treatment with seladelpar resulted in robust and clinically meaningful reductions in markers associated with liver injury, including ALT, ALP and GGT, in a dose-dependent manner. Treatment with seladelpar also resulted in reductions in LDL-C and TG. There were no significant changes in high-density lipoprotein cholesterol. The most common (>5%) treatment emergent adverse events included nausea, constipation, dizziness, headache, gastroesophageal reflux disease and upper abdominal pain. The majority of treatment emergent adverse events (TEAE) were mild to moderate in severity and deemed unrelated to study drug. There were two serious adverse events that occurred after randomization through week 12, neither of which were deemed to be related to study drug.

Based on the identified pharmacologic activities *in vitro*, in animals and in humans as well as the treatment effect and safety/tolerability profile to date, seladelpar represents a potentially important therapeutic option for the treatment of NASH.

1.3 Nonclinical Experience

Please see the Investigator's Brochure for details on the nonclinical studies conducted with seladelpar.

1.4 Human Experience

Please see the Investigator's Brochure for details on the clinical studies conducted with seladelpar.

1.5 Rationale for Dose Selection in the DB Phase

The proposed dosing for the DB phase of the study is 10, 20, and 50 mg administered once daily for up to 52 weeks.

The clinical experience thus far with seladelpar at daily doses of 50 mg and 100 mg for 8 weeks in obese males and females with mixed dyslipidemia (Bays et al., 2011), and at a daily dose of up to 200 mg for 3 weeks in healthy volunteers, indicates that seladelpar was well tolerated and appeared generally safe.

The beneficial treatment effects in the dyslipidemia study (lowering of TG, LDL-C, free fatty acids, and hs-CRP) do not appear to be meaningfully better at 100 mg/day than at 50 mg/day. Because the baseline characteristics of the study population enrolled in the Phase 2 mixed dyslipidemia study (obese, hyperlipidemic, insulin resistant, hypertension) overlaps with the NASH population, it is anticipated that the beneficial metabolic effect of seladelpar at doses of 50 mg/day will be translated to the NASH population. Thus, this dose has been selected as the maximum dose to be studied in the proposed NASH study.

In PBC, studies have indicated that seladelpar at dose of 2, 5, and 10 mg, retains a relevant clinical activity to improve markers of cholestasis, markers of inflammation, and improve metabolic markers. There was a dose ranging activity from 2 to 10 mg/day with 10 mg/day demonstrating the best risk/benefit profile. For these reasons, a seladelpar a dose of 10 mg/day has been selected for the proposed NASH study as the dose with a potentially minimal level of activity.

The dose of 20 mg/day has been selected to complete the approximate 2-log dose range evaluation in the study. Given there are no approved treatments for NASH, the risks versus benefit of seladelpar in NASH patients at doses of 10, 20, and 50 mg/day is acceptable.

1.6 Rationale for Dose Selection in the OLE Phase

The proposed seladelpar daily doses to be studied in the OLE phase of the study is 50 mg dosed daily for an additional 52 weeks. This dose and duration of exposure are supported by the estimated safety exposure margins from the repeat dose toxicity studies of 26 weeks in Sprague-Dawley rats and 52 weeks in cynomolgus monkeys (Table 4).

Table 4: Estimated Safety Exposure Margin of Seladelpar for NASH

Species	Rat (26-week)		Monkey (52-week)	
	M	F	M	F
NOAEL (mg/kg/day)	15	80	1	5
AUC (ng*h/mL)	26,900	77,300	2,450	12,000
Margin (AUC) NASH – 50 mg	9.9X	28X	0.9X	4.4X

AUC=area under the concentration versus time curve; NOAEL=no-observed-adverse-effect-level.

The dose selection is further supported by the treatment effect and safety/tolerability at the 12-week primary endpoint interim analysis from the ongoing DB phase of this study. Although there was no significant reduction in liver fat content, seladelpar significantly decreased key markers of hepatic injury (ALT, ALP, GGT) in a dose dependent manner was the greatest magnitude of effect observed with the 50 mg dose (Table 5). ALT declined up to 37.5% or 32 U/L in 12 weeks. These

reductions in ALT are significantly greater than the 17 U/L threshold that has been correlated with histologic improvement in NASH. GGT also decreased significantly, suggesting a reduction in hepatocellular oxidative stress. Significant reductions in ALP at 12 weeks were observed, supportive of a decrease in hepatocellular bile acids. The marked changes in these liver enzymes collectively suggest the potential to impact ballooning and lobular inflammation, the two key components of NASH resolution.

Table 5: Mean Relative Changes in Hepatic Injury Biomarkers Observed from Baseline to Week 12 in Study CB8025-21730

%, LS Mean (SE)	Placebo (n = 27)	10 mg (n = 53)	20 mg (n = 51)	50 mg (n = 50)
ALT	-8.9 (5.1) p=0.08	-22.9 (3.8) p<0.0001	-32.0 (4.0) p<0.0001	-37.5 (4.0) p<0.0001
AST	-12.9 (5.8) p=0.03	-11.6 (4.4) p=0.009	-15.2 (4.5) p=0.001	-17.3 (4.5) p=0.0002
GGT	-4.5 (4.3) p=0.3	-28.2 (3.2) p<0.0001	-37.6 (3.3) p<0.0001	-43.1 (3.4) p<0.0001
AP	4.4 (2.9) p=0.12	-19.1 (2.1) p<0.0001	-25.1 (2.2) p<0.0001	-33.4 (2.2) p<0.0001

* LS=Least Squares. SE=Standard error. P-values are for relative change from baseline.

Seladelpar demonstrated a favorable safety and tolerability profile at all doses evaluated in this study. The most common (>5%) TEAEs in the overall total population are listed in Table 6. The majority of TEAEs were mild in severity and deemed unrelated to study drug. Lipid and metabolic parameters remained stable or improved, supportive of a favorable cardiovascular risk profile. In general, the TEAEs were comparable across the dosing groups, with no overt safety signals to suggest the 50 mg dose is more poorly tolerated than the overall study population.

Table 6: Most Common (>5%) Treatment Emergent Adverse Events Observed from Baseline to Week 12 in Study CB8025-21730

n (%)	Placebo (n = 27)	10 mg (n = 53)	20 mg (n = 51)	50 mg (n = 50)	Total (n= 181)
Arthralgia	1 (3.7)	3 (5.7)	4 (7.8)	2 (4.0)	10 (5.5)
Abdominal Pain (Upper) [a]	-	-	-	-	11 (6.1)
Constipation	1 (3.7)	3 (5.7)	4 (7.8)	4 (8.0)	12 (6.6)
Dizziness	2 (7.4)	3 (5.7)	4 (7.8)	2 (4.0)	11 (6.1)
Fatigue	1 (3.7)	2 (3.8)	3 (5.9)	3 (6.0)	9 (5.0)
GERD	3 (11)	4 (7.5)	2 (3.9)	3 (6.0)	12 (6.6)
Headache [a]	-	-	-	-	14 (7.7)
Nausea	3 (11.1)	7 (13.2)	6 (11.8)	6 (12.0)	22 (12.2)
Rash [a]	-	-	-	-	9 (5.0)
Upper Resp. Infection	2 (7.4)	5 (9.4)	1 (2.0)	2 (4.0)	10 (5.5)
Urinary Tract Infection	-	-	-	-	10 (5.5)
Worsening T2D	2 (7.4)	4 (7.5)	1 (2.0)	3 (6.0)	10 (5.5)
Vomiting	1 (3.7)	1 (1.9)	4 (7.8)	3 (6.0)	9 (5.0)

[a] Certain TEAEs presented as study total in order to not unblind the specific dosing groups

In summary, the aggregate of the nonclinical and clinical data to date support the 50 mg dose as the selected single dose in the OLE in order to optimally assess the long-term continued safety and tolerability at the dose with greatest magnitude of effect on relevant biomarkers.

1.7 Rationale for SFU Phase

A key secondary endpoint of the current study is change from Baseline in fibrosis and NASH histology at Week 52/End of Treatment. As part of the assessment plan for the histologic endpoint, an initial batch 52-week biopsies (n=112) were grouped for pathology review. Two highly experienced NASH pathologists, blinded to study treatment, convened on 20 November 2019 to initiate the reading of the initial Week 52/End of Treatment biopsy slides. The NASH-CRN scoring system for NASH and fibrosis was used as well as the identification of any portal inflammation or other significant non-NASH incidental findings. Upon reading the initial set of slides, the pathologists identified significant non-NASH histologic findings in 31 subjects. These findings included histopathology consistent with interface hepatitis, bile duct injury and/or porto-sinusoidal vascular disease (PSVD) and were described as concerning and atypical in NASH.

In contrast to the histological findings, there were no biochemical signals of drug-induced liver disease or injury during the study period. A review of TEAEs in subjects with histological findings did not reveal any outlier events and were consistent with the full population. In

addition, no significant liver-related adverse effects or clinical evidence of hepatic decompensation have been observed in the full population dosed to date, nor in the 31 subjects with histological findings.

These findings were reported to the FDA, and upon review a decision was made to terminate and unblind the Phase 2 studies in NASH (CB8025-21730). Follow-up correspondence from the FDA has requested CymaBay to obtain additional histologic, laboratory and imaging assessments in order to assess the resolution or persistence of the histologic findings as well potentially identify any predictive markers for these unexpected events. Information collected during the SFU phase will be used to assess on-going subject safety.

2 STUDY OBJECTIVES

2.1 Primary Objectives

1. To evaluate the effect of seladelpar on hepatic fat fraction, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) at Week 12 in the DB phase
2. To evaluate the safety and tolerability of seladelpar in subjects with NASH in the DB, OLE and SFU phases

1.2 Secondary Objectives

1. To evaluate the effect of seladelpar on MRI-PDFF at Week 26 and Week 52 in the DB phase
2. To evaluate the effect of seladelpar on histological improvement of NAFLD activity score (NAS) at week 52 in the DB phase
3. To evaluate the effect of seladelpar on histological improvement of fibrosis at week 52 in the DB phase
4. To evaluate the effect of seladelpar on metabolic biochemical markers and biochemical markers of inflammation over 52 weeks of treatment in the DB and OLE phases

2.3 Exploratory Objectives

1. To evaluate the effect of seladelpar on biochemical markers of fibrosis in the DB and OLE phases
2. To evaluate the effect of seladelpar on fibrosis and inflammation as assessed by magnetic resonance elastography (MRE) and Liver*MultiScan* (LMS) in the DB phase
3. To evaluate AST/platelet ratio index (APRI) and Fibrosis-4 (FIB-4) score in the DB and OLE phases
4. To assess markers of target engagement as measured by 7-α-hydroxy-4-cholesten-3-one (C4), serum bile acids and fatty acid oxidation (FAO tests) in the DB and OLE phases
5. To evaluate histology, biochemical markers and imaging parameters during the SFU phase in subjects with significant histologic findings on the Week 52 or Early Termination (ET) liver biopsy

3 STUDY DESIGN

DB Phase

This phase of the study is designed as a dosing ranging proof-of-concept study to evaluate the safety and potential efficacy effects of seladelpar on MRI-PDFF. The study includes liver biopsies to confirm that subjects have histological evidence of NASH at screening and to evaluate histological improvement in NASH and fibrosis after 52 weeks of treatment.

Approximately 175 subjects will be randomly assigned to receive placebo, seladelpar 10 mg/day, seladelpar 20 mg/day or seladelpar 50 mg/day (1:2:2:2 ratio). Subjects will be stratified by diabetic status (yes/no) and fibrosis stage (F1 versus F2-3). Study drug (placebo or seladelpar) will be taken in a blinded manner orally once a day for a period of 52 weeks.

The screening period will be up to 10 weeks, the blinded treatment period will be up to 52 weeks, and a follow-up period of 4 weeks after the last dose of study drug. During the treatment period, the first on-treatment visit will occur 4 weeks after initiation of the study drug. Subjects will then be evaluated in clinic every 4 weeks until Week 12. After Week 12, visits will be 6-7 weeks apart. Subjects will also be contacted by phone or email at Weeks 19, 32 and 45. The amount of fat in the liver will be evaluated by MRI-PDFF at baseline, Weeks 12, 26, and 52. A liver biopsy will be performed twice during the study: at baseline and at Week 52.

The primary efficacy analysis will be the change from baseline to Week 12 in MRI-PDFF. The study will continue in a blinded fashion until the Week 52 biopsy is collected.

OLE Phase

All subjects who participate in the DB phase, complete the 52-week biopsy and the 56-week follow-up labs, and meet the specified enrollment criteria will be offered participation in the OLE phase of the study. Subjects will not be required to have any additional liver histology, imaging or elastography assessments for enrollment or on-treatment assessments of treatment effect. The OLE Day 1 visit may be combined with the Week 56 visit in the DB phase. Informed Consent may occur at Week 52 or Week 56 in the DB phase for subjects still active in the DB phase or any time prior to any OLE procedures in patients who have completed the DB phase. Eligibility assessment may occur on or after the Week 56 in the DB phase. Laboratory assessment for OLE suitability may be required if more than 45 days have elapsed since last lab collection to anticipated first OLE dosing. If greater than 45 days have elapsed since the last lab collection, subjects must complete an unscheduled visit where all labs collected at Week 56 will be retested, with the results available and assessed prior to the Day 1 visit. Subjects must also be clinically stable based on the investigator's medical judgement and key enrollment criteria to enter the OLE. Clinic visits during the 52-week OLE phase will occur at Day 1 and Weeks 2, 13, 26, 39 and 52 with a final EOS visit at approximately Week 56 visit. The primary objective of the OLE phase is to assess long-term safety and treatment effect as measured by biochemical tests after an additional 52 weeks of treatment.

SFU Phase

All subjects who participated in the DB phase that have significant histologic findings other than NASH on the Week 52 or ET liver biopsy and received active seladelpar for at least 6 months will be asked to enroll in the SFU phase. Subjects in the placebo dosing group will not be enrolled into the SFU phase. After informed consent is obtained, an SFU visit will be performed at a minimum of 6 months after the Week 52 or ET liver biopsy. A repeat liver biopsy will be obtained to reassess the status of the original significant histologic findings. Other study procedures performed during the visit include a physical exam, vital signs, safety laboratory assessments, exploratory liver injury biomarker assessments, and FibroScan®. Subjects with resolution or stabilization of the observed histologic findings will have completed the SFU phase, and no further visits or assessments will be required. Subjects worsening of the observed histologic findings will be followed up by phone at 3-month intervals and may be requested to have additional SFU visits with a repeat of some or all of the above procedures.

4 STUDY POPULATION

4.1 DB Phase Eligibility Criteria

Inclusion Criteria

1. Must be able to provide written informed consent (signed and dated) and any authorizations required by local law
2. 18 to 75 years old (inclusive)
3. Histological evidence of definite NASH on a liver biopsy (obtained during the screening period or historical liver biopsy obtained no more than 90 days prior to the initial screening visit)
4. NAS of 4 points or greater with a score of at least 1 point in each component (steatosis, lobular inflammation, and ballooning)
5. Fibrosis stage 1, 2, or 3 on liver biopsy
6. MRI-PDFF ≥ 10%
7. Females of reproductive potential must use at least one barrier contraceptive and a second effective birth control method during the study and for at least 30 days after the last dose of study drug. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose of study drug.

Exclusion Criteria

1. Significant alcohol consumption, defined as more than 2 drink units per day (equivalent to 20g) in women and 3 drink units per day (equivalent to 30g) in men, or inability to reliably quantify alcohol intake
2. Treatment with drugs associated with NAFLD (amiodarone, methotrexate, oral glucocorticoids at doses greater than 5 mg/day, tamoxifen, estrogens at doses greater than those used for hormone replacement or contraception, anabolic steroids (such as testosterone) and valproic acid for more than 4 weeks within the last 2 months prior to the initial screening
3. Treatment with pioglitazone or high-dose vitamin E (>400 IU/day) within the last 2 months prior to the initial screening
4. Initiation of treatment with a glucagon-like peptide-1 (GLP-1) agonist or a dose change within the last 2 months prior to the initial screening
5. Prior or planned bariatric surgery (a prior reversed sleeve gastrectomy is permitted)
6. Poorly controlled type 2 diabetes mellitus as defined by hemoglobin A1c (HbA1c) of 9.5% or higher or type 1 diabetes mellitus
7. Diabetic patients who are taking sodium/glucose cotransporter 2 (SGLT-2) inhibitors must be on a stable dose within 2 months prior to the initial screening and throughout the study
8. Significant weight loss within the last 6 months (e.g., > 10%)
9. Use of any weight loss medication 3 months prior and during the study period
10. Body mass index (BMI) < 18.5 kg/m^2

11. Hepatic decompensation defined as the presence of any of the following:
    - Serum albumin less than 3.5 g/dL
    - INR greater than 1.4 unless due to therapeutic anticoagulants
    - Total bilirubin greater than 2 mg/dL with the exception of Gilbert syndrome
    - History of esophageal varices, ascites, or hepatic encephalopathy
12. Other chronic liver diseases:
    - Active hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg)
    - Active hepatitis C as defined by presence of hepatitis C virus antibody (HCV) plus a positive HCV RNA
    - History or evidence of current active autoimmune hepatitis
    - History or evidence of PBC
    - History or evidence of primary sclerosing cholangitis
    - History or evidence of Wilson's disease
    - History or evidence of alpha-1-antitrypsin deficiency
    - History or evidence of hemochromatosis
    - History or evidence of drug-induced liver disease, as defined by exposure and history
    - Known bile duct obstruction
    - Suspected or proven liver cancer
13. ALT > 200 U/L
14. AST < 20 U/L
15. Creatine kinase > upper limit of normal (ULN)
16. Serum creatinine > ULN
17. Platelet < lower limit of normal (LLN)
18. Inability to obtain a liver biopsy
19. History of biliary diversion
20. Known history of human immunodeficiency virus (HIV) infection
21. History of malignancy diagnosed or treated within 2 years
    - Recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted
    - Cervical carcinoma in-situ is allowed if appropriately treated prior to Screening
    - Participants under active evaluation for malignancy are not eligible
22. Active substance abuse, based on Investigator judgment, including inhaled or injected drugs, within 1 year prior to the initial screening
23. Females who are pregnant or breastfeeding
24. Patients unable to undergo MRI-PDFF due to:
    - Contraindication to MRI examination

- Severe claustrophobia impacting ability to perform MRI during the study, despite mild sedation/treatment with an anxiolytic
- Weight or girth exceeds the scanner capacities

25. Treatment with any other investigational therapy or device within 30 days or within five half-lives, whichever is longer, prior to the initial screening
26. Active, serious medical disease with likely life expectancy <5 years
27. Any other condition(s) that would compromise the safety of the subject or compromise study quality, as judged by the Investigator.

4.2 OLE Phase Enrollment Criteria Assessment

Subjects must fulfill the following before allowing to start OLE dosing:

- Provided informed consent to enter OLE phase on or before Day 1, prior to any procedures being performed. Consent may be obtained at Week 52 or Week 56 in the DB phase for subjects who have not completed the DB phase. Consent can be obtained after Week 56 in any subject who has completed the DB phase but must be prior to any OLE related study procedures.
- Complete the Week 52 biopsy and Week 56 lab assessments in the DB phase
- Meet the above Inclusion and Exclusion Criteria before Day 1 of the OLE phase, with the exception of the following:
    - AST <20 U/L
    - Inability to obtain a liver biopsy (no new biopsy required for OLE phase)
    - Unable to undergo MRI-PDFF (no imaging performed in OLE phase)

Week 56 labs from the DB phase may be used for eligibility assessment if less than 45 days from OLE Day 1. If greater than 45 days, an Unscheduled visit must be performed to collect safety and eligibility labs.

4.3 SFU Phase Enrollment Criteria Assessment

Subjects entering the SFU phase of the study must fulfill the following criteria:

- Presence of significant histologic findings other than NASH on the Week 52 or Early Termination liver biopsy
- Received seladelpar during the DB phase for at least 6 months.

5. STUDY OUTCOME MEASURES

5.1 Primary Outcome Measures

1. Relative change in MRI-PDFF at Week 12 in the DB phase
2. Adverse events (AEs) and treatment emergent adverse events (TEAEs), physical exams, vital signs, electrocardiograms (ECGs), biochemistry, hematology, and urinalysis as determined by investigator assessment for causality and grading by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 in the DB, OLE and SFU phases

5.2 Secondary Outcome Measures

1. Absolute change in MRI-PDFF at Week 12, 26, and 52 in the DB phase
2. Relative change in MRI-PDFF at Week 26 and 52 in the DB phase
3. Proportion of subjects with a relative decrease in MRI-PDFF ≥ 30% at Week 12, 26, and 52 in the DB phase
4. Proportion of subjects with normalization of MRI-PDFF (defined as an absolute fat fraction of < 5%) at Week 12, 26, and 52 in the DB phase
5. Proportion of subjects with an absolute MRI-PDFF change > 5% at Weeks 12, 26, and 52 in the DB phase
6. Proportion of subjects with reversal of NASH and no worsening of hepatic fibrosis at Week 52 in the DB phase. The reversal of NASH is defined as the absence of hepatocellular ballooning (score of 0) and no or minimal inflammation (score of 0 or 1)
7. Proportion of subjects with improvement by at least one stage in fibrosis without worsening of NASH in the DB phase
8. Proportion of subjects with a 2-point improvement in NAS in the DB phase
9. Percent and absolute change in alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) in the DB and OLE phases
10. Percent and absolute change in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL), homeostatic model assessment of insulin resistance (HOMA-IR) in the DB and OLE phases
11. Percent and absolute change in high-sensitivity C-reactive protein (Hs-CRP) and fibrinogen in the DB and OLE phases

5.3 Exploratory Outcome Measures

1. APRI and FIB-4 in the DB and OLE phases
2. Enhanced Liver Fibrosis (ELF) score and its components (hyaluronic acid [HA], procollagen III N-terminal peptide [PIIINP], tissue inhibitor of matrix metalloproteinases [TIMP-1]) in the DB and OLE phases
3. MRE changes at Week 52 in the DB phase

4. LMS (iron corrected T1 – cT1) changes at Week 12, 26, and 52 in the DB phase
5. FibroScan® changes (kPa and CAP) at Week 52 and at SFU visits
6. C4, serum bile acids and FAO tests in DB and OLE phases

5.4 Safety Outcome Measures

In those subjects with significant histological findings other than NASH in the of treatment biopsy (Week 52 or Early Termination), resolution, worsening or no change in significant histologic findings on biopsy at the SFU visits.

6 STUDY MEDICATIONS

6.1 Clinical Supplies

6.1.1 Investigational Product, Dosage, and Mode of Administration

In the DB phase, seladelpar will be supplied in a blinded fashion in 5 mg, 10 mg, and 25 mg capsules. Matching placebo capsules will also be provided.

The study drug (seladelpar or placebo) will be administered orally, once daily. The subject will take 2 capsules daily, approximately at the same time each day. If dose adjustment occurs, the study drug might be administered at doses of 5 mg, 10 mg, and 25 mg. In case of dose adjustment, the subject will take 1 capsule daily.

In the OLE phase, Seladelpar will be supplied only as 25 mg capsules. No placebo capsules will be provided.

6.1.2 Packaging, Labeling and Shipping

The Sponsor will provide the Investigator with packaged study drug labeled in accordance with specific country regulatory requirements. For the subjects who meet the criteria for dose adjustment (per Section 7.4), the subject will be instructed to use the same study drug kit but take 1 capsule per day instead of 2 capsules per day.

6.1.3 Accountability of Clinical Supplies

The Investigator or a designee will keep a record of the dates and amounts of study medication received, the amount dispensed to study subjects, and the amount unused.

6.1.4 Stability of Study Medication

All supplies of medication must be stored as defined on the primary packaging to ensure quality.

6.2 Randomization

Randomization will only be done in the DB phase. Subjects will be centrally randomized in a blinded manner to placebo or seladelpar in a 1:2:2:2 scheme (placebo: seladelpar 10 mg: 20 mg: 50 mg). In addition, randomized subjects will be stratified by diabetic status (yes/no) and fibrosis stage (Stage F1 vs. Stage F2-3).

6.2.1 Randomization/Registration Procedure

Once all laboratory, imaging evaluations and liver biopsy report are available and the subject has been confirmed to meet all the inclusion and none of the exclusion criteria, the subject will be invited to Day 1 visit (Baseline). Randomization will occur at Day 1 visit via a centrally administered Interactive X Response Technology System (IXRS) and dosing will be initiated.

6.2.2 Emergency Unblinding

In the event of a medical emergency, where knowledge of the subject's treatment assignment is necessary per the medical judgment of the Investigator, the Investigator or the Sponsor can break the blind. The unblinding must be clearly justified and explained by a comment in the source

documentation, along with the date on which the code was broken and the identity of the person authorizing the unblinding.

6.3 Method of Administration and Compliance

Study drug (seladelpar or placebo) will be dispensed on Study Day 1, and at Weeks 4, 8, 12, 26 and 39 in the DB phase. Subjects will be instructed to take study drug orally once daily.

Study drug (seladelpar) will be dispensed on Study Day 1, and at OLE Weeks 13, 26 and 39 of the OLE phase.

Compliance with study drug administration and study drug accountability will be evaluated on all study visits during the treatment period, between Study Day 1 and the Week 52 End of Treatment (EOT) visit. Compliance and accountability will also be performed on the Early Termination Visit (if applicable).

6.4 Concomitant Medications and Procedures

The use of concomitant medications or procedures (defined below), must be documented on the subject's electronic Case Report Form (eCRF). AEs related to the administration of these medications or procedures must also be documented on the appropriate section in the eCRF.

6.4.1 Concomitant Medications

A concomitant medication is any drug or substance other than the study drug (seladelpar or placebo), including over-the-counter medications, herbal medications, and vitamin supplements, administered during subjects' participation in this trial.

Subjects will be instructed about a healthy lifestyle and appropriate diet to follow during study participation.

6.4.1.1 Permitted Concomitant Medications

- Hypertension, hyperlipidemia and type 2 diabetes mellitus will be managed in conjunction with the subject's treating physician
- GLP-1 agonists are permitted, if taken at a stable dose. SGLT-2 inhibitors should be kept at a stable dose whenever possible, but dose changes may be considered in consultation with the medical monitor
- There are no restrictions on these concomitant medications during the SFU phase

6.4.1.2 Prohibited Concomitant Medications

The following medications are prohibited during the DB and OLE phases only:

- Obeticholic acid
- Fibrates (e.g., fenofibrate)
- High-dose Vitamin E (> 400 IU/day)
- Pioglitazone
- Weight loss medications 3 months prior to and during the study period

6.4.2 Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed during subjects' participation in this trial. Subjects will be allowed to receive required procedures to treat new or existing medical conditions.

7 STUDY PROCEDURES

7.1 Study Schedule for DB Phase

The schedule of study procedures is presented in Table 1.

The total duration of a subject's participation is up to 66 weeks, during the DB phase, and consists of the following periods:

- Screening: Up to 10 weeks
- Treatment: Up to 52 weeks
- Follow-up: 4 weeks

Visits which occur within ± 7 days of the planned date will not be considered as protocol violations. Imaging and biopsy procedures that occur out of window (more than ± 7 days of the planned visit date) will be considered as protocol violations. Additional visits may be scheduled to evaluate an abnormal laboratory value or reported AE.

7.1.1 DB Screening (Week -10 to Day -1)

All screening procedures must be completed within 10 weeks. After signing an informed consent form (ICF), the following screening procedures will be performed:

- Medical history, including:
  - NASH history and detailed treatment history
  - Review of medications and prior procedures
  - Alcohol consumption review as relates to Eligibility Criterion #1
  - Results of prior liver biopsies and FibroScan®
  - Concomitant medications used in the last 6 months, including any anti-NASH, antidiabetic, statin, and fibrate medications, pioglitazone and Vitamin E
  - The subject's medical chart will be reviewed for evidence of other forms of chronic liver disease (as per Eligibility Criterion #11 & 12), as well as for HIV infection
- Vital signs, weight and height will be collected
- Complete physical examination will be performed prior to Day 1
- 12-lead ECG will be performed
- Fasting blood samples for hematology and biochemistry, hepatitis B and hepatitis C, and serum pregnancy test in women of childbearing potential will be collected
- A back-up blood sample will be collected
- FibroScan® will be performed
- AEs occurring after the ICF is signed will be recorded
- Subjects will be instructed about a healthy lifestyle and appropriate diet to follow during study participation

- Subjects who are eligible for the study based on the review of medical history, concomitant medications, procedures, and laboratory parameters will be invited to have imaging tests performed, including:
    - MRI-PDFF
    - LMS
    - MRE (at selected centers where MRE are available)
    - Laboratory tests can be repeated at the Investigator's discretion. PT, INR, and platelets must be performed and results available per the window specified by the local biopsy center.
- Baseline Liver Biopsy: Subjects who meet all non-biopsy related inclusion criteria and none of the exclusion criteria will be invited to have a liver biopsy (if not already available as per Inclusion Criterion #3). Subjects that have had a liver biopsy done previously per standard of care within 90 days of the initial screening visit, and if the pathology slides are available for review and of an adequate quality, the Baseline liver biopsy can be waived

For more detailed information about screening activities, please refer to Appendix A.

Once results of the Baseline liver biopsy are available, the subject's eligibility will be confirmed. Subjects who meet all inclusion criteria and none of the exclusion criteria will be invited to DB Day 1 (Baseline) visit.

7.1.2 DB Day 1 (Baseline) Visit

- Randomization
- AEs since the last visit will be evaluated
- Medication history, including baseline medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete physical examination will be performed
- 12-lead ECG will be performed
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, serum pregnancy test in women of childbearing potential will be collected (pre-dose of study drug)
- Back-up blood sample will be collected
- Study drug will be dispensed per the subject's randomization with instructions to take orally once a day. The first dose of study drug will be administered onsite.
- Subjects will be instructed about a healthy lifestyle and appropriate diet to follow during study participation

If a subject terminates study participation at any point after Day 1, an Early Termination Visit will be completed.

7.1.3 DB Week 4 and Week 8 Visits

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete physical examination will be performed
- Fasting blood samples for hematology, biochemistry, and exploratory biochemistry will be collected (pre-dose of study drug)
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated
- Additional study drug will be dispensed

7.1.4 DB Week 12 Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight
- Complete physical examination will be performed
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, and serum pregnancy test in women of childbearing potential will be collected (pre-dose of study drug)
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated
- Additional study drug will be dispensed
- MRI-PDFF LMS will be performed (as closely as possible to Week 12 visit, ±1 week from the planned visit date)

7.1.5 DB Week 19, Week 32, and Week 45 Contact

Subjects will be contacted by phone or email for the following:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Compliance with study drug administration
- After phone/email contact, Unscheduled Visit may be scheduled, if deemed necessary by Investigator

7.1.6 DB Week 26 Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed

- Vital signs and weight will be collected
- 12-lead ECG will be performed
- Complete physical examination will be performed
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, and serum pregnancy test in women of childbearing potential will be collected (pre-dose of study drug)
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated
- Additional study drug will be dispensed
- MRI-PDFF LMS will be performed (as closely as possible to Week 26 visit, ±1 week from the planned visit date)

7.1.7 DB Week 39 Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete examination will be performed
- Fasting blood samples for hematology, biochemistry, and exploratory biochemistry, serum pregnancy test in women of childbearing potential will be collected (pre-dose of study drug)
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated
- Additional study drug will be dispensed

7.1.8 DB Week 52 End of Treatment (EOT) Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete physical examination will be performed
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, and serum pregnancy test in women of childbearing potential will be collected
- Back-up blood sample will be collected
- 12-lead ECG will be collected
- Compliance with study drug administration and final drug accountability will be evaluated. Unused drug will be collected
- FibroScan® will be performed as closely as possible to Week 52 visit (±1 week from planned Week 52 visit date)

- MRI-PDFF, LMS, and MRE (at selected centers) will be performed as closely as possible to Week 52 and as contemporaneously as possible to and no more than 2 weeks before or after the planned Week 52 visit date
- A new liver biopsy will be performed ±1 week from the planned Week 52 visit date. PT, INR, and platelets must be collected and results available per the window specified by the local biopsy center. Week 52 biopsy will be performed
- Subjects will discontinue DB study drug dosing at the Week 52 visit. No additional study drug should be taken after that visit and the imaging and/or biopsy procedure(s) must be done within 1 week of the Week 52 visit
- Subjects may consent to the OLE phase at this visit

7.1.9 DB Week 56 End of Study (EOS) Visit

All subjects will be followed through the Week 56 visit in the DB phase or 4 weeks after their last dose of study drug:

- Any previously dispensed study drug should be returned to site staff and accountability completed

The following procedures will be performed:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete physical examination will be performed
- 12-lead ECG will be performed
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, serum pregnancy test in women of childbearing potential will be collected
- Back-up blood sample will be collected
- Subjects may consent to OLE phase at this visit if they have not consented at Week 52
- The Week 56 DB study visit may be combined with Day 1 of the OLE
- Complete pre-entry assessment for OLE
- Dispense OLE study drug if eligible

7.1.10 DB Early Termination (ET) Visit

If a subject terminates study participation at any point after Day 1, an Early Termination Visit will be completed:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected

- Complete physical examination will be performed
- 12-lead ECG will be collected
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, serum pregnancy test in women of childbearing potential will be collected
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated

For subjects who terminated from study after Week 26, liver biopsy, MRI-PDFF, LMS and MRE (at selected centers) will be performed:

- FibroScan® will be performed as close as possible to ET visit (±1 week from ET visit date).
- MRI-PDFF, LMS and MRE will be performed as closely as possible to ET visit and as contemporaneously as possible to and no more than 1 week before or after the ET visit
- Liver biopsy will be performed as closely as possible to ET visit (±1 week from ET visit date). PT, INR, and platelets must be performed with results available per the window specified by the local biopsy center

Subjects that early terminate from the study will not be eligible for the OLE.

7.1.11 DB Unscheduled (UNS) Visit

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments is needed. The following assessments may be performed if determined necessary by the investigator:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Fasting blood samples for biochemistry and hematology will be collected (pre-dose of study drug)
- A brief symptom-directed physical examination
- For subjects with symptoms suggestive for cardiac origin (e.g., chest pain), ECG will be performed.
- Compliance to study drug will be evaluated
- Additional assessments may be performed, as deemed necessary by the Investigator

7.2 OLE Phase Study Schedule

The schedule of study procedures is presented in Table 2.

The total duration of a subject's participation is up to 56 weeks during the OLE phase:

OLE periods are:

- OLE Treatment: Up to 52 weeks
- OLE Follow-up: 4 weeks

Visits which occur within ± 7 days of the planned date will not be considered as protocol violations. Imaging and biopsy procedures that occur out of window (more than ± 7 days of the planned visit date) will be considered as protocol violations. Additional visits may be scheduled to evaluate an abnormal laboratory value or reported AE.

Laboratory assessments from the DB phase Week 52 visit should be used to determine OLE eligibility if the DB phase Week 56 visit and OLE Day 1 visit are planned to be completed on the same day. Lab assessments from the DB Week 56 visit may be used for OLE eligibility assessment if less than 45 days from that visit. If greater than 45 days have elapsed from DB phase Week 56 visit, subjects should complete an unscheduled visit where all lab assessments required for DB phase Week 56 are retested. The results from the re-test must be available and assessed for eligibility prior to the Day 1 visit.

7.2.1 OLE Day 1 Visit

- Review enrollment eligibility criteria
- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Symptom-driven physical examination, vital signs and weight
- Fasting blood samples for hematology, biochemistry, exploratory biochemistry, and serum or urine pregnancy test in women of childbearing potential will be collected
- Back-up blood sample will be collected
- Dispense study drug

7.2.2 OLE Week 2, Week 13, Week 26, Week 39 Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Symptom-driven physical examination vital signs and weight
- Fasting blood samples for hematology, biochemistry, and exploratory biochemistry
- Urine pregnancy test in women of childbearing potential (Weeks 13 and 26 only)
- Back-up blood sample will be collected
- Compliance with study drug administration and drug accountability will be evaluated. Unused drug will be collected (Weeks 13, 26, 39 only)

- Dispense new study drug (Weeks 13, 26, 39 only)

7.2.3 OLE Week 52 End of Treatment (EOT) or Early Termination Visits

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Symptom-driven physical examination, vital signs and weight
- 12-lead ECG will be performed
- Fasting blood samples for hematology, biochemistry, and exploratory biochemistry
- Urine pregnancy test in women of childbearing potential will be collected
- Back-up blood sample will be collected
- Compliance with study drug administration and final drug accountability will be evaluated. Unused drug will be collected
- Any unused study drug should be returned at this visit.

7.2.4 OLE Week 56 End of Study (EOS) Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Symptom-driven physical examination, vital signs and weight
- Fasting blood samples for hematology, biochemistry, and exploratory biochemistry
- Back-up blood sample will be collected

7.2.5 OLE Unscheduled (UNS) Visits

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments is needed. The following assessments may be performed if determined necessary by the investigator:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight
- Fasting blood samples for biochemistry and hematology
- Symptom-directed physical examination, vital sign and weight
- Compliance to study drug will be evaluated
- Additional assessments may be performed, as determined by the Investigator

7.3 SFU Phase Study Schedule

The schedule of study procedures is presented in Table 3.

The total duration of a subject's participation is up to 1 year after the Week 52 or Early Termination liver biopsy. The initial SFU visit will be performed 6 months ± 4 weeks, from the date of the Week 52 or Early termination liver biopsy. Subjects with worsening of the observed histologic findings will be followed up by phone at 3-month intervals and may be requested to have additional SFU visits with a repeat of some or all of the above procedures.

7.3.1 SFU Visit

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight will be collected
- Complete physical examination will be performed
- Blood samples for hematology, biochemistry, exploratory biochemistry, and serum pregnancy test in women of childbearing potential will be collected. Back-up blood samples will be collected.
- FibroScan® will be performed
- A new liver biopsy will be performed ±1 week from the planned SFU visit date. PT, INR, and platelets must be collected and results available per the window specified by the local biopsy center.

7.3.2 SFU Unscheduled (UNS) Visits

Unscheduled visits may be conducted at the Investigator's discretion and/or when repeat of laboratory assessments is needed. The following assessments may be performed if determined necessary by the investigator:

- TEAEs will be evaluated
- Concomitant medications and procedures since last visit will be reviewed
- Vital signs and weight
- Blood samples for biochemistry and hematology
- Symptom-directed physical examination, vital sign and weight
- Additional assessments may be performed, as determined by the Investigator

7.4 Study Assessments

7.4.1 Medical History and Physical Examination

In the DB phase, medical history at Screening will include NASH history, detailed treatment history, liver biopsy history, FibroScan® results, and a review of medications and prior procedures.

In the DB phase, complete physical examinations will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat, neck, breasts, and respiratory, cardiac, gastrointestinal, peripheral vascular, genitourinary, musculoskeletal, neurologic, mental health, endocrine and hematologic.

Brief, symptom-directed physical examinations are allowed for Unscheduled visits in both study phases and for a condition that warrants the exam, as determined by the Investigator.

Any clinically significant change in physical examination findings that occur after signing the ICF at the initial screening visit will be recorded as an AE.

In the OLE phase, symptomatic-directed physical examinations will be performed at scheduled OLE clinic visits.

In the SFU phase, complete physical examinations will include a full review of the following systems: general, skin, eyes, nose/sinuses, ears, mouth/throat, neck, breasts, and respiratory, cardiac, gastrointestinal, peripheral vascular, genitourinary, musculoskeletal, neurologic, mental health, endocrine and hematologic.

7.4.2 Vital Signs and Weight/Height

Vital sign measurements include temperature, heart rate, respiratory rate, and blood pressure, recorded in the sitting position after at least 5 minutes rest. Vital signs may be obtained more frequently if a condition develops that warrants additional monitoring.

Height measurement will be performed at Baseline only; weight will be taken at each study visit per the Schedule of Assessments (Table 1 and Table 2).

7.4.3 Electrocardiogram

A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest (DB phase only).

7.4.4 Laboratory Tests

Blood samples for laboratory testing will be collected after at least an 8-hour overnight fast and prior to dosing. If the subject forgets to fast, the site will continue to draw labs. Subjects should not be dosed with study drug until blood is collected. Additional details about sample collection, processing, handling and laboratory determination techniques are provided in the Laboratory Manual. If lab sample is not analyzable or reported for any reason, medical monitor will be consulted to assess whether a recollection/retest is required.

Laboratory testing will be as follows:

Biochemistry:

Albumin, Aldolase, ALT, Amylase, ALP, AST, Bicarbonate, BUN/Urea, Chloride, CK (if > ULN, CK-BB, CK-MB, and CK-MM), Conjugated Bilirubin, Creatinine, eGFR, Free Fatty Acid, GGT, HDL-C, Insulin, LDH, LDL-C, Lipase, non-HDL, Potassium, Total Protein, Sodium, TC, TG, Total Bilirubin, Troponin I, Unconjugated Bilirubin, Venous Blood Glucose, Uric Acid

Hematology:

Erythrocyte Count (RBC), Hemoglobin, Hematocrit, Leukocyte Count (white blood cell count [WBC]), WBC Differential (absolute and percentage), Platelets, PT/INR

Exploratory Biochemistry:

Fibrinogen, hs-CRP, ELF score, HA, PIII-NP, TIMP-1, C4, serum bile acids, FAO markers

Back-Up Blood Sample:

One of the blood samples collected at each study visit will be archived as a back-up sample. These samples can be stored for up to 5 years following completion of the study and used to measure drug levels, potential new biochemical markers, and/or to replace any missing or discarded samples.

Serum Pregnancy Test: Serum pregnancy test in women of childbearing potential only.

Hepatitis B and C Testing: At screening only. The tests will include HBsAg and HCV antibody and HCV RNA if HCV AB is positive.

7.4.5 Liver Biopsy (DB and SFU Phases Only)

A liver biopsy will be performed twice during the trial: during the screening period (Baseline liver biopsy), approximately Week 52 after the Baseline liver biopsy or after early termination visit (if withdrawn after Week 26 visit), and approximately 6 months after Week 52 or after early termination visit, in SFU phase for those subjects who have significant histological findings other than NASH (Table 3).

Liver biopsy will be used to determine histological improvement in NASH and fibrosis. Liver biopsies will generally be obtained from the right lobe of the liver, however, if the Baseline biopsy is obtained from the left lobe, then the Week 52/ET liver biopsy must also be obtained from the left lobe. Biopsies should be performed using a 16G or larger biopsy instrument and samples should be at least 1.5 cm in length.

Baseline Liver Biopsy: An eligible subject must have histological evidence of definite NASH on a liver biopsy and a NAS of 4 points or greater, with a score of at least 1 point in each component (steatosis, lobular inflammation, and ballooning). This will be used for enrollment into the DB phase. A new Baseline biopsy is not required for enrollment into the OLE phase.

Subjects who meet all non-biopsy related inclusion criteria and none of the exclusion criteria will be invited to have a liver biopsy (if not already available as per Inclusion Criterion #3). If subjects had a liver biopsy done previously per standard of care but within 90 days prior to the initial screening visit, and if the pathology slides are available for review and of an adequate quality, the Baseline liver biopsy can be waived.

Week 52/ET Liver Biopsy: The Week 52 and ET liver biopsy will be performed ± 1 week from the scheduled study visit.

SFU Liver Biopsy: The SFU liver biopsy will be performed in eligible subjects at 6 months ±4 weeks, from the Week 52/ET liver biopsy.

Pre-Liver Biopsy Instructions: The subject must have PT, INR and platelets performed with results available per the window specified by the local biopsy center. Subjects will be instructed, if possible, to fast 6 to 8 hours prior to the scheduled liver biopsy.

Liver Biopsy Analysis: Central reader will review and analyze the tissue samples. The NAS and fibrosis score will be calculated using the NASH CRN criteria for the biopsies collected in the DB phase. The SFU biopsy will only be evaluated for persistence or resolution of the non-NASH significant histologic findings; NAS and fibrosis will not be scored on these samples.

7.4.6 Imaging Tests

7.4.6.1 MRE Exam (DB Phase Only)

MRE exam will be used to evaluate liver fibrosis through a noninvasive imaging technique. As collagen deposition associated with fibrosis imparts parenchymal rigidity, the leading biomarker for assessing fibrosis is through elastography. MRE uses a modified phase-contrast pulse sequence to visualize rapidly propagating mechanical shear waves (typically delivered at around 60 Hz). Cross-sectional elastogram images will be created depicting the stiffness generated from the wave propagation information. Technically, elastography assessments can be accomplished with most magnetic resonance scanners by adding hardware to generate mechanical waves and adding specific software for acquisition and processing. Because the waves can be visualized and analyzed deep into the liver, MRE evaluates a large portion of the liver and can be performed in conjunction with conventional MRI. For these reasons, MRE is considered to be a reliable, highly accurate, and precise method for assessing hepatic fibrosis.

Clinical sites will screen subjects for MRI safety and eligibility per institutional standards.

MRE Exam Schedule and Timing: MRE will be performed at selected centers and only in the DB phase. Subjects will undergo two MRE exams. Clinical sites will determine the logistics of scheduling the MRE exam.

- The first MRE exam will be performed during the screening period (prior to the invasive Baseline liver biopsy), as contemporaneously as possible to, and no more than 90 days from the Baseline liver biopsy
- The second MRE exam will be performed as contemporaneously as possible to, and no more than 1 week before or after the Week 52/ET liver biopsy

After completion of the exam, clinical sites will transfer MRE images to the Central MRI Reader.

Pre-MRE Exam Instructions: Subjects will be instructed, if possible, to fast for 4 or more hours prior to the scheduled MRE exam but will be allowed to take necessary medications and small quantities of water.

MRE Exam Analysis: Central MRI Reader will review and analyze images. The liver fibrosis (stiffness) will be calculated.

7.4.6.2 MRI-PDFF Exam (DB Phase Only)

MRI-PDFF exam will be used to quantify the hepatic proton density fat fraction noninvasively. The fat fraction is the proportion of mobile protons in liver tissue attributable to fat and thus, is a noninvasive magnetic resonance-based biomarker of liver triglyceride concentration.

To quantify the fat fraction, the MRI-PDFF exam will use a fast spoiled gradient recalled echo (FSPGR) sequence that uses a low flip angle to reduce T1 bias, acquires multiple echoes after a single excitation to measure and correct for T2*decay, and uses spectral modeling to address fat-water and fat-fat signal interference effects. Using MR spectroscopy as the reference standard, the proposed MRI technique measures hepatic fat fraction accurately in human subjects at 1.5T or 3T and across different vendors. The technique provides high within-examination and between-examination precision. Linearity is maintained across the entire relevant biological range from <1% to >40% hepatic fat fraction. The technique is robust to minor variations in acquisition parameters, including those that may be encountered during usage in a clinical trial.

The FSPGR sequence proposed for imaging-based hepatic fat fraction quantification can be implemented on any up-to-date clinical scanner and can be used at clinical centers with access to such a scanner. Moreover, the technique is imaging based and covers the whole liver, thus providing information on both the quantity and distribution of hepatic fat fraction. These characteristics represent critical advantages over the alternative technique of single-voxel proton MR spectroscopy to measure hepatic fat fraction in a multicenter clinical trial.

Clinical sites will screen subjects for MRI safety per institutional standards and will determine the logistics of scheduling the MRI-PDFF exam.

MRI-PDFF Exam Schedule and Timing: Subjects will undergo four MRI-PDFF examinations in the DB phase only. The goal will be to schedule the second, third, and fourth MRI exams at the same or similar time of day as the first MRI-PDFF exam.

- The first MRI-PDFF exam will be performed during the screening period prior to the Baseline liver biopsy but as contemporaneously as possible to and no more than 90 days from the Baseline liver biopsy
- The second MRI-PDFF exam will be performed as close as possible to the Week 12 visit (±1 week from planned visit date)
- The third MRI-PDFF exam will be performed as close as possible to the Week 26 visit (±1 week from planned visit date)
- The fourth MRI-PDFF exam will be performed as contemporaneously as possible to and no more than 1 week before or after the Week 52/ET Visit (if applicable)

Pre-MRI-PDFF Exam Instructions: Subjects will be instructed, if possible, to fast for 4 or more hours prior to the scheduled MRI-PDFF exam. However, they will be allowed to take necessary medications and small quantities of water.

MRI-PDFF Exam Performance: Subjects will be positioned supine with a phased-array coil centered over the liver. After localizing sequences, an axial multi-echo-echo two dimensional FSPGR sequence will be performed through the liver. Imaging parameters will be selected as appropriate for 1.5T or 3T scanners. After completion of the exam, clinical sites will transfer MRI images to the Central MRI Reader.

MRI-PDFF Exam Analysis: The Central MRI Reader will review and analyze images. The analysts will place 3 regions of interest on a PDFF image. The fat fraction will be calculated from all pixel values within the selected regions of interest and reported as the average value for each image.

7.4.6.3 FibroScan® Exam (DB and SFU Phases Only)

FibroScan® exam will be used to evaluate liver fibrosis through a noninvasive imaging technique. FibroScan® uses a modified ultrasound probe to measure the velocity of a shear wave. Cross-sectional elastogram images will be created depicting the stiffness generated from the wave propagation information. FibroScan® is considered to be a reliable, highly accurate, and precise method for assessing hepatic fibrosis.

Clinical sites will screen subjects for FibroScan® safety per institutional standards.

FibroScan® Exam Schedule and Timing: Subjects will undergo FibroScan® exams at centers when the test is available. Clinical sites will determine the logistics of scheduling the FibroScan® exam.

- The first FibroScan® exam will be performed during the screening period prior to the Baseline liver biopsy
- The second FibroScan® exam will be performed as closely as possible to Week 52/ (±1 week from planned Week 52 visit date)/±1 week from ET visit date (if applicable)
- FibroScan® exam will be performed in conjunction with each SFU biopsy

Pre-FibroScan Exam Instructions: Subjects will be instructed, if possible, to fast for 4 or more hours prior to the scheduled FibroScan® exam but will be allowed to take necessary medications and small quantities of water.

FibroScan Exam Analysis: Local Reader will review and analyze scans.

7.4.6.4 LMS Exam (DB Phase Only)

LMS is a noninvasive medical imaging software tool which, combined with MRI, can be a diagnostic tool to assess patients with liver disorders. The LMS provides quantitative measure of liver fat, and correlates iron and fibro-inflammation using multi-parametric MRI. The tool is U.S. FDA 510(k) cleared to aid clinicians in the diagnosis of liver disorders and abnormalities.

Clinical sites will determine the logistics of scheduling the LMS exam and follow any additional provided guidelines on the use of this imaging software tool. Subjects will undergo 4 *LiverMultiScan* examinations during the DB phase only.

- LMS Exam Schedule and Timing: Subjects will undergo 4 LMS examinations
- The first LMS exam will be performed during the screening period (prior to the Baseline liver biopsy), as contemporaneously as possible to and no more than 90 days from the Baseline liver biopsy
- The second LMS exam will be performed as close as possible to the Week 12 visit (±1 week from planned visit date)
- The third LMS exam will be performed as close as possible to the Week 26 visit (±1 week from planned visit date)
- The fourth LMS exam will be performed as contemporaneously as possible to and no more than 1 week before or after the Week 52/ET Visit (if applicable)

LMS Exam Analysis: The Central MRI Reader will review and analyze images.

8 ADVERSE EVENTS

8.1 General

8.1.1 Definition of Adverse Events (AEs)

An AE is any medical occurrence in a subject administered a pharmaceutical product in a clinical study, regardless of 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 product, whether or not related to the medicinal product.

An AE includes any condition (including a pre-existing condition) that: 1) was not present prior to study treatment, but appeared or reappeared following initiation of study treatment, or 2) was present prior to study treatment, but worsened during study treatment. This would include any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states. Pregnancy should be documented as an adverse event and should be reported to the clinical monitor and to the Sponsor immediately upon learning of the event. Pregnancies will be followed up through delivery or termination of the pregnancy.

8.1.2 Definition of Serious AEs (SAEs)

A serious adverse event (SAE) is any medical occurrence that:

- Results in death
- Is life-threatening (was at risk of death) at the time of the event
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity defined as a substantial disruption of a person's ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is an important medical event that, when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition for an SAE. Examples of such events include allergic bronchospasm, requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse

8.1.3 AE Severity

The severity of an AE will be graded from 1 to 5 according to Table 7 and CTCAE version 4.0 criteria (Appendix C).

The CTCAE general guideline will be used to assess AE severity. Not all Grades are appropriate for all AEs. Therefore, some AEs listed in the CTCAE have fewer than five options for Grade selection.

Table 7: Grading of AE Severity

Grade	Clinical Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

8.1.4 Adverse Event Outcome

Subjects will be followed until AEs have either resolved, returned to baseline status, or are deemed stable or commensurate with ongoing disease processes, per the Investigational judgment.

One of the four outcomes listed below must be recorded:

Resolved – The subject has fully recovered from the event with no residual effects observable or returned to baseline status.

Resolved with sequelae – The subject has recovered from the event with some residual effects observable.

Ongoing – Effects of the event are still present, regardless of whether the effect is changing or stable and persistent.

Fatal outcome (for serious adverse events only)

8.1.5 Relationship to Treatment

The relationship or association of the AE to a study treatment will be characterized as "**unrelated**", "**unlikely**," "**possible," "probably", or "definite**", as shown in Table 88.

Table 8: AE Relationship Attribution

Relationship	Attribution	Description
Unrelated to the study drug	Unrelated	The AE is ***clearly not related*** to the study drug
	Unlikely	The AE is ***doubtfully related*** to the study drug
Related to the study drug	Possible	The AE is ***maybe related*** to the study drug
	Probable	The AE is ***likely related*** to the study drug
	Definite	The AE is ***clearly related*** to the study drug

8.1.6 Action Taken with Study Medication

As a consequence of an AE, the action taken with study drug can be:

- None: no changes were made to study drug administration or dose

- Permanently discontinued: study drug was stopped and not restarted
- Temporarily interrupted, restarted at the same dose: dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose
- Temporarily interrupted, restarted at a decreased dose: dosing was temporarily interrupted or delayed due to the AE and restarted at a decreased dose
- Dose decreased: study drug dose was decreased without previous study drug interruption
- Not applicable: e.g. in case the AE occurred after signing the ICF but before the administration of study drug was commenced

8.2 Recording, Reporting and Follow-Up of Adverse Events

Details about the safety reporting process are presented in the Safety Reporting Plan.

All AEs must be recorded by the Investigator in the eCRF, regardless of association with the use of the study treatment. An AE will be recorded any time after the time of signed ICF and captured until the last study visit.

To avoid colloquial expressions, the AE should be reported in standard medical terminology. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.

For each AE, the Investigator or an adequately qualified designee will evaluate and report the onset, duration, severity, seriousness, and relationship to (association with) the study treatment, and indicate the action taken.

Abnormal laboratory findings will be determined by review of all laboratory data collected on the subjects. At each visit, the Investigator is responsible for assuring that the subject is questioned regarding all potential AE and concurrent illnesses.

Any laboratory abnormalities deemed clinically significant by the Investigator should be reported as an AE. A clinically significant abnormality is a confirmed abnormality that is changed sufficiently from baseline, so that in the judgment of the Investigator, a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, or administering treatment. Whenever possible, the etiology of the abnormal findings will be documented in the eCRF. Repeated, additional tests and/or other evaluations required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

Any clinically significant laboratory abnormalities that are either unexplained or considered treatment-related should be promptly reported to the Sponsor. Any additional relevant laboratory results obtained by the Investigator during this study will be supplied to the Sponsor and recorded in the eCRF.

A change in diabetes medication dose may not be reported as an adverse event, however, *Worsening* of Diabetes from baseline must be documented as an adverse event during the course of study participation.

8.2.1 SAE Reporting Process

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including Suspected Unexpected Serious Adverse Reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6, and per the United States Code of Federal Regulations (CFR); 21 CFR § 312.32. Country specific regulatory requirements will be followed in accordance with local country regulations and guidelines. Independent Ethics Committees will be notified of any SAE according to applicable regulations.

Any SAE, including death due to any cause, that occurred from the signing of ICF through, regardless of relationship to the study treatment, must be reported immediately (no later than 24 hours) by the Investigator to the Sponsor's representative (safety vendor) using the SAE Report Form. Planned hospitalizations or procedures will not be considered as SAEs.

The criteria for seriousness will be indicated on the SAE Report Form as follows:

- Hospitalization or prolongation of hospitalization
- Life threatening
- Death
- Persistent or significant disability/incapacity
- Congenital anomaly
- Other important medical events

The outcome for the event will be listed on the SAE Report Form as follows:

- Resolved
- Resolved with sequelae
- Ongoing
- Fatal

If additional information regarding a previously submitted SAE is obtained, a follow-up SAE must be sent to the Sponsor's representative (safety vendor).

The Sponsor and/or its designee will identify and report to regulatory authorities within the required timeframes, all serious and unexpected suspected adverse reactions (SUSARs) and clinically important increases in rate of serious suspected adverse reactions.

SAEs must be collected and reported by the Investigator for the whole period from the signing of ICF until the last study visit. If the event of death occurs after the last study visit, the death will not have to be reported as an SAE.

The Investigator will document all available information regarding the SAE on the standard form. The Investigator should not wait to receive additional information to fully document the event before notifying the Sponsor's representative of an SAE. The initial notification should include, as a minimum, sufficient information to permit identification of:

- Subject's study number
- Time and date of study drug administration

- Time and date of the start of the event and either the date and time of the resolution of the event or a statement that the event is ongoing
- A brief description of the event and actions taken
- Investigator's opinion of the relationship of the event and the investigational product

Follow-up report(s) should follow the initial report, using the SAE form detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained. All source information provided to the Sponsor must be appropriately anonymized.

8.2.2 Follow-up of Reported AEs

SAEs recorded during the study will be followed by the Investigator until resolution or stabilization.

After the Post-Treatment Visit, non-serious AEs should be followed up until they resolve or have failed to resolve, for a duration determined by the Investigator.

Follow-up procedures will be determined by the nature of the event and the judgment of the Investigator.

8.3 Distribution of Responsibilities

Details about the distribution of safety responsibilities are presented in the Safety Reporting Plan.

8.4 Safety Monitoring Criteria, Dose Adjustment, and Withdrawal Criteria

Enrolled subjects with the following lab abnormalities will be monitored closely and may be discontinued from the study drug or go through study drug dose adjustment if criteria are met as outlined in Tables 9, Table 10, and 11.

8.4.1 Drug-Induced Liver Injury (DILI) Safety Monitoring

Table 9: DILI Criteria for Participants with Normal Baseline ALT and AST

	ALT or AST during Study Treatment	**Other Concurrent Parameters Required during ALT or AST Elevation**	**Study Action**
ALT, AST and Total Bilirubin ≤ ULN	ALT or AST > 8 × ULN	--	**Stop study drug permanently**
	ALT or AST > 5 × ULN for more than 2 weeks	--	
	ALT or AST > 3 × ULN	**AND** total bilirubin > 2 × ULN **OR** INR > 1.5	
	ALT or AST > 3 × ULN	**AND** clinical symptoms*	

* Clinical symptoms: appearance of fatigue, nausea, right upper quadrant pain or tenderness, fever, rash, jaundice and/or eosinophilia (> 5%).

Table 10: DILI Criteria for Participants with Abnormal Baseline ALT or AST

	ALT or AST during Study Treatment	**Other Concurrent Parameters Required during ALT or AST Elevation**	**Study Action**
ALT or AST > ULN	ALT or AST > 2 × baseline measurement (BLM)	AND concomitant total bilirubin > 2 × BLM **OR** INR increase by 0.2	**Stop study drug permanently**
	Regardless of ALT or AST levels	Clinical symptoms* **AND** concomitant total bilirubin > 2 × BLM	
ALT or AST ≥ ULN but < 2 × ULN	ALT or AST > 5 × BLM	--	**Interrupt study drug**
ALT or AST ≥ 2 × ULN but < 5 × ULN	ALT or AST > 3 × BLM		
ALT or AST ≥ 5 × ULN	ALT or AST > 2 × BLM		

* Clinical symptoms: appearance of fatigue, nausea, right upper quadrant pain or tenderness, fever, rash, jaundice and/or eosinophilia (> 5%).

- **Interrupt study drug:** Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the participant (see Appendix B). Study drug can be restarted at the same dose level only if a firm competing etiology is identified and liver tests return to baseline. Down titration to a lower dose can also be considered at this time
- **Stop study drug permanently:** Repeat AST, ALT, total bilirubin, and PT/INR within 3 days and closely observe the participant (see Appendix B)
- If close observation of a participant is not possible, **stop study drug permanently**

8.4.2 Muscle Safety Monitoring

Table 11: Muscle Injury Safety Criteria for Study Drug Interruption or Stopping Rules

Creatine Kinase (CK) during Study Treatment	Grade 3 CTCAE Myalgia or Myopathy	Repeat CK Test Results	Study Action
CK > 2.5 × ULN	Not observed	CK level is ≤ 2.5 × ULN	• **Study drug may be reinitiated** at this time at the current dose level.
	Not observed	CK level is > 2.5 × ULN	• Study drug should remain held and CK testing should be performed weekly until CK ≤ 2.5 × ULN. **Study drug may then be reinitiated** at this time at a decreased dose level as outlined in Section 6.1.1 of the study protocol.
	Observed	CK level is ≤ 2.5 × ULN	• **Study drug may be reinitiated** at the current dose level once symptoms are resolved. • **Study drug should be permanently discontinued** if symptoms reappear after re-challenge and there is no clinical explanation.
	Observed	CK level is > 2.5 × ULN	• **Study drug should remain held** and CK testing should be performed weekly until CK ≤ 2.5 × ULN and clinical symptoms are resolved. • **Study drug may then be reinitiated** at this time at a decreased dose level as outlined in Section 6.1.1 of the study protocol. • **Study drug should be permanently discontinued** If symptoms reappear after re-challenge and there is no clinical explanation. The participant should continue to be routinely monitored until complete resolution of symptoms or study completion, whichever comes first.

8.4.3 Cardiac Safety Monitoring

- Subjects with new symptoms suggestive of cardiac origin (e.g. left-sided chest pain, etc.): **Interrupt study drug.** Perform ECG and Troponin I, AST, CK, CK-MB within 5 days. Follow the subject weekly until the event resolution or stabilization. Study drug can be resumed if the event is deemed related to the subject pre-existing condition

8.4.4 Pancreatic Safety Monitoring

- If serum lipase > 3 × ULN with clinical symptoms of acute pancreatitis, interrupt study drug and repeat the test within 3 days

- If test is confirmed, perform abdominal imaging to exclude an alternative cause for the event
- Study drug may be reinitiated at the same or lower dose if there is no evidence of acute pancreatitis or an alternative etiology for the pancreatitis is identified

8.4.5 Withdrawal Criteria and Replacement of Subjects

Subjects may be discontinued from the study for the following reasons:

- Entered the study in violation of this protocol
- Required the use of a prohibited concomitant medication
- Withdrawal of Informed Consent
- At the discretion of the Investigator for medical reasons
- Female subjects who become pregnant
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor or designee
- Lost to follow-up

The date the subject is withdrawn and the reason for discontinuation will be recorded in the eCRF.

Subjects will not be considered to have completed the study if, for any reason, they do not complete the liver biopsy and clinical laboratory assessments at the End-of-Study Visit (Week 52).

If a subject withdraws from the study, he/she will not be replaced.

8.5 Precautions

8.5.1 Pregnancy

No specific studies have been performed to determine the reproductive and developmental toxicity of seladelpar.

As a precaution, women of childbearing potential participating in this study must use one barrier contraceptive and a second effective birth control method during the study and for at least 30 days after the last dose. Male subjects who are sexually active with female partners of reproductive potential must use barrier contraception and their female partners must use a second effective birth control method during the study and for at least 90 days after the last dose of study drug. Sexual abstinence, defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, is acceptable as an effective birth control method. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

A second effective birth control method includes the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:

    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

8.6 Study Stopping Rules

If any of the three criteria below are met and adverse events are considered related to study drug, the study must be stopped:

- Three participants develop the same Grade 3 CTCAE related to study drug,
- Two participants develop any Grade 4 CTCAE related to study drug, or
- One participant develops a Grade 5 CTCAE

9 STUDY TERMINATION

CymaBay Therapeutics, Inc. reserves the right to discontinue the study if it becomes aware of information concerning the quality or safety of the trial medication (based on recommendation from Medical Monitor), as well as other important information that may affect proper conduct of the trial. Should the study be discontinued by the Sponsor, then the Investigator, Ethics Committee, and competent authorities should be notified by the Sponsor or Sponsor's delegate, in accordance with applicable regulatory regulations.

The study may be prematurely terminated by the Investigator, due to specific clinical observations relating to safety concerns. If the Investigator intends to prematurely terminate the trial at his/her site, he/she must immediately inform the Sponsor on his/her intention as well as of the reasons why.

10 DATA MANAGEMENT AND STATISTICAL ANALYSES

10.1 Data Management

10.1.1 Processing of Electronic Case Report Forms

Electronic CRFs (eCRFs) will be completed for all study subjects enrolled in the study. At scheduled monitoring visits, eCRFs will be verified against source documentation. Upon completion of this review, finalized eCRFs will be submitted to the Sponsor's designated Contract Research Organization (CRO). Any subsequent changes to the eCRFs will be performed in accordance with the CRO's Standard Operating Procedures (SOP) for editing and clarifying eCRFs.

10.1.2 Database

Data entry will be performed through username and password-protected access to a secure database. All data will be entered using electronic eCRFs. Internally developed programs for plausibility, consistency, and out-of-range data fields will supplement the review of the data. A 100% manual review of AEs, drug accountability and termination summary data, will be performed by Data Management personnel. The Medical Dictionary for Regulatory Activities (MedDRA) coding thesaurus will be used to classify AEs, medical history and concomitant procedures while the World Health Organization (WHO) Drug classification will be used to code medications.

10.1.3 Data Discrepancies

After all subjects complete the study and data discrepancies are resolved, protocol deviations during both enrollment and study execution will be reviewed. Significant protocol deviations and procedural discrepancies will be discussed. All data will be included in the safety analyses.

10.2 Statistical Analysis

Full details on the statistical methodology to be used will be included in a SAP to be developed prior to study unblinding.

10.2.1 Sample Size Estimation

A sample size of 175 subjects (50 subjects per each dose of seladelpar and 25 subjects for placebo) provides at least 80% power to detect a pairwise treatment difference of at least 20% between the active and placebo groups with respect to a relative change from baseline in hepatic fat fraction, as assessed by MRI-PDFF at Week 12. Power calculations were performed using a standard t-test, allowed for a 12% dropout rate (6 subjects per seladelpar arm, 3 subjects for the placebo arm), and a pooled standard deviation of 26 for the relative change endpoint.

10.2.2 Analysis Populations

The safety analysis will be conducted on the Safety Population. Efficacy analyses will be conducted on the intent-to-treat (ITT) population, the modified intent-to-treat (mITT) population, the modified intent-to-treatment population with biopsy (mITTb), and the per-protocol (PP) populations. The mITT population will be used for the primary efficacy analysis.

10.2.2.1 Safety Population

The Safety population is defined as any subject who receives at least one dose of study drug.

10.2.2.2 Intent-to-Treat Population (ITT)

The Intent-to-Treat (ITT) population is defined as any subject who is randomized and receives at least one dose of study drug.

10.2.2.3 Modified Intent-to-Treat Population (mITT)

The mITT population is defined as any subject who is randomized, receives at least one dose of study drug, and has Baseline and Week 12 MRI-PDFF.

10.2.2.4 Modified Intent-to-Treat Population with Biopsy (mITTb)

The mITTb population is defined as any subject who is randomized, receives at least one dose of study drug, and has Baseline and Week 52/ET liver biopsies.

10.2.2.5 Per-protocol population (PP)

The PP population is defined as any subject who is randomized and receives at least one dose of study drug, has Baseline and Week 52/ET liver biopsies, and does not have a protocol violation that is deemed to impact the efficacy analysis.

10.2.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics (medical histories, physical examinations, and concomitant medications) will be summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum) for continuous variables and frequency distributions (counts and percentages) for discrete variables.

10.2.4 Efficacy Analysis

10.2.4.1 Primary Efficacy Analysis

Pairwise comparisons between each dose of seladelpar versus placebo with respect to the relative change in hepatic fat fraction as assessed by MRI-PDFF at Week 12 will be conducted using ANCOVA. The LS means, standard errors, 95% CIs, and p-values will be provided from the ANCOVA model with percent change from baseline in MRI-PDFF as the dependent variable, treatment group, diabetic status, and fibrosis stage as factors and baseline MRI-PDFF as covariates.

Relative change will be calculated as

$[\text{MRI-PDFF}_{\text{WEEK12}} - \text{MRI- PDFF}_{\text{BASELINE}}] \times 100 / \text{MRI-PDFF}_{\text{BASELINE}}$.

All statistical comparisons will be made at a two-sided alpha of 0.05.

Other analyses will be secondary.

In primary, mITT analyses, subjects with missing efficacy data will be considered unimproved on the primary outcome measure.

10.2.4.1.1 Top-Line Results

The 12-week Primary Analysis, including top-line results for efficacy and safety, will be provided and communicated when it becomes available and before study completion. These results will be provided by treatment group, but individual patient data will remain blinded and the study will continue as a double-blind study until its completion. Details of the conduct of the Primary Analysis will be provided in the SAP.

10.2.4.2 Secondary Efficacy Analysis

Comparisons between each seladelpar dose versus placebo with respect to the absolute change in hepatic fat fraction as assessed by MRI-PDFF at Week 12, 26 and 52 will be conducted using mixed model repeated measures analyses, with factors for scheduled time point, treatment, time point by treatment interaction, baseline diabetic status, and fibrosis stage, with the baseline hepatic fat fraction as a covariate. Supportive analyses will be conducted using Wilcoxon rank-sum tests, stratified by diabetic status and fibrosis stage.

Comparisons between each seladelpar dose versus placebo with respect to the relative change in hepatic fat fraction as assessed by MRI-PDFF at Week 26 and 52 will be conducted using mixed model repeated measures analyses with factors for scheduled time point, treatment, time point by treatment interaction, baseline diabetic status, and fibrosis stage, with the baseline hepatic fat fraction as a covariate. Supportive analyses will be conducted using Wilcoxon rank-sum tests, stratified by diabetic status and fibrosis stage.

Each seladelpar dose will be compared versus placebo for the number and percent of subjects with normalization of hepatic fat content (<5%) at Week 12, 26, and 52 using Cochran-Mantel-Haenszel tests, stratified by diabetic status and fibrosis stage. Similar analyses will be performed for:

- Number and percent of subjects with an absolute change > 5% on MRI-PDFF at Week 12, 26, and 52
- Number and percent of subjects with a relative decrease in hepatic steatosis of > 30% on MRI-PDFF at Week 12, 26, and 52
- Number and percent of subjects with reversal of NASH with no worsening of fibrosis as defined by centrally scored histology assessment at 52 weeks of treatment
- Number and percent of subjects with decrease by at least one stage in fibrosis (NASH Clinical Research Network Classification) without worsening of NASH
- Number and percent of subjects with a 2-point improvement in NAS score

Efficacy-related laboratory data will be summarized by laboratory parameter, treatment group and study visit for the DB and OLE phases.

Alpha control procedures for testing of the secondary efficacy endpoints will be described in the SAP.

10.2.5 Safety Analysis

Safety analysis will be conducted on the Safety Population.

Safety data, including AEs, safety laboratory results, physical examination results, vital signs, and ECG will be summarized by treatment group and/or listed.

The safety measures will be incidence rate of AEs and TEAEs, ECG, biochemistry, hematology and urinalysis, physical exams and vital signs as measured by NCI CTCAE Version 4.0.

Safety data will be summarized by study treatment (placebo vs. seladelpar) and by seladelpar dose administered during the treatment period for the DB, OLE and SFU phases. Baseline values in the DB and OLE phases for laboratory tests, vital signs, and electrocardiograms will be defined as the last evaluation performed prior to administration of study drug. Baseline values in the SFU phase for laboratory tests, vital signs, and electrocardiograms will be defined as the last evaluation prior to obtaining informed consent for the SFU phase.

10.2.5.1 Adverse Events

The subset of AEs occurring after the first dose of study drug will be considered to be TEAEs in the DB and OLE phases. The incidence of TEAEs will be tabulated. All AEs will be reported and tabulated for the SFU phase; there is no TEAE subset for this study phase.

10.2.5.2 Vital Signs

Descriptive statistics and mean or median change from baseline will be determined for vital signs (temperature, heart rate, respiratory rate, blood pressure) at each assessment. Vital signs collected at all study time points will be recorded in the eCRF and analyzed or listed.

10.2.5.3 Physical Examination

Clinically significant abnormalities on physical examination will be recorded as AEs in the eCRF.

10.2.5.4 Laboratory Tests

Descriptive statistics for the result and change from baseline will be summarized for each laboratory test by study treatment and visit. Abnormal laboratory values will be graded by the investigator as “clinically significant” or “not clinically significant”, where applicable. Clinically significant abnormal laboratory values will be reported as AEs, after study treatment has been initiated. Investigators may repeat laboratory tests for any parameter that is abnormal and/or clinically significant.

10.2.5.5 Electrocardiograms

Clinically significant abnormalities on ECGs will be recorded as AEs in the eCRF. Summaries of ECG parameters by study treatment and visit will be prepared.

10.2.5.6 Concomitant Medications

Concomitant medications will be listed and summarized by World Health Organization Drug Classification (WHODrug) for Drug Statistics Methodology, Anatomical Therapeutic Chemical (ATC) system class, generic term, and treatment group.

11 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1 Study Monitoring

The Investigators and institution(s) will permit trial-related monitoring of the eCRF data by CymaBay Therapeutics, Inc. or their assignee by providing direct access to source data and/or documents. The study monitor will verify the CRFs against the source documentation. Deviations from the protocol with regard to subject enrollment or study conduct will also be noted in the source documentation, in the eCRF and a complementary database. A Sponsor representative will visit the site to initiate the study, prior to the first treatment of the first subject, and at agreed upon times throughout the study, including at the end of the study. Medication dispensing, and clinical drug supply records will be 100% verified at the study site by the study monitor. It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

11.2 Audits and Inspections

Regulatory authorities, the EC, and/or CymaBay Therapeutics Inc. or its designee(s) may request access to all source documents, eCRF data, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

It is understood that all subject specific information is confidential and no documentation that can link study information to the specific subject will be collected or retained by the Sponsor.

11.3 Ethics Committees

The Investigators will provide ethics committees with all information impacting the risk profile of the drug. The trial will not commence until written ethics committee approval for the protocol and ICF is received by the Sponsor. The Investigator has the responsibility to conform to all of the local requirements for periodic updates and notification to the committee.

12 QUALITY CONTROL AND QUALITY ASSURANCE

Clinical data will be recorded in eCRF. Data will be verified and confirmed by the Investigators.

All data that will be used in the primary efficacy analyses and the safety analysis will be source documents verified by the monitors. Additionally, the Sponsor will conduct audit reviews of monitored eCRFs.

A final audit of the electronic database against the final eCRF will be done.

13 ETHICS

13.1 Ethics Review

The protocols, ICFs, any information provided to the subject, recruitment advertisements, and any amendments to these items must be reviewed and approved by the EC prior to their use in the trial.

The study will not start before written approval by EC(s) has been obtained and the local regulatory requirements have been complied with.

The EC must meet all the appropriate International Committee on Harmonisation (ICH) requirements for composition, documentation, and operational procedures.

13.2 Ethical Conduct of the Study

The study will be conducted in strict accordance with the Declaration of Helsinki, ICH Good Clinical Practice (GCP) guidelines, applicable laws and regulations, and the procedures outlined in EC approved version of this protocol.

13.3 Written Informed Consent

There will be a separate ICFs for the DB phase and the OLE phase.

The subject must give consent to participate in the trial, only after having been fully informed by the Investigator or a person designated by him/her of the nature, significance, and implications of the trial, as well as to the associated risks involved. Such meetings must be carried out on an individual basis and adapted to the educational background and previous knowledge of the subject. Participation in this meeting should be documented in the subject's file. The subject must be allowed ample time to inquire about details and to decide whether or not to participate in the study. Written informed consent will be obtained for all subjects enrolled in the trial and before study related activities are performed on a subject. The process of obtaining written informed consent will be documented in the source documents of the subject. Only ICFs approved by the EC will be used.

The ICF must be personally dated and signed by the investigator or qualified person delegated by the investigator to conduct the consent and the subject. The original document will be retained by the Investigator and filed in the Investigator's Site File.

14 RETENTION OF RECORDS

All study related material, including source documents, eCRFs, competent authority, and EC correspondence and analyses, and any other documentation required by applicable laws and regulations will be maintained for 15 years after completion of the study, or notification from the Sponsor that the data can be destroyed, whichever comes first.

15 PROTOCOL AMENDMENTS

Any change or addition to this protocol will only be made when a protocol amendment has been written, approved, and signed by CymaBay Therapeutics, Inc. and the Principal Investigator before the change or addition can be considered effective. This amendment must also be submitted to the EC for approval and, when necessary, competent authority approval before implementation. Protocol amendments may affect consent forms of current and future subjects. CymaBay Therapeutics, Inc. will clearly specify when a protocol amendment includes safety, procedural, and/or efficacy information that will require specific ICF text changes.

16 DISCLOSURE OF INFORMATION

Information concerning the investigational medication and patent application processes, scientific data or other pertinent information is confidential and remains the property of CymaBay Therapeutics, Inc. The Investigator may use this information for the purposes of the study only. It is understood by the Investigator that CymaBay Therapeutics, Inc. will use information developed in this clinical study in connection with the development of the investigational medication and, therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

The Investigator may not submit for publication or presentation the results of this study without first receiving written authorization from CymaBay Therapeutics, Inc. CymaBay Therapeutics, Inc. agrees that, before it publishes any results of the study, it shall provide the Investigator with at least 30 days for review of the pre-publication manuscript prior to the submission of the manuscript, to the publisher.

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APPENDIX A – ELIGIBILITY LOG (DB PHASE)

All Screening procedures will be completed within 10 weeks. DB phase Screening activities will be performed during multiple screening visits. Screening visits can be combined but must follow the listed below order.

Screening Visit 1:

- Medical History review (including alcohol consumption review per Exclusion Criterion #1)
- Review of previous FibroScan® result (if available)
- Review of previous imaging tests (ultrasound, computed tomography, MRI) (if available)
- Review of previous liver biopsy (if available)
- NASH history review, including evaluation of risk factors associated with NASH (obesity, diabetes, race, etc.)
- Concomitant Medications review, including the use of anti-NASH, antidiabetic, statins, and fibrate medications.
- Physical Examination, ECG, vitals, weight, and height measurements
- Collection of blood

Screening Visit 2:

- FibroScan®
- Laboratory tests can be repeated at the Investigator's discretion

Screening Visit 3:

- MRI-PDFF
- LMS
- MRE (at selected sites where available)
- Laboratory tests can be repeated at the Investigator's discretion. PT, INR, and Platelets must be performed per the window specified by the local biopsy center

Subjects who meet all inclusion criteria and none of the exclusion criteria, including MRI-PDFF, will be invited for Screening Visit 4.

Screening Visit 4:

- Baseline liver biopsy
- Laboratory tests can be repeated at the Investigator's discretion

APPENDIX B – CLOSE OBSERVATION CRITERIA FOR DILI EVENTS

The "close observation" will be performed on subjects meeting the DILI safety monitoring criteria per Section 7.4.1. If "close observation" is not feasible, study drug must be stopped.

1. Comprehensive Medical History and Health Status Review
    a. Provide detailed history of current liver-related symptoms (eg., right upper quadrant pain or tenderness, nausea, vomiting, fatigue)
    b. Provide all current diagnoses, diseases, procedures, and symptoms
    c. Provide comprehensive medical history including prior diagnoses, procedures and symptoms
    d. Provide concomitant drug use, including prescription medications, nonprescription medications, herbal supplements, dietary supplements, alcohol use, recreational drug use, special diets and exposure to environmental chemical agents
    e. Provide comprehensive medication and drug use history, including nonprescription medications, herbal supplements, dietary supplements, alcohol use, recreational drug use, special diets and exposure to environmental chemical agents
2. Laboratory Testing
    a. Repeat ALT, AST, bilirubin (total), and PT/INR within 5 days
    b. Monitor the subject every 5 days until the lab abnormality stabilization
    c. After lab abnormality is stabilized, monitor the subject once a week until the event resolution
3. Rule out the following diagnoses:
    a. Acute viral hepatitis types A, B, C, D and E
    b. Autoimmune or alcoholic hepatitis
    c. Hypoxic/ischemic hepatopathy
    d. Biliary Tract Disease

APPENDIX C – NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI CTCAE)

The NCI CTCAE will be used to assess an AE severity. The NCI CTCAE will be provided as a separate document with the study protocol, but may also be accessed here:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.0/

INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

PROTOCOL CB8025-21730

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Followed by Open-Label Extension and Safety Follow-Up Phases to Evaluate the Activity of Seladelpar in Subjects with Nonalcoholic Steatohepatitis (NASH)

PROTOCOL VERSION NUMBER: Version 3.0

DATE OF PROTOCOL: 20-DEC-2019

SPONSOR:

CymaBay Therapeutics, Inc.
7575 Gateway Blvd, Suite 110
Newark, CA 94560
United States of America

I have read all pages of this clinical study protocol for which CymaBay Therapeutics, Inc. is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and the provisions of Declaration of Helsinki. I will also ensure that sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines and Declaration of Helsinki, to enable them to work in accordance with the provisions of these documents.

Investigator:

Printed Name: _____

Signature: _____

Date (DD/MM/YYYY): _____

Site Address: _____

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