CLINICAL STUDY PROTOCOL

Unique Protocol ID: CB8025-21629

Official Title: An 8-week, dose ranging, open label, randomized, Phase 2 study with a 44-week extension, to evaluate the safety and efficacy of MBX-8025 in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response to or intolerance to ursodeoxycholic acid (UDCA)

NCT number: NCT02955602

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Date Of Protocol: 20-JUL-2017

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SPONSOR: CymaBay Therapeutics, Inc.
7999 Gateway Blvd, Suite 130
Newark, CA 94560
United States of America

SPONSOR CONTACT: [redacted]

EudraCT number: 2016-002996-91

CONFIDENTIALITY STATEMENT

PROTOCOL CB8025-21629

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1. LIST OF ABBREVIATIONS

7α-HC	7α-hydroxycholesterol
7-DHC	7-dehydrocholesterol
AE	Adverse Event
ALT	Alanine Aminotransferase
AMA	Anti-Mitochondrial Antibodies
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
Apo B-100	Apolipoprotein B-100
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATV	Atorvastatin
AUC	Area Under the Curve
β-SITO	β-sitosterol
BUN	Blood Urea Nitrogen
C4	7α-hydroxy-4-cholesten-3-one (bile acid precursor)
CA	Cholic Acid
CAMP	Campesterol
CD-1	Crl:CD1(ICR) Mice
CDCA	Chenodeoxycholic Acid
CK	Creatine Kinase
CK-BB	Creatine Kinase Brain Type
CK-MB	Creatine Kinase Heart Type
CK-MM	Creatine Kinase Muscle Type
Cmax	Maximum Plasma Concentration
COPR	Coprostanol
CRO	Contract Research Organization
CSTN	Cholestanol
CTX	C-terminal Telopeptide
CYP	Cytochrome P450
DCA	Deoxycholic Acid
DESM	Desmosterol
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EOS	End of Study
EOT	End of Treatment
FDA	U.S. Food and Drug Administration
FGF19	Fibroblast Growth Factor 19

GCA	Glycocholic Acid
GCDCA	Glycochenodeoxycholic Acid
GCP	Good Clinical Practice
GDCA	Glycodeoxycholic Acid
GGT	Gamma-glutamyl Transferase
GLCA	Glycolithocholic Acid
GUDCA	Glycoursodeoxycholic Acid
HDL-C	High Density Lipoprotein Cholesterol
HoFH	Homozygous Familial Hypercholesterolemia
hs-CRP	High sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgM	Immunoglobulin M
IXRS	Interactive Voice/Web Response System
LANO	Lanosterol
LATH	Lathosterol
LCA	Lithocholic Acid
LDH	Lactate Dehydrogenase
LDL-C	Low Density Lipoprotein Cholesterol
LOAEL	Lowest Observed Adverse Effect Level
LOCF	Last Observation Carried Forward
M	MBX-8025 Metabolite
MedRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OCA	Obeticholic Acid, Ocaliva
P1NP	Procollagen Type 1 N-terminal Propeptide
PBC	Primary Biliary Cholangitis/Primary Biliary Cirrhosis
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
PPARδ	Peroxisome Proliferator-activated Receptor Delta
PV	Pharmacovigilance
q.d.	Once Daily
QoL	Quality of Life
RBC	Red Blood Cells
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SQLN	Squalene
STIG	Stigmasterol
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Half-life

TC	Total Cholesterol
TCA	Taurocholic Acid
TCDCA	Taurochenodeoxycholic Acid
TDCA	Taurodeoxycholic Acid
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TLCA	Taurolithocholic Acid
Tmax	Time to Cmax
TUDCA	Tauroursodeoxycholic Acid
UDCA	Ursodeoxycholic acid
UK-PBC	United Kingdom Primary Biliary Cirrhosis Score
ULN	Upper Limit of Normal
UNS	Unscheduled
VAS	Visual Analog Score
VLDL-C	Very Low Density Lipoprotein Cholesterol
WBC	White Blood Cells
WHO	World Health Organization
WHOCC	World Health Organization Collaborating Centers

2. LIST OF SPONSOR CONTACTS

Sponsor Contact

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CymaBay Therapeutics, Inc.
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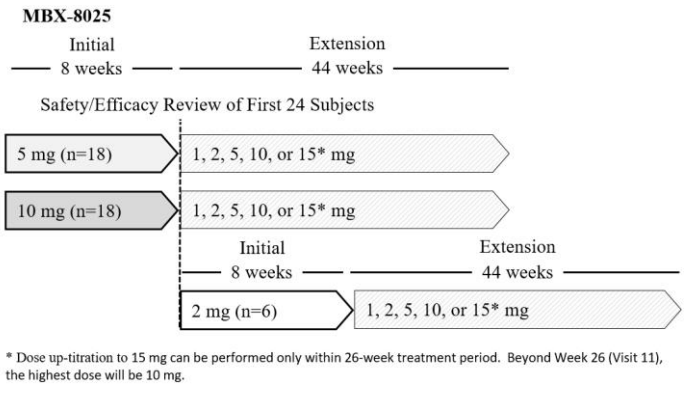
The Sponsor will notify the Investigator(s) in writing with any change to the above information.

3. SYNOPSIS

Study Number	CB8025-21629
Title	An 8-week, dose ranging, open label, randomized, Phase 2 study with a 44-week extension, to evaluate the safety and efficacy of MBX-8025 in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response or intolerance to ursodeoxycholic acid (UDCA)
Phase	2
Objectives	Primary: To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 8 weeks of treatment Secondary: To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 12 and 26 weeks of treatment To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 52 weeks of treatment To evaluate the pharmacokinetics (PK) of MBX-8025 Exploratory: To evaluate the effect of MBX-8025 on bile acids, additional markers of inflammation and renal function MBX-8025 doses of 1 mg and 15 mg may be evaluated if dose adjustment occurs
Study Outcome Measures	Primary: Serum alkaline phosphatase (AP) Adverse events (AE) and Treatment Emergent Adverse Events (TEAEs), ECG, biochemistry, hematology, and urinalysis (NCI CTCAE Version 4.0) Secondary: Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), 5'nucleotidase, Bilirubin (Total, Conjugated, Unconjugated), Bone-specific AP, Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL- C), and Low Density Lipoprotein Cholesterol (LDL-C) Composite endpoint of AP and Total Bilirubin: • AP < 1.67 × upper limit of normal (ULN) • Total Bilirubin within normal limit • ≥ 15% decrease in AP Published PBC response criteria (Barcelona, Paris I and II, Toronto I and II), UK- PBC risk score

	5D-itch scale and pruritus Visual Analog Score (VAS) PBC-40 QoL PK of MBX-8025 and metabolites (at 0, 0.5, 1, 2, 4, 6 and 24 hours for C_{max}, T_{max}, $T_{1/2}$ and AUC; trough level) <u>Exploratory Measures:</u> Anti-Mitochondrial Antibodies (AMA), C-terminal telopeptide (CTX), cystatin C, IgM, fibrinogen, fibroblast growth factor 19 (FGF19), haptoglobin, high-sensitivity C-Reactive Protein (hs-CRP), homocysteine, microRNA-122, and procollagen type 1 N-terminal propeptide (P1NP); Bile acids: Primary Bile Acids and Salts: Cholic acid (CA), chenodeoxycholic acid (CDCA), glycocholic acid (GCA), taurocholic acid (TCA), glycochenodeoxycholic acid (GCDCA), taurochenodeoxycholic acid (TCDCA); Secondary Bile Acids and Salts: Deoxycholic acid (DCA), lithocholic acid (LCA), glycodeoxycholic acid (GDCA), glycolithocholic acid (GLCA), taurodeoxycholic acid (TDCA), taurolithocholic acid (TLCA); Other Bile Acids: ursodeoxycholic acid (UDCA), glycoursodeoxycholic acid (GUDCA), tauroursodeoxycholic acid (TUDCA); Sterols: desmosterol (DESM), lanosterol (LANO), lathosterol (LATH), 7-dehydrocholesterol (7-DHC), cholestanol (CSTN), coprostanol (COPR), squalene (SQLN); β-sitosterol (β-SITO), campesterol (CAMP), stigmasterol (STIG) 7α-hydroxycholesterol (7 α HC); C4 (7α-hydroxy-4-cholesten-3-one); 24-hour urinary excretion of MBX-8025 and metabolites
Design	Open label, randomized, uncontrolled, 8-week dose ranging parallel groups (2 mg, 5 mg, and 10 mg) Open label extension for a total of up to 52-week treatment Selected centers will perform PK (24-hour) testing  * Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg.

Treatment Groups	Initial 8-week treatment: • MBX-8025 2 mg • MBX-8025 5 mg • MBX-8025 10 mg Extension: 1mg, 2 mg, 5 mg, 10 mg, or 15 mg. Subjects will initially enter the extension on their assigned dose. The dose might be up- or down-titrated after safety and efficacy data review of the first 8 weeks of treatment. During the extension, a subject's dose might be re-adjusted for safety or efficacy reasons. Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg.
Number of Subjects	Approximately 116 subjects • 2 mg treatment group: up to 18 subjects • 5 mg treatment group: approximately 49 subjects • 10 mg treatment group: approximately 49 subjects PK (24-hour): up to 30 subjects • 2 mg treatment group: up to six subjects • 5 mg and 10mg treatment groups: up to twelve subjects per group
Number of Investigational Sites	Approximately 40
Randomization	MBX-8025 5 mg and MBX-8025 10 mg (1:1 ratio) Subjects in the MBX-8025 2 mg group will enter the study in chronological order
Duration	Screening: up to two weeks Initial Treatment: eight weeks Extension: 44 weeks Follow-up: four weeks Total Duration: up to 58 weeks
Test Product Formulation/packaging Dose Frequency Administration Route	MBX-8025 1, 5, and 10mg capsules in bottle 2, 5, and 10 mg; 1 and 15 mg through dose adjustment Once a day Oral

Population and Criteria for Eligibility	Inclusion Criteria: 1. Must have given written informed consent (signed and dated) and any authorizations required by local law 2. 18 to 75 years old (inclusive) 3. Male or female with a diagnosis of PBC, by at least two of the following criteria: • History of AP above ULN for at least six months • Positive AMA titers (>1/40 on immunofluorescence or M2 positive by enzyme linked immunosorbent assay (ELISA) or positive PBC-specific antinuclear antibodies • Documented liver biopsy result consistent with PBC 4. On a stable and recommended dose of UDCA for the past twelve months or intolerant to UDCA 5. AP ≥ 1.67 × ULN 6. 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 90 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 Exclusion Criteria: 1. A medical condition, other than PBC, that in the investigator's opinion would preclude full participation in the study or confound its results (e.g., cancer on active treatment) 2. AST or ALT > 3 × ULN 3. Total bilirubin > 2.0 mg/dL 4. Total bilirubin > ULN AND albumin < LLN with the exception to subjects with Gilbert's Syndrome. Subjects with Gilbert's syndrome are excluded if Direct Bilirubin > ULN. 5. Auto-immune hepatitis 6. Primary sclerosing cholangitis 7. Known history of alpha-1-Antitrypsin deficiency 8. Known history of chronic viral hepatitis 9. Creatine kinase above ULN 10. Serum creatinine above ULN 11. For females, pregnancy or breast-feeding 12. Use of colchicine, methotrexate, azathioprine, or systemic steroids in the two months preceding screening 13. Current use of fibrates or simvastatin 14. Current use of obeticholic acid 15. Use of an experimental or unapproved treatment for PBC 16. Use of experimental or unapproved immunosuppressant

	17. Adverse event leading to MBX-8025 discontinuation from CymaBay's phase 2 PBC study (CB8025-21528) 18. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study, as judged by the Investigator
Procedures	Initial 8-Week Treatment Period <u>V1 Screening (Week -2):</u> After signing an informed consent form (ICF), subjects will enter the screening period to confirm eligibility. A medical history will be taken, including PBC history, liver-related symptoms, detailed treatment history and a review of medications. A complete physical examination will be performed as well as a 12-lead Electrocardiogram (ECG). Liver-related symptoms will be evaluated. Vital signs will be collected. Height and weight will be collected for BMI calculation. A blood sample will be taken for hematology, biochemistry, and AMA. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. Subjects who will meet all inclusion criteria and do not meet any exclusion criteria will enter the study. Subjects in the 5 mg and 10 mg treatment groups will be randomized. Subjects in the 2 mg treatment group will be registered. Randomization/registration will occur ideally at least seven days prior to Visit 2 (Day 1). Subject-specific study drug supplies will be shipped to the site. <u>V2 (Day 1) Baseline Visit:</u> AEs since last visit will be evaluated. Medication history including medications since last visit will be reviewed. Vital signs and weight will be collected. A brief physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. The subject will complete the 5D-itch scale, the pruritus VAS and the PBC-40 QoL. Subjects will be dispensed MBX-8025 to be taken orally once a day and immediately begin dosing. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Subjects participating in the PK analysis (selected centers): 24-hour blood samples for PK and bile acids will be collected within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after dosing. The subject will leave the site after the hour 6 blood draw and return to the site on the following day for the hour 24 blood draw.

	For 24-hour urine collection, subjects will be instructed to empty their bladder before MBX-8025 administration. Urine will be collected over the following intervals: 0-6 hours and 6-24 hours. If a subject terminates study participation at any point after Day 1, an Early Termination visit will be completed. <u>V3 (Week 1):</u> TEAEs will be evaluated. Concomitant Medications history since last visit will be reviewed. Vital signs and weight will be collected. A brief physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale and the pruritus VAS. A 12-lead ECG will be performed approximately 60- 90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. <u>V4 (Week 2):</u> TEAEs will be evaluated. Concomitant Medications history since last visit will be reviewed. Vital signs and weight will be collected. A brief physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, bile acids/sterols, and PK trough level. A back-up serum sample will be collected. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale and the pruritus VAS. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. <u>V5 (Week 4):</u> TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A brief physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. Women of child-bearing potential will have a serum pregnancy test performed. A back-up serum sample will be collected. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed.

	V6 (Week 6): TEAEs will be evaluated. Concomitant Medications history since last visit will be reviewed. Vital signs and weight will be collected. A brief physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale and the pruritus VAS. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. V7 (Week 8) Completion of Initial Treatment/Initiation of Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A complete physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, bile acids/sterols, and PK trough level. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. At this visit, the subject will complete eight weeks of initial treatment with MBX-8025 and will be registered into the extension. Subjects will continue into the extension on their originally assigned dose unless otherwise specified. Subject's safety and efficacy review will be performed by the Investigator in collaboration with Medical Monitor. Based on this individual subject review and the overall study safety and efficacy review, the dose might be up- or down-titrated for the extension part of the study. MBX-8025 will be dispensed. EXTENSION Post-Dose Adjustment Visit (for subjects with dose adjustment only) Subjects will return to the clinic in two weeks after dose adjustment occurs. If dose adjustment occurs approximately two weeks prior to the next scheduled visit, post-dose adjustment visit and the next planned visit can be combined. TEAEs will be evaluated. Concomitant medications will be reviewed. Vital signs and weight will be collected. A brief symptom-directed physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile

	acids/sterols. A back-up serum sample will be collected. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. Additional assessments as determined by the Investigator. V8 (Week 12), Extension: TEAE since last visit will be evaluated. Medication history since last visit will be reviewed. Vital signs and weight will be collected. A brief symptom-directed physical examination will be performed and liver-related symptoms will be evaluated. Blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed. Subjects participating in the PK analysis (selected centers): 24-hour blood samples for PK and bile acids will be collected within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after dosing. The subject will leave the site after the hour 6 blood draw and return to the site on the following day for the hour 24 blood draw. For 24-hour urine collection, subjects will be instructed to empty their bladder before MBX-8025 administration. Urine will be collected over the following intervals: 0-6 hours and 6-24 hours. V9 (Week 16), Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A brief symptom directed physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed.

	V10 (Week 20), Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A brief symptom directed physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed. V11 (Week 26), Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A complete physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed. V12 (Week 32), Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A brief symptom directed physical examination will be performed. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed. V13 (Week 39), Extension: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A brief symptom directed

	physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be dispensed. V14 (Week 52), Completion of Extension/ End of Treatment: TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A complete physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. MBX-8025 will be administered. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. A 12-lead ECG will be performed approximately 60-90 minutes after dosing. Compliance to medication and drug accountability will be evaluated. MBX-8025 will be stopped and the subject will enter the four-week follow-up period. V15 (Week 56) Post-Treatment Follow-up/End of Study: Four weeks post-treatment, subjects will return to the clinic for a follow-up visit. This will be the subject's last visit. TEAEs will be evaluated. Concomitant medications will be reviewed. Vital signs and weight will be collected. A complete physical examination will be performed, as well as a 12-lead ECG. Liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. Early Termination Visit TEAEs will be evaluated. Concomitant Medications will be reviewed. Vital signs and weight will be collected. A complete physical examination will be performed as well as a 12-lead ECG. Liver-related symptoms will be evaluated. A blood sample will be taken for hematology, biochemistry, exploratory biochemistry, and bile

	acids/sterols. A back-up serum sample will be collected. Women of child-bearing potential will have a serum pregnancy test performed. Spot urine sample will be collected for urinalysis. The subject will complete the 5D-itch scale, the pruritus VAS, and the PBC-40 QoL. Compliance to medication and drug accountability will be evaluated. Unscheduled Visit (UNS) TEAEs will be evaluated. A brief symptom directed physical examination will be performed and liver-related symptoms will be evaluated. A blood sample will be taken for biochemistry, hematology. Spot urine sample will be collected for urinalysis. Compliance to medication and drug accountability will be evaluated. Additional assessments as determined by the Investigator.
Concomitant Treatment	UDCA will be continued approximately at the same dose during the study. During the extension, dose adjustment or interruption in UDCA is not recommended but acceptable. This must be documented. Subjects will be allowed to receive required medication to treat new or existing medical conditions.
Prohibited Treatment	Obeticholic acid Fibrates (e.g. fenofibrate, bezafibrate) Simvastatin Colchicine, methotrexate, azathioprine or long-term systemic steroids (>2 weeks)
Dose adjustment for extension periods	Unless otherwise specified, subjects will continue on their originally assigned dose. During the extension, the subject's dose might be re-adjusted for safety or efficacy reasons. For individual subjects in the 2 mg, 5 mg and 10 mg treatment group, an ongoing safety and efficacy review will determine the dose to be used in the extension (1 mg, 2 mg, 5 mg, 10 mg, or 15 mg). Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg.
Safety Monitoring, Dose Adjustment, and Drug Interruption	Liver Safety Monitoring I. Elevation of ALT/AST *Normal ALT/AST at baseline* • ALT/AST > 5 × ULN AND Total bilirubin is < 1.5 × ULN or < 2 mg/dL: interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix

	B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline. • ALT/AST > 5 × ULN AND Total bilirubin is ≥ 1.5 × ULN or ≥ 2 mg/dL: stop MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). *Elevated ALT/AST at baseline:* • ALT/AST > 3 × baseline AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice)/ INR < 1.5 × ULN: MBX-8025 can be continued. Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B) and discuss results with Medical Monitor to determine MBX-8025 intake. II. Symptoms of clinical hepatitis (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) AND ALT/AST > 3 × baseline (irrespective of baseline levels): interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline. III. Elevation of total bilirubin (> 2 × ULN or > 1.5 × baseline), regardless of ALT or AST levels, indicators of immunological reaction (e.g., rash, eosinophilia > 5%), or symptom of clinical hepatitis (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline. IV. Hepatic decompensation (eg., progression to cirrhosis, gastro-esophageal variceal bleeding, ascites) during the trial: stop MBX-8025. V. Close monitoring of a subject is not possible: stop MBX-8025 (see Appendix B for more details). <u>Muscle Safety Monitoring</u> I. CK > 5 × ULN with musculoskeletal symptoms: stop MBX- 8025. Repeat the test within 3 days. Follow the subject weekly until resolution or stabilization. II. CK > 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If on repeat test CK is > 2.5 × ULN, stop MBX-8025. Follow the subject weekly until the event resolution or stabilization. III. CK > 2.5 × ULN and ≤ 5 × ULN with musculoskeletal symptoms: interrupt MBX-8025. Repeat the test within 3 days. Follow the

	subject weekly until the event resolution or stabilization. MBX-8025 might be resumed at a decreased dose after event resolution. IV. CK > 2.5 × ULN and ≤ 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If the test is confirmed, MBX-8025 will be continued at a decreased dose. Serum Creatinine Monitoring I. Serum Creatinine > 2.0 × ULN: stop MBX-8025. The subject should be monitored weekly until resolution or stabilization. II. Serum Creatinine > 1.5 × ULN and ≤ 2.0 × ULN: interrupt MBX- 8025. Repeat the test within 3 days. If the test is confirmed and no alternative etiology is identified, stop MBX-8025. If alternative etiology is identified, MBX-8025 may be restarted after serum creatinine returns to baseline values. The subject should be monitored weekly until event resolution or stabilization. Pancreatic Safety Monitoring I. Amylase > 3 × ULN and/or lipase > 3 × ULN without clinical symptoms of acute pancreatitis: repeat the test within 3 days. If the test confirms suspicion, interrupt MBX-8025. Abdominal imaging is to be performed to exclude an alternative cause for the event. MBX-8025 might be restarted only if a firm competing etiology of acute pancreatitis is identified. II. Amylase > 3 × ULN and/or lipase > 3 × ULN with clinical symptoms of acute pancreatitis: interrupt MBX-8025. Abdominal imaging is to be performed to exclude an alternative cause for the event and repeat amylase/lipase within 3 days. MBX-8025 might be restarted only if a firm competing etiology of acute pancreatitis is identified.
Statistics	Population: Safety: Any subject who receives at least one dose of medication Modified intent to treat (mITT): Any subject who receives at least one dose of medication and has at least one post baseline AP evaluation on treatment Per-protocol (PP): Any subject who receives at least one dose of medication, has at least one post baseline AP evaluation, and does not have a protocol violation that is deemed to impact the efficacy analysis Analysis: Safety analysis will be conducted on the safety population. Efficacy analysis will be conducted on the mITT population and the PP population. The mITT population will be used for the primary efficacy analysis.

	Baseline will be defined as the mean between V1 and V2 (Week-2 and Day 1, baseline 1) for the primary analysis and composite endpoint, and as V2 (Day 1, baseline 2) values for other analyses. Descriptive statistics such as means, medians and measures of dispersion will be presented. The last observation carried forward (LOCF) approach will be used for missing laboratory data. The primary efficacy analysis will compare the mean percentage change from baseline to end of 8-week treatment in AP levels. This analysis will be conducted using an analysis of covariance (ANCOVA) model with treatment group as a factor and the baseline AP as a covariate. Other analyses will be secondary. Sample Size and Power: It is assumed that the 5 mg and 10 mg treatment groups will have at least 10% difference in the mean AP percent change with a 15 % standard deviation. Based on this assumption, and on the use of two-sided, two-sample t-test at the alpha =0.05 level of significance, a study sample size of 49 subjects per group will have a 90% power to detect a 10% mean difference between 5 mg and 10 mg treatment groups. There is no formal sample size justification for 2 mg treatment group.

Table 1: Schedule of Assessments

Visit	V1	V2	V3	V4	V5	V6	V7	Post Dose Adjust[12]	V8	V9	V10	V11	V12	V13	V14/ EOT	V15/ EOS	ET	UNS
Week	W -2 to Day 1	Day 1	W1	W2	W4	W6	W8		W12	W16	W20	W26	W32	W39	W52	W56		
Visit/Study Periods	Screening	Baseline	Initial Treatment					Extension								Follow-up		
Informed Consent	X																	
Eligibility Evaluation	X																	
Randomization[1]	X																	
Medical History[2]	X																	
Physical Exam[3]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X		X[4]	X[4]	X[4]	X	X[4]	X[4]	X	X	X	X[4]
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																	
ECG[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry[6,7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory Biochemistry[6,8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Bile Acids/Sterols		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum Pregnancy Test	X	X			X		X		X	X	X	X	X	X	X	X	X	
Back-up Serum Sample		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Trough Level				X			X											
24-hour Blood Samples (selected centers only)[9]		X							X									
24-hour Urine Samples (selected centers only)[10]		X							X									
Urinalysis (spot)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
5D-itch Scale		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Pruritus VAS		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	
PBC-40 QoL		X			X		X		X	X	X	X	X	X	X	X	X	
AE/TEAE		X	X	X	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	X	X	X	
MBX-8025 Intake On-site		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
MBX-8025 Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
MBX-8025 Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
MBX-8025 Dispensing		X			X		X		X	X	X	X	X	X				
Safety/Efficacy Review[11]							X											

1. Randomization will occur only for 5 mg and 10 mg treatment groups. Subjects in the 2 treatment group will be registered for the study. Randomization/registration will occur ideally at least 7 days prior to Visit 2 (Baseline). Study drug kits will be shipped from the drug depot facility to the site on a subject-by-subject basis.
2. Including PBC history
3. Liver-related symptoms will be evaluated as part of physical exam. UNS visit might be scheduled, if needed per PI judgment.
4. Symptoms-directed (brief) physical examination
5. ECG will be performed approximately 60-90 minutes after dosing (Visit 2 through Visit 11)
6. 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
7. If at Visit 1 (Screening) an unexpected abnormal CK level is observed, re-test the subject to confirm eligibility
8. At Visit 1 (Screening) only AMA is to be performed
9. The 24-hour blood sample (selected centers) will be collected at the following time points: within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hours after the dosing
10. The 24-hour urine sample (selected centers) will be collected over the following intervals: 0-6 hours and 6-24 hours.
11. Safety and efficacy data review will be performed after a subject completes the initial 8-week treatment period. The review will be done by the Investigator in collaboration with Medical Monitor. Based on this review, the dose might be up- or down-titrated for the extension period.
12. Applicable only for subjects who had dose adjustment at any time during extension. The visit will occur in two weeks after initiation of the extension dose. If dose adjustment occurs approximately two weeks prior to the next scheduled visit, post-dose adjustment visit and the next planned visit can be combined.

4. INTRODUCTION

4.1 Primary Biliary Cholangitis (PBC)

Primary Biliary Cholangitis (PBC, formerly known as Primary Biliary Cirrhosis) is a serious and potentially life threatening autoimmune disease of the liver characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids. The hallmarks of PBC is cholestasis with accompanying elevation in serum markers including AP, GGT and, depending on the severity of the disease, bilirubin and liver transaminases.

Serologically, PBC is characterized by the presence of anti-mitochondrial antibodies, which are present in nearly all patients and are often detectable years before the appearance of clinical signs (Selmi et al., 2010). Histopathologically, PBC is characterized by portal inflammation and immune-mediated destruction of intrahepatic bile ducts. The loss of bile duct function leads to decreased bile secretion and the retention of toxic substances within the liver, resulting in further hepatic damage, fibrosis, cirrhosis and eventually, liver failure (Kaplan et al., 2005; Lindor et al., 2007; Kumagi et al., 2008). It is a long-term debilitating disease whose progression is associated with an increased risk of hepatocellular carcinoma and liver related mortality (Kaplan et al., 2005; Lindor et al., 2007; Kumagi et al., 2008).

Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age (Kaplan et al., 2005). The diagnosis of PBC in a patient often occurs at an early stage when following up on abnormal liver tests (especially elevated AP) that suggest the presence of cholestasis. Fifty to 60% of patients are asymptomatic at diagnosis (Kaplan, et al 2005). Fatigue and pruritus are the most common presenting symptoms (Kaplan et al., 2005). Fatigue has been noted in up to 78% of patients and can be a significant cause of disability (Kaplan et al., 2005). Pruritus, whose cause is uncertain, occurs in 20 to 70% of patients and can be extremely distressing (Rishe et al., 2008). Other common findings of PBC include jaundice, hyperlipidemia (notably hypercholesterolemia), hypothyroidism, osteopenia and osteoporosis and coexisting autoimmune diseases (Kaplan et al., 2005; Kumagi et al., 2008). Portal hypertension is a late complication of the disease, as is malabsorption, deficiencies of fat-soluble vitamins, and steatorrhea. Rarely, patients present with ascites, hepatic encephalopathy, or hemorrhage from esophageal varices (Kaplan et al., 2005).

The long standing Food and Drug Administration (FDA)-approved treatment for PBC is UDCA, also known as ursodiol (Ursodiol Package Insert, 2005; Tsochatzis et al., 2009). UDCA acts as a choleretic agent and at a dose of 12 to 15 mg per kilogram of body weight per day, decreases serum levels of AP, GGT, bilirubin, ALT, AST, TC, and IgM, all of which are elevated in patients with PBC and can serve as biochemical markers of the disease (Heathcote et al., 1994; Kaplan, et al., 2005). A recent systematic review, however, did not substantiate any significant benefit of Ursodiol on all-cause mortality, liver transplantation, pruritus, or fatigue in patients with PBC (Rudic, et al., 2012). It is also known that up to 50% of PBC patients fail to respond to Ursodiol (Rudic, et al., 2012).

In May of 2016, obeticholic acid (OCA, Ocaliva) was conditionally approved by the FDA as second line therapy for PBC patients with an inadequate response to UDCA (Ocaliva Prescribing Information). At 12 months, 48 and 46% of the patients on the 10 mg and 5 mg titrated to 10 mg groups, respectively (Ocaliva Prescribing Information) met the composite endpoint of biochemical response (AP < 1.67 x ULN plus a decrease of AP of at least 15% plus normal TB levels). A majority of patients treated with OCA continued to be above the biochemical response criterion of AP < 1.67 x ULN. OCA was associated with dose-dependent pruritus as an adverse event and was also associated with dose-dependent reductions in HDL (Ocaliva Prescribing Information).

A number of studies have been conducted with fibrates (peroxisome proliferator-activated receptor (PPAR)-α and dual PPARα/δ agonists) documenting biochemical improvements in patients with PBC, sometimes in combination with UDCA. Fenofibrate (Ghonem et al., 2013) and bezafibrate (Ghonem et al., 2013; Honda et al., 2013, Lens et al., 2014, and Hosonuma et al.,2015) have limited data from randomized clinical trials and are not currently approved for treatment of PBC.

Unapproved therapies, such as colchicine, methotrexate, prednisone and multiple immunosuppressive regimens have been attempted. However, their efficacy is controversial, limited, or unproven, and they are associated with multiple side-effects impacting tolerance and safety (Kumagi, et al., 2008).

In summary, despite the previously mentioned therapeutic interventions and recent approval of OCA, it is evident that many PBC patients do not respond adequately to therapy and continues to have a progression of their disease (Kaplan, et al., 2005; Kumagi, et al., 2008, Momah, et al., 2014) and additional treatments are needed.

4.2 MBX-8025

4.2.1 Overview

MBX-8025 is a potent and selective PPARδ agonist being developed for the treatment of PBC in subjects who are inadequate responders to UDCA or intolerant to UDCA and for the treatment of HoFH.

4.2.2 Mechanism of Action

MBX-8025 is a selective agonist of human PPARδ. PPARδ agonists have been shown to affect the transport, storage and metabolism of lipids (Barish, et al., 2006). The precise linkage between PPARδ agonism to improve cholestasis is not fully elucidated, a situation somewhat similar to the mechanism of action of bile acids and bile acid derivatives in PBC (Lindor et al., 2007). The results from non-clinical studies with MBX-8025 as well as with other PPARδ agonists suggest that PPARδ agonism by MBX-8025 has the potential to decrease cholestasis (increases bile flow) while mitigating its consequences (inflammation, fibrosis and survival). For more detailed information, see the Investigator's Brochure (IB).

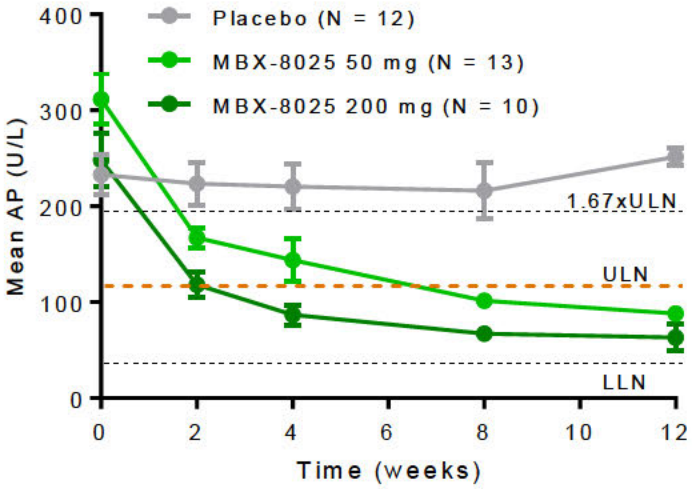
4.2.3 MBX-8025 in PBC

CymaBay conducted a 12-week dose ranging (50 or 200 mg daily), placebo-controlled Phase 2 study (NCT02609048) of MBX-8025 in subjects with PBC who had an inadequate response to UDCA (enrollment target of 75). The study was stopped early by the decision of the sponsor

because of a transaminase elevation signal and because the proof of concept that MBX-8025 was active in PBC subjects was demonstrated. At the time of study was stopped 41 subjects had been randomized. Of these 41, ten had completed the study and 31 were at different time points in the study, mostly in the immediate post randomization period. The study results are presented below.

MBX-8025 showed pronounced decreases in biochemical markers of cholestasis. The changes in AP are shown in Figure 1.

Figure 1: Mean Alkaline Phosphatase Levels over 12 Weeks by Treatment Group (mITT Population)



Both MBX-8025 treatment groups showed significantly greater LSmean percentage reductions in AP levels at the end of treatment than did the placebo group. The MBX-8025 200 mg group had an LSmean reduction of 62.834% (standard error [SE] 4.312) and the MBX-8025 50 mg group had an LSmean reduction of 53.21% (SE 3.961) compared with an LSmean reduction of 1.84% (SE 4.020) in the placebo group (LSmean difference 51.37%, $p < 0.0001$ for the MBX-8025 50 mg group versus placebo; and LSmean difference 60.99%, $p < 0.0001$ for the MBX-8025 200 mg group versus placebo). The reductions from Baseline to the end of treatment were comparable between the MBX-8025 treatment groups (LSmean difference 9.62%, $p = 0.1167$). Substantial between-group differences in response were observed at the first post-treatment visit (Week 2) and persisted through the end of treatment. These results indicate a positive treatment effect on an important marker of cholestasis. All MBX-8025-treated subjects that completed 12-week treatment had normalized (i.e., within the ULN) AP levels.

A composite endpoint was also analyzed defining responders as having an AP level of $<1.67 \times$ ULN that had decreased at least 15% from their Baseline 2 level and a total bilirubin value within the normal range. At the end of treatment, there was a significantly higher percentage of responders in both MBX-8025 treatment groups than in the placebo group. All subjects (10/10) in the MBX-8025 200 mg group were responders and 9 of 13 subjects (69.2%) in the 50 mg group were responders compared to 1 of 12 subjects (8.3%) in the placebo group (Fisher exact test for

proportion difference p <0.0001 and p = 0.0036 for the MBX-8025 200 mg and MBX-8025 50 mg groups, respectively, compared to placebo). Additional biochemical markers of cholestasis were also reduced by MBX-8025. Both MBX-8025 treatment groups showed significantly greater LSmean percentage reductions in GGT and total bilirubin levels at the end of treatment than did the placebo group. The MBX-8025 200 mg group had an LSmean reduction in GGT of 47.17% (SE 9.084) and the MBX-8025 50 mg group had an LSmean reduction of 42.60% (SE 7.796) compared with a mean reduction of 1.83% (SE 7.889) in the placebo group (LSmean difference 40.78%, p = 0.0007 and LSmean difference 40.78%, p = 0.0008 for the MBX-8025 200 mg and MBX-8025 50 mg groups, respectively, compared to the placebo group). At the end of treatment, the MBX-8025 200 mg group had an LSmean increase in total bilirubin of 1.40% (SE 6.384), the MBX-8025 50 mg group had an LSmean reduction of 16.79% (SE 5.586), and the placebo group had an LSmean reduction of 4.79% (SE 5.793). The LSmean percentage change in total bilirubin in the MBX-8025 200 mg group was comparable to that in the placebo group. Although the LSmean percentage change in the MBX-8025 50 mg group was numerically greater than the placebo group, the between-group difference in total bilirubin did not achieve statistical significance (LSmean difference 12.00%, p = 0.1459).

MBX-8025 also produced potentially beneficial metabolic and anti-inflammatory effects. Hs-CRP levels were reduced in response to MBX-8025 treatment. Median percentage changes at the end of treatment were an increase of 0.39% in the placebo group and decreases of 47.83%, and 4.26% in the MBX-08025 50 mg and MBX-8025 200 mg groups, respectively. Both MBX-8025 treatment groups showed greater LSmean percentage reductions in LDL-C levels at the end of treatment than did the placebo group. The MBX-8025 200 mg group had an LSmean reduction of 17.63% (SE 4.372) and the MBX-8025 50 mg group had an LSmean reduction of 12.83% (SE 3.763) compared with a mean reduction of 2.78% (SE 3.958) in the placebo group.

The two bile acid precursor oxysterols (7α- hydroxycholesterol and C4), potential bile acid synthesis biomarkers, were decreased by MBX-8025 treatment. Median percentage changes from Baseline 2 in C4 at the last observation on treatment were an increase of 29.46% and decreases of 54.85% and 77.02% in the placebo, MBX-8025 50 mg and MBX-8025 200 mg groups, respectively. Changes in the MBX-8025 50 mg group and the MBX-8025 200 mg group were substantially different from placebo. The C4 decreases in the MBX-8025 groups were associated with decreases in 7-α-hydroxycholesterol (median decreases of 54.26% and 43.04% in the MBX-8025 50 mg and 200 mg groups, respectively, at the last observation on treatment compared with a median increase of 11.89% in the placebo group).

Three subjects developed a CTCAE grade 3 ALT and AST elevation (ALT and AST > 5.0-20.0 x ULN) and discontinued treatment. Of these subjects, two were receiving MBX-8025 200 mg (one case was considered drug related and the other possibly drug related) and one was receiving MBX-8025 50 mg (considered possibly drug related). For these three subjects, the clinical picture was similar. The transaminase elevations were documented at the first active treatment planned protocol visit, after two weeks of treatment. The transaminase elevations were asymptomatic, not associated with an abnormal increase in bilirubin, and fully reversible upon treatment discontinuation. Of note, the transaminase elevations were associated with a decrease in biochemical markers of cholestasis (AP and GGT).

Although, the number of subjects enrolled in this study was small, there was no indication MBX-8025 caused or worsen pruritus.

MBX-8025 has also exhibited reductions in biochemical markers of cholestasis in prior clinical studies. MBX-8025 has been studied in a Phase 2 study in overweight subjects with mixed dyslipidemia. The study was a randomized, double-blind, placebo-controlled, parallel group proof-of-concept study in 181 men and women (Bays, et al., 2011). Subjects were administered once daily placebo, atorvastatin (ATV) 20 mg, MBX-8025 at 50 or 100 mg alone or combined with ATV 20 mg for eight weeks. MBX-8025 has also been studied in a Phase 2 study in patients with HoFH. This study had an open-label, single-arm, dose-escalating (50, 100, and 200 mg/day) design with 3 consecutive 4-week treatment periods. In both studies, the AP decrease was rapid (onset within 4 days), consistent, sustained, and reversible upon MBX-8025 discontinuation (within a week or two). AP did not decrease below the lower limit of normal and was associated with a concomitant decrease in GGT of similar amplitude. A transaminase signal was not previously observed in other populations that received multiple MBX-8025 at doses of up to 100 mg in subjects with mixed dyslipidemia and up to 200 mg in healthy volunteers and subjects with HoFH.

In conclusion, MBX-8025 has demonstrated potent and rapid decreases in biochemical markers of cholestasis (AP, GGT, and total bilirubin), decreases in a marker of inflammation (hs-CRP) and decrease in LDL-C in PBC subjects who had an inadequate response to UDCA. The transaminase elevations signal appears to be dose-related with more elevation at 200 mg than at 50 mg. Because of the frequency, the timing of the transaminase elevations (within 2-4 weeks) and the absence of sign of hypersensitivity (clinical or biological) a toxic mechanism is favored rather than an idiosyncratic one. Recent data from a mass balance study in rodents indicate that MBX-8025 and its metabolites are largely cleared by the bile and consequently MBX-8025 and its metabolites might be accumulating within the liver tissues in subjects affected with a cholestatic syndrome (such as PBC subjects). No clear transaminase elevation signal was seen in subject not affected with a cholestatic syndrome (healthy volunteers, mixed dyslipidemia and HoFH) despite using the same doses of MBX-8025. It is hypothesized that MBX-8025 liver exposure is higher in subjects with PBC who have impaired bile excretion. This would have potentially resulted in toxic accumulation of MBX-8025 in hepatocytes or too rapid intra-cellular changes in bile acids.

4.3 NONCLINICAL INVESTIGATIONS WITH MBX-8025

Please see the IB for details on the nonclinical studies conducted with MBX-8025.

4.4 HUMAN EXPERIENCE

To date, MBX-8025 has been investigated in five Phase 1 clinical studies in healthy volunteers and in three Phase 2 studies. Phase 2 studies were conducted on dyslipidemic, overweight subjects treated with and without ATV; on subjects with HoFH, and on subjects with PBC and an inadequate response to UDCA.

4.4.1 Phase 1 studies

Five Phase 1 clinical studies have been conducted in healthy male subjects. The aims of these studies were to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of MBX-8025. A total of 117 healthy male subjects have been dosed with either MBX-8025, MBX-8025 in

combination with other agents, or placebo in the five completed clinical studies. One hundred and seven subjects received at least one dose of MBX-8025 (alone or in combination), and 27 subjects received at least one dose of placebo. MBX-8025 was administered as a solution in sterile water, or as a hard gelatin capsule. In the five Phase 1 clinical studies MBX-8025 was generally well tolerated. There were no deaths or serious adverse events (SAEs) recorded. All AEs were mild or moderate in severity. The type and incidence of AEs were generally similar across the various MBX-8025 and placebo dose groups. Please see the Investigator's Brochure (IB) for more complete details on the Phase 1 studies conducted with MBX-8025.

4.4.2 Phase 2 studies

Study M8025-20711 was a multicenter randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, PK and efficacy of MBX-8025 in moderately obese hyperlipidemic subjects with or without concomitant ATV (Bays, et al., 2011; Choi, et al., 2012). This study evaluated 181 overweight men and women with mixed dyslipidemia. Subjects were administered once daily placebo, ATV 20 mg, or MBX-8025 at 50 or 100 mg alone or combined with ATV. The treatment duration was eight weeks. There were no significant gender differences in the PK parameters of MBX-8025 or its metabolites, M1, M2 and M3 PK (T_{max}, C_{max} and $AUC_{(0\text{-}8h)}$). Compared to placebo, MBX-8025 alone and in combination with ATV significantly reduced Apo B-100 20-38%, LDL-C 18-43%, TG 26-30%, non-HDL-C 18-41%, FFA 16-28%, and hs-CRP 43-72%. MBX-8025 raised HDL-C 1-12% and also reduced the number of subjects with a metabolic syndrome and a preponderance of small LDL particles. MBX-8025 was safe and generally well-tolerated. Three subjects experienced a total of 6 SAEs, none of which was deemed "related" to the study drug. The most frequently related AEs were increase in CK and headache. As previously noted, MBX-8025 also reduced transaminases, AP and GGT levels (Bays et al., 2011).

Study CB8025-21427 was the pilot study of MBX-8025 in the treatment of HoFH. The study was a 12-week, open label, multicenter, non-controlled, monthly dose escalation study (MBX-8025: 50, 100, and 200 mg; p.o. daily) in adults with genetically confirmed HoFH. A total of 13 subjects were enrolled, received treatment, and completed this study; 8 subjects were on concomitant LDL-C apheresis group. All of the subjects were on stable lipid-lowering therapy and were receiving maximum dose of statins and ezetimibe. During the study, five subjects (42%), had a ≥ 20% LDL-C decrease from baseline (including one LDL-R null mutation) of which three (25%) had a ≥ 30% LDL-C decrease. Five subjects had a decrease of <15%. Overall, the mean decrease in LDL-C was 10% with no clear dose response. Mean PCSK9 was elevated at baseline (543.9 +/- 132.7 ng/mL) and increased during treatment (mean +43%). A total of 13 subjects were evaluated for safety; of these, 13 (100%) subjects were exposed to MBX-8025 50 mg; 13 were exposed to MBX-8025 100 mg; and 10 (77%) subjects were exposed to MBX-8025 200 mg. The overall incidences of AEs were similar between study drug doses. There were 3 SAEs, none drug related, and three discontinuations for AEs possibly related to MBX-8025. The investigators considered the TEAEs leading to study drug discontinuation (angina pectoris, arthralgia, and musculoskeletal pain) to be mild or moderate in severity and the relationship to study drug possible. The most commonly reported TEAE was nasopharyngitis. In conclusion, MBX-8025 showed meaningful lipid lowering effect in a number of subjects and was generally well tolerated.

Study CB8025-21628 was a 12-week dose ranging (50 or 200 mg daily), placebo-controlled Phase 2 study (NCT02609048) of MBX-8025 in subjects with PBC who had an inadequate response to UDCA. The study was conducted in North America, UK, Germany and Poland. The enrollment target was approximately 75 subjects (25 per treatment group). The study was stopped early by the decision of the sponsor because of a transaminase elevation signal and because the proof of concept that MBX-8025 was active in PBC subjects was demonstrated. At the time of study was stopped 41 subjects had been randomized. Of these 41, ten had completed the study and 31 were at different time points in the study, mostly in the immediate post randomization period. Treatments with MBX-8025 at doses of 50 mg daily and 200 mg were associated with profound, rapid, and sustained decreases in biochemical markers of cholestasis (AP, GGT, 5'nucleotidase and total bilirubin) and marker of inflammation (hs-CRP). Three subjects developed a CTCAE grade 3 ALT and AST elevation (ALT and AST > 3.0-20.0 x ULN) and discontinued treatment. Two of these subjects were receiving MBX-8025 200 mg and one was receiving MBX-8025 50 mg. For these three subjects, the clinical picture was similar. The transaminase elevations were documented at the first active treatment planned protocol visit, after two weeks of treatment. The transaminase elevations were asymptomatic, not associated with an abnormal increase in bilirubin, and fully reversible upon treatment discontinuation. One subject discontinued treatment because of an adverse event of myopathy. The subject was taking MBX-8025 200 mg. The adverse event was reversible upon treatment discontinuation and was considered possibly related to treatment. One additional subject discontinued the study before starting blinded treatment because of upper gastro-intestinal bleeding associated with previously undiagnosed esophageal varices. One subject, who did develop grade 3 transaminase elevations and was on MBX-8025 200 mg, had a concomitant increase in serum creatinine from 0.93 mg/dL at baseline (normal range 0.49-1.12 mg/dL) to 1.49 mg/dL. The serum creatinine returned to normal upon treatment discontinuation. The investigator considered this elevation as an adverse event of acute kidney injury that was possibly related to treatment. There was no serious adverse event during the treatment phase of the study or the two-week follow up period. For more details about this study, please refer to the IB.

4.5 RISK/BENEFIT ASSESSMENT

The study being proposed is an 8-week, open-label, randomized, uncontrolled, Phase 2 study with a 44-week extension to evaluate the effects of MBX-8025 in PBC subjects who have inadequate response or intolerance to UDCA.

4.5.1 Potential Benefits

Patients selected for this study do not respond adequately to UDCA. A potential benefit is to demonstrate that the addition of MBX-8025 to UDCA will improve cholestasis-related biochemical markers as well as the PBC-associated inflammation.

In previous PBC study, subjects receiving placebo showed no relevant change, while all subjects receiving MBX-8025 exhibited a pronounced decrease in AP, already evident over the first 2 weeks. Subjects who received MBX-8025 beyond 2 weeks showed a consistent and continually progressive decrease. Additional biochemical markers of cholestasis such as GGT and 5'

nucleotidase were also reduced by MBX-8025. MBX-8025 also produced potentially beneficial metabolic and anti-inflammatory effects.

4.5.2 Potential Risks

4.5.2.1 Non-clinical safety findings
Please see the IB for more complete details on the nonclinical studies conducted with MBX-8025.

4.5.2.2 Human safety
Currently, MBX-8025 has been used for a maximum of 21 days in healthy volunteers at a maximum dose of 200 mg per day; in overweight subjects with mixed dyslipidemia, with and without atorvastatin, for a maximum of eight weeks and with a maximum dose of 100 mg per day; in subjects with HoFH, on concomitant ezetimibe and maximum statin therapy (+/- LDL-C apheresis), with dose escalation from 50 mg to a maximum of 200 mg per day; and in subjects with PBC on concomitant UDCA, for a maximum of 12 weeks and with a maximum dose of 200 mg per day.

MBX-8025 has been associated with increases in transaminases (AST and ALT), particularly in subjects with PBC. The increases were seen at 50 mg per day and 200 mg per day and appears to be dose dependent and population dependent. The increases were fully reversible upon treatment discontinuation. In rodents, MBX-8025 and its metabolites are almost exclusively cleared by the bile and consequently MBX-8025 and its metabolites might be accumulating within the liver tissues in subjects affected with a cholestatic syndrome (such as PBC subjects). No clear transaminase elevation signal was seen in subject not affected with a cholestatic syndrome (healthy volunteers, mixed dyslipidemia and HoFH) despite using the same doses of MBX-8025.

MBX-8025 has been associated with a pre-clinical muscle toxicity signal. One PBC subject taking 200 mg per day discontinued drug for acute muscle pain associated with increased muscle enzymes. The adverse event was reversible upon treatment discontinuation and was considered possibly related to treatment.

MBX-8025 has been associated with increase in serum creatinine. These increases are generally mild (in the 10% range) and serum creatinine shifts are within the normal range. Similar increases have been observed with drugs of the PPAR-α class or the mixed PPAR-α/δ class. In the short term, these increases in serum creatinine have not been associated with relevant decreases in measured glomerular filtration rate. In the long run, data from controlled clinical trials do not support that PPAR-α or mixed PPAR-α/δ are associated with a degradation of renal function. It is hypothesized that the increase in serum creatinine is of muscle origin (with an increase in creatine synthesis which is later metabolized into creatinine). However, caution must be exercised. One subject with HoFH and a chronic renal insufficiency, treated with MBX-8025 100 mg and one subject with PBC treated with MBX-8025 200 mg had serum creatinine elevation above the normal range that were reversible upon treatment discontinuation and considered possibly related to MBX-8025.

4.5.3 Conclusions

In conclusion, MBX-8025 demonstrated the potent and rapid decrease in biochemical markers of cholestasis (AP, GGT, and total bilirubin), decrease a marker of inflammation (hs-CRP) and decrease LDL-C in PBC subjects who had an inadequate response to UDCA. However, the clinical experience with MBX-8025 is still limited. Precautions should be exercised particularly towards transaminase elevations, potential muscle-related toxicities and potential increases in serum creatinine.

4.6 RATIONALE FOR DOSE SELECTION

Available clinical data suggest that MBX-8025 at daily dose of up to 100 mg for up to eight weeks in obese males and females with mixed dyslipidemia (Bays, et al., 2011) and at daily dose of 200 mg for up to three weeks in healthy volunteers are well tolerated and generally safe. In subjects with HoFH, with dose escalation from 50 mg daily to up to 200 mg daily, no consistent safety signal was elicited. However, few HoFH subjects were studied (N=13) and most of them were affected with multiple co-morbidities and were on multiple concomitant therapies (e.g. ezetimibe, maximum statin therapy, LDL-C apheresis, etc.) which makes the interpretation of safety data difficult.

In subjects with PBC, who were inadequately responding to UDCA, treatments with MBX-8025 at doses of 50 mg daily and 200 mg were associated with profound, rapid, and sustained decreases in biochemical markers of cholestasis (AP, GGT, 5'nucleotidase and total bilirubin) and marker of inflammation (hs-CRP). However, at these doses, MBX-8025 was associated with an increase in transaminases levels. As, in rodents, MBX-8025 is largely excreted through the bile, it is hypothesized that MBX-8025 exposure to liver tissues is higher in subjects with cholestasis than in subjects with normal biliary function. Indeed, no transaminase elevations signal has been seen in normal healthy volunteers, subjects with dyslipidemia or HoFH at doses up to 200 mg daily. Because of the timing of transaminase elevations (early on in exposure) and the absence of any clinical or biological signs of allergic reactions, it is hypothesized that the mechanism is a direct toxicity rather than an idiosyncratic reaction. Also, it appears that in PBC subjects more transaminases elevations were seen at 200 mg daily compared to 50 mg daily, supporting a dose response toxicity-based mechanism. Hence, lower doses of MBX-8025 should be tested in subjects with PBC who are inadequately responding, or intolerant to UDCA, to test whether the activity of MBX-8025 is retained without eliciting a transaminases elevation signal.

Doses of 5 mg and 10 mg have been initially selected to be tested in subjects with PBC because they are 10- and 5-fold lower than the dose previously used doses while having the potential to retain pharmacodynamics activities. Dose of 2 mg daily will also be tested.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVES

The primary objective of this study is to evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 8 weeks of treatment.

5.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 12 and 26 weeks of treatment

- To evaluate the safety and efficacy of MBX-8025 2 mg, 5 mg, and 10 mg over 52 weeks of treatment

- To evaluate the pharmacokinetics of MBX-8025

5.3 EXPLORATORY OBJECTIVES

The exploratory objectives of this study are to evaluate the effect of MBX-8025 on bile acids, additional markers of inflammation and renal function

MBX-8025 doses of 1 mg and 15 mg may be evaluated if dose adjustment occurs.

6. STUDY POPULATION

Approximately 116 subjects with PBC who have inadequate response or intolerance to UDCA will be recruited.

6.1 SELECTION CRITERIA

6.1.1 Inclusion Criteria

For inclusion into the study, subjects must fulfill all of the following criteria:

1. Must have given written informed consent (signed and dated) and any authorizations required by local law
2. 18 to 75 years old (inclusive)
3. Male or female with a diagnosis of PBC by at least two of the following criteria:
   - History of AP above ULN for at least six months
   - Positive AMA (Anti-Mitochondrial Antibodies) titers (>1/40 on immunofluorescence or M2 positive by ELISA) or positive PBC-specific antinuclear antibodies
   - Documented liver biopsy result consistent with PBC
4. On a stable and recommended dose of UDCA for the past twelve months or intolerant to UDCA
5. AP $\geq$ 1.67 × ULN
6. 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 90 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

6.1.2 Exclusion Criteria

1. A medical condition, other than PBC, that in the investigator's opinion would preclude full participation in the study or confound its results (e.g., cancer on active treatment)
2. AST or ALT > 3 × ULN
3. Total bilirubin > 2.0 mg/dL
4. Total bilirubin > ULN AND albumin < LLN with the exception to subjects with Gilbert's Syndrome. Subjects with Gilbert's syndrome are excluded if Direct Bilirubin > ULN.
5. Auto-immune hepatitis
6. Primary sclerosing cholangitis
7. Known history of alpha-1-Antitrypsin deficiency
8. Known history of chronic viral hepatitis
9. Creatine kinase above ULN
10. Serum creatinine above ULN
11. For females, pregnancy or breast-feeding
12. Use of colchicine, methotrexate, azathioprine or systemic steroids in the two months preceding screening
13. Current use of fibrates or simvastatin
14. Current use of obeticholic acid

15. Use of an experimental or unapproved treatment for PBC
16. Use of experimental or unapproved immunosuppressant
17. Adverse event leading to MBX-8025 discontinuation from CymaBay's phase 2 PBC study (CB8025-21528)
18. Any other condition(s) that would compromise the safety of the subject or compromise the quality of the clinical study as judged by the Investigator

7. STUDY DESIGN

This will be an international, multicenter study in males and females with PBC who have inadequate response or intolerance to UDCA.

The study will utilize an open-label, randomized, uncontrolled, 8-week dose ranging parallel groups (2 mg, 5 mg, and 10 mg) design with an open-label extension for a total of up to 52 weeks of treatment.

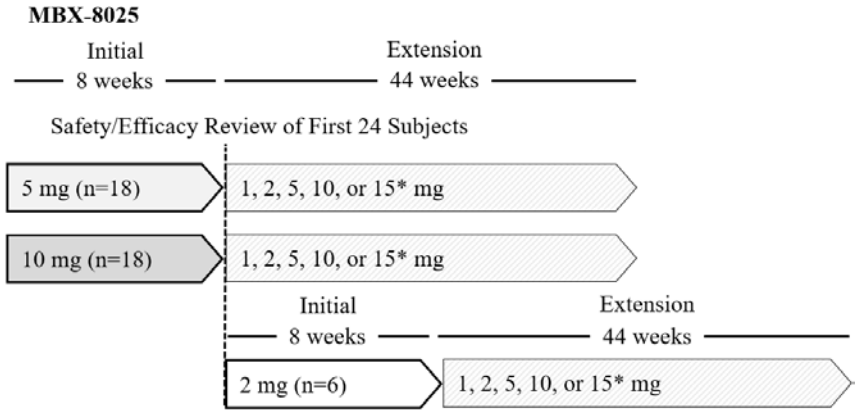
After signing an ICF, subjects will enter a screening period (up to two weeks). Subjects in 5 mg and 10 mg treatment groups will enter the 8-week initial treatment period study in parallel. Subjects in the 2 mg groups will enter the 8-week initial treatment period in chronological order.

Randomization will occur only for 5 mg and 10 mg treatment groups; subjects in the 2 mg treatment group will be registered for the study. Randomization/registration will occur ideally at least 7 days prior to first dose of MBX-8025 (study drug). A subject will be considered formally entered in the trial at randomization/registration. Study drug kits will be shipped from the drug deposit facility to the site on a subject-by-subject basis. Subject-specific study drug supplies (MBX-8025) will be taken orally once a day, for a period of eight weeks. To confirm study drug compliance, MBX-8025 trough level will be measured after two and eight weeks of treatment.

After completion of the 8-week initial treatment period, subjects will enter the open-label extension for a total of up to 52 weeks of treatment. Subjects will initially enter the extension on their assigned dose. Based on this individual subject review and the overall study safety and efficacy review, the dose might be up- or down-titrated for the extension part of the study. During the extension, the subject's dose might be re-adjusted for safety or efficacy reasons. For individual subjects in the 2 mg, 5 mg and 10 mg treatment groups, an ongoing safety and efficacy review will determine the dose to be used (1 mg, 2 mg, 5 mg, 10 mg, or 15 mg). Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg. Subject's safety and efficacy review will be performed by the Investigator in collaboration with Medical Monitor. During the extension period, subject-specific study drug supplies (MBX-8025) will be taken orally once a day, for a total maximum duration of up to 52 weeks.

After the end of treatment, subjects will enter a four-week follow-up period.

At selected centers, subjects will participate in 24-hour PK testing. 24-hour PK testing will be performed at the time of initiation of study treatment and after twelve of treatment. Subjects participating in 24-hour PK testing will have PK blood and urine samples, and bile acids samples collected multiple times within 24 hours.



* Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg.

7.1 TREATMENT AND ALLOCATION OF SUBJECTS

Each new subject will receive a unique subject number assigned by IXRS (interactive voice/web response) system.

Approximately 116 subjects will participate in the study:

- 2 mg treatment group: up to 18 subjects
- 5 mg treatment group: approximately 49 subjects
- 10 mg treatment group: approximately 49 subjects

PK (24-hour): up to 30 subjects

- 2 mg treatment group: up to six subjects
- 5 mg, and 10mg treatment groups: up to twelve subjects per group

7.2 STUDY DURATION

The screening period will be a maximum of two weeks (14 days) in duration (Week -2 to Day 1). The 8-week initial treatment period will be eight weeks (56 days) in duration (Day 1 to Week 8). The extension period will be 44 weeks (308 days). The follow-up period will be four weeks (28 days) in duration (Week 52 to Week 56). The follow-up period concludes the study. In total, the duration of study per subject will be 406 days (58 weeks).

7.3 STUDY OUTCOME MEASUREMENTS

7.3.1 Primary measures

- Serum AP levels
- Adverse events (AE) and Treatment Emergent Adverse Events (TEAEs), ECG, biochemistry, hematology, and urinalysis (NCI CTCAE Version 4.0)

7.3.2 Secondary measures

- Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), 5'nucleotidase, Bilirubin (Total, Conjugated, Unconjugated), Bone- specific AP, Triglycerides (TG), Total Cholesterol (TC), High Density Lipoprotein Cholesterol (HDL-C), and Low Density Lipoprotein Cholesterol (LDL-C)
- Composite endpoint of AP and Total Bilirubin:
  - ✓ AP < 1.67 × upper limit of normal (ULN) and
  - ✓ Total Bilirubin within normal limit and
  - ✓ ≥ 15% decrease in AP
- Published PBC response criteria (Barcelona, Paris I and II, Toronto I and II), UK-PBC risk score
- 5D-itch scale and pruritus Visual Analog Score (VAS)
- PBC-40 QoL
- PK of MBX-8025 and metabolites (at 0, 0.5, 1, 2, 4, 6 and 24 hours for C_{max}, T_{max}, $T_{1/2}$ and AUC; trough level)

7.3.3 Exploratory measures

- Anti-Mitochondrial Antibodies (AMA), C-terminal telopeptide (CTX), cystatin C, IgM, fibrinogen, fibroblast growth factor 19 (FGF19), haptoglobin, high-sensitivity C-Reactive Protein (hs-CRP), homocysteine, microRNA-122, and N-terminal propeptide of type 1 procollagen (P1NP);
- Bile acids: Primary Bile Acids and Salts: Cholic acid (CA), chenodeoxycholic acid (CDCA), glycocholic acid (GCA), taurocholic acid (TCA), glycochenodeoxycholic acid (GCDCA), taurochenodeoxycholic acid (TCDCA); Secondary Bile Acids and Salts: Deoxycholic acid (DCA), lithocholic acid (LCA), glycodeoxycholic acid (GDCA), glycolithocholic acid (GLCA), taurodeoxycholic acid (TDCA), taurolithocholic acid (TLCA); Other Bile Acids: ursodeoxycholic acid (UDCA), glycoursodeoxycholic acid (GUDCA), tauroursodeoxycholic acid (TUDCA);
- Sterols: desmosterol (DESM), lanosterol (LANO), lathosterol (LATH), 7- dehydrocholesterol (7-DHC), cholestanol (CSTN), coprostanol (COPR), squalene (SQLN); β-sitosterol (β-SITO), campesterol (CAMP), stigmasterol (STIG) 7α-hydroxycholesterol (7 α HC);
- C4 (7α-hydroxy-4-cholesten-3-one);
- 24-hour urinary excretion of MBX-8025 and metabolites

8. STUDY MEDICATIONS

8.1 CLINICAL SUPPLIES

8.1.1 Investigational product, dosage and mode of administration

MBX-8025 will be supplied as 1 mg, 5 mg, and 10 mg capsules. The study drug will be administered orally, once daily in doses of 2 mg, 5 mg, and 10 mg as described in the protocol. If dose adjustment occurs, the study drug might be administered at doses of 1 mg and 15 mg. 15 mg dose can be administered only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest administered dose will be 10 mg.

8.1.2 Packaging, Labeling and Shipping

The Sponsor will provide the Investigator with packaged study drug labeled in accordance with specific country regulatory requirements. Following randomization, subject-specific study drug supplies will be shipped to the site. Study drug kits will be shipped from the drug depot facility to the site on a subject-by-subject basis.

8.1.2.1 Dose Adjustment

For the subjects who meet the criteria for dose adjustment (per Section 10.5), a new study drug kit will be shipped to the site.

8.1.3 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.

8.1.4 Replacement Study Medication

Additional replacement study medication will be available as required. All replacement shipments must be accounted for in the same manner as the initial medication supply.

8.1.5 Stability of Study Medication

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

8.2 RANDOMIZATION

Subjects on 5 mg and 10 mg treatment group will be centrally randomized in a 1:1 ratio to receive MBX-8025 5 mg or MBX-8025 10 mg. Subjects in 2 mg treatment group will be registered to the study.

8.2.1. Randomization/Registration Procedure

Once all laboratory evaluations are available and the subject has been confirmed to meet all of the inclusion and none of the exclusion criteria, the clinical site will centrally randomize/register an eligible subject via IXRS. The subject will then return to the clinic as soon as possible (ideally within seven days) to receive study drug supplies and begin dosing (the first day of dosing will be Day 1).

8.3 METHOD OF ADMINISTRATION AND COMPLIANCE

MBX-8025 will be dispensed on study Visit 2 (Day 1), Visit 5 (Week 4), Visit 7 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 26), Visit 12 (Week 32) and Visit 13 (Week 39) to be taken orally once a day, according to the study schedule.

Compliance to medication and drug accountability will be evaluated on all study visits during the treatment period, between Visit 3 (Week 1) and Visit 14 (Week 52).

Compliance and accountability will also be performed at the Early Termination Visit.

8.4 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.

8.4.1 Concomitant Medications

A concomitant medication is any drug of substance other than MBX-8025, including over-the-counter medications, herbal medications and vitamin supplements, administered during subjects' participation in this trial.

UDCA will be continued at approximately the same dose during the study. During the extension, dose adjustment or interruption in UDCA is not recommended but acceptable. This must be documented.

All subjects will be instructed to remain on their current diet and lifestyle, including drinking habits, specifically alcoholic beverages, throughout the entire study.

8.4.1.1 Allowed Concomitant Medication:

Subjects will be allowed to receive required medication to treat new or existing medical conditions.

8.4.1.2 Prohibited Concomitant Medication

Use of obeticholic acid, fibrates (e.g. fenofibrate, bezafibrate), simvastatin, colchicine, methotrexate, azathioprine or long term systemic steroids (>2 weeks) will be prohibited during the study.

8.4.2 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.

9. STUDY PROCEDURES

9.1 STUDY SCHEDULE

The schedule of study procedures is presented in Table 1.

The study for an individual subject consists of the following periods:

- Screening (up to two-weeks): Visit 1 to Visit 2 (Week -2 to Day 1)
- Initial treatment (eight-weeks): Visit 2 to Visit 7 (Day 1 to Week 8)
- Extension (forty-four-weeks): Visit 7 to Visit 14 (Week 8 to Week 52)
- Follow-up (four-weeks): Visit 14 to Visit 15 (Week 52 to Week 56)

Visits, which occur within +/- three days of the calculated date during the initial treatment period and within +/- seven days of the calculated date during the extension period will not be considered protocol violations.

Additional visits may be scheduled to evaluate an abnormal laboratory value or reported AE.

9.1.1 Screening: Visit 1 to Visit 2 (Week -2 to Day 1)

All subjects will review and sign the ICF prior to any screening procedures.

Screening evaluations (Visit 1 or Week -2) will be performed within two weeks prior to entering the initial treatment period at baseline randomization (Visit 2 or Day 1).

The evaluations will consist of:

- Assessment of all inclusion and exclusion criteria
- Review of medical history including PBC history and liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice)
- Documentation of prior and concomitant medications (including supplements and vitamins)
- Vital signs (as described in Section 9.2.2) This will include temperature, heart rate, respiration rate and blood pressure
- Height and weight measurement
- Complete physical examination (as described in Section 9.2.1)
- This 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 and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice)
- 12-lead ECG after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, and AMA (exploratory biochemistry) as outlined in Section 9.2.4 and Appendix A
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis.

If unexpected abnormal CK level is observed at Screening (Visit 1), the subject can be re-tested to confirm his/her eligibility.

Subjects who meet all inclusion criteria and do not meet any exclusion criteria will enter the study. Subjects in the 5 mg and 10 mg treatment groups will be randomized and subjects in the 2 mg treatment group will be registered into the study using IXRS system. Randomization/registration will occur ideally at least seven days prior to Visit 2 (Day 1). Subject-specific study drug supplies will be shipped to the site.

Untoward event occurred any time after ICF is signed will be recorded as AE. Any laboratory abnormality deemed clinically significant by the Investigator will be considered an AE.

Subjects will be reminded of the following restrictions:

- To comply with diet and lifestyle, including drinking habits
- To continue UDCA at approximately the same dose
- Not to use prohibited concomitant medications
- Females of reproductive potential will be reminded to use at least one barrier contraceptive and a second effective birth control method during the study and for at least 90 days after the last dose
- Male subjects who are sexually active with female partners of reproductive potential will be reminded to use barrier contraception and their female partners to use a second effective birth control method during the study and for at least 90 days after the last dose

9.1.2 Baseline: Visit 2 (Day 1)

Subjects who have been deemed eligible during the screening period will return for Visit 2 (Day 1) and the following evaluations will be performed:

- Documentation of AEs that occurred since the signing of the ICF
- Documentation of medication (including supplements and vitamins) since the last visit
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols as outlined in Appendix A
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis
- 5D-itch scale, Pruritus VAS, and PBC-40 QoL
- MBX-8025 administration
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing

- The subjects will be dispensed four weeks' worth of MBX-8025 to be taken once daily.

Subjects participating in the PK analysis (selected centers) only:

- 24-hour blood samples for PK and bile acids/sterols will be collected within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after dosing. The subject will leave the site after the hour 6 blood draw and return to the site on the following day for the hour 24 blood draw.
- For 24-hour urine collection, subjects will be instructed to empty their bladder before MBX- 8025 administration. Urine will be collected over the following intervals: 0-6 hours and 6-24 hours.

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

9.1.3 Initial Treatment: Visit 3 (Week 1) to Visit 7 (Week 8)

Visit 3 (Week 1)

At Visit 3 (Week 1) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols as outlined in Appendix A
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis
- 5D-itch scale and pruritus VAS
- MBX-8025 administration
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability

Visit 4 (Week 2)

At Visit 4 (Week 2) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)

- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- MBX-8025 trough level (only for non-PK subjects)
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale and Pruritus VAS
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability

Visit 5 (Week 4)

At Visit 5 (Week 4) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL
- 12-lead ECG after at least 5 minutes rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability
- Dispense of MBX-8025 (four weeks' worth) to be taken once daily.

Visit 6 (Week 6)

At Visit 6 (Week 6) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale and Pruritus VAS
- 12-lead ECG after at least 5 minutes rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability.

Visit 7 (Week 8), Completion of Initial Treatment/Initiation of Extension:

At Visit 7 (Week 8) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described in Section 9.2.1)
  This 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 and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- MBX-8025 trough level
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed (performed
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL

- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability
- Dispense of MBX-8025 (four weeks' worth) to be taken once daily. Subjects will continue into the extension on their originally assigned dose unless otherwise specified.
- Subject's safety and efficacy review. This review will be performed by the Investigator in collaboration with Medical Monitor. Based on this individual subject review and the overall study safety and efficacy review, the dose might be up- or down-titrated for the extension part of the study

9.1.4 Extension: Visit 8 (Week 12) to Visit 14 (Week 52)

Post-Dose Adjustment Visit

Subjects who had dose adjustment at any time during the extension will return to the clinic in two weeks after initiation of the extension dose. If dose adjustment occurs approximately two weeks prior to the next scheduled visit, post-dose adjustment visit and the next planned visit can be combined. The following will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability
- Additional assessments as determined by the Investigator.

Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 12 (Week 32) and Visit 13 (Week 39)

At Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20) and Visit 13 (Week 39) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability
- Dispense of MBX-8025 (four weeks' worth for Visit 8 and Visit 9, six weeks' worth for Visit 10, and thirteen weeks' worth for Visit 12) to be taken once daily.

At Week 8 (week 12) subjects participating in the PK analysis (selected centers) only:

- 24-hour blood samples for PK blood and bile acids/sterols will be collected within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after dosing. The subject will leave the site after the hour 6 blood draw and return to the site on the following day for the hour 24 blood draw.
- For 24-hour urine collection, subjects will be instructed to empty their bladder before MBX-8025 administration. Urine will be collected over the following intervals: 0-6 hours and 6- 24 hours.

Visit 11 (Week 26):

At Visit 11 (Week 26) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)

- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability
- Dispense of MBX-8025 (thirteen weeks' worth) to be taken once daily.

Visit 14 (Week 52), Completion of Extension/End of Treatment (EOT):

At Visit 14 (Week 52) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described in Section 9.2.1)
- This 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 and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Women of child-bearing potential will have a serum pregnancy test performed
- Spot urine sample will be collected for urinalysis
- MBX-8025 administration
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL
- 12-lead ECG after at least 5 minutes' rest and approximately 60-90 minutes after dosing
- Compliance to study medication and drug accountability

MBX-8025 will be stopped and the subject will enter the four-week follow-up period.

9.1.5 Follow-up Period: Visit 15 (Week 56) and Early Termination Visit

Visit 15 (Week 56), Post-Treatment Follow-up/End of Study (EOS)

The subject will return to the clinic for a follow-up visit in approximately four weeks after the last dose was taken. This will be the subject's last visit.

At Visit 15 (Week 56) the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described in Section 9.2.1)
- This 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 and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- 12-lead ECG after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols (as outlined in Appendix A)
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis
- Women of child-bearing potential will have a serum pregnancy test performed
- 5D-itch scale, Pruritus VAS, and the PBC-40 QoL

Visit 15 (Week 56) concludes the follow-up period and defines the end of the study. Any clinically significant abnormalities should be followed up by the Investigator, until resolution, or stabilization of those abnormalities.

Early Termination Visit

Subjects who discontinue participation in the study prematurely should return for an Early Termination Visit and the following evaluations should be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Review and documentation of concomitant medication (including supplements and vitamins)
- Vital signs and weight (as described at Section 9.2.2)
- Complete physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- 12-lead ECG after at least 5 minutes rest
- Blood drawn for hematology, biochemistry, exploratory biochemistry, and bile acids/sterols as outlined in Appendix A
- Back-up blood sample will be collected
- Spot urine sample will be collected for urinalysis

- 5D-itch scale, Pruritus VAS, and PBC-40 QoL
- Compliance to study medication and drug accountability
- Women of reproductive status will have the serum pregnancy test performed.

Any clinically significant abnormalities should be followed up by the Investigator until resolution or stabilization of those abnormalities.

Unscheduled Visit

At Unscheduled Visit the following evaluations will be performed:

- Documentation of TEAEs that occurred since the signing of the ICF
- Symptom-directed (brief) physical examination (as described at Section 9.2.1) and evaluation of liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice). UNS visit might be scheduled if needed per PI judgement
- Blood drawn for biochemistry and hematology
- Spot urine sample will be collected for urinalysis
- Compliance to study medication and drug accountability
- Additional assessments as determined by the Investigator

9.2 STUDY ASSESSMENTS

9.2.1 Medical History and Physical Examination

A detailed medical history (including PBC history and detailed treatment history) will be taken at screening (Visit 1 or Week -2).

Complete physical examinations will be performed at screening (Visit 1 or Week -2), Visit 7 (Week 8), Visit 11 (Week 26), Visit 14 (Week 52) and Visit 15 (Week 56), and ET visit (of applicable). These 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.

Symptom-directed (brief) examinations will be performed at Visit 2 (Day 1) through Visit 6 (Week 6) and from Visit 8 (Week 12) though Visit 10 (Week 20), Visit 12 (Week 32), Visit 13 (Week 39) and UNS. Brief physical exam will be performed for a condition that warrants the exam as determined by the PI. Subjects with platelet level above 500×10^3 µL on hematology panel will be evaluated for thrombolytic events.

Liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) will be evaluated at each visit from Screening (Visit 1) till Week 15 (Week 56). UNS visit might be scheduled if needed per PI judgement.

Any clinically significant change in physical examination findings that occur after signing the ICF at screening (Visit 1 or Week -2) will be recorded as an AE.

9.2.2 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 and weight will be assessed on all visits, i.e. Visit 1 (Week -2) through Visit 15 (Week 56), and ET Visit (if applicable). Height measurement will be performed only on Visit 1 (Week -2).

Vital signs may be obtained more frequently if a condition develops that warrants additional monitoring.

9.2.3 Electrocardiograms

A 12-lead ECG will be obtained in supine position after at least 5 minutes of rest at Visit 1 (Week - 2) through Visit 15 (Week 56), and ET Visit (if applicable). At Visit 2 (Day 1) through Visit 14 (Week 52) ECG will be performed approximately 60-90 minutes after dosing.

9.2.4 Laboratory Tests

Laboratory testing (as described below) will be carried out at Visit 1 (Week -2) through Visit 15 (Week 56) or ET Visit.

Blood samples 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.

Hematology will be assessed at all visits.

Biochemistry will be assessed at all visits. Exploratory biochemistry will be assessed at Visit 1 (Week -2) (AMA only), and Visit 2 (Day 1) through Visit 15 (Week 56), and ET Visit.

Bile acids/sterols will be assessed from Visit 2 (Day 1) through Visit 15 (Week 56), and ET Visit (if applicable).

Women of child-bearing potential will have a serum pregnancy test performed at Visit 1 (Week - 2), Visit 2 (Day 1), Visit 5 (Week 4), and Visit 7 (Week 8) through Visit 15 (Week 56)/EOS, and ET visit (if applicable).

Urinalysis (spot) will be assessed at Visit 1 (Week -2), Visit 2 (Day 1) through Visit 15 (Week 56), and ET and UNS visits (if applicable).

For subjects participating in 24-hour PK testing:

Samples for bile acids/sterols will be collected at the same time points as 24-hour PK blood samples - within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after the dosing at Visit 2 (Day 1) and Visit 8 (Week 12).

Samples for the 24-hour urine collection will be collected over two intervals, 0 to 6 hours and 6 to 24 hours at Visit 2 (Day 1) and Visit 8 (Week 12).

Laboratory testing will be obtained as follows:

a) Biochemistry:

AP, AST, ALT, GGT, 5' nucleotidase, Protein, Albumin, Total Bilirubin, Conjugated Bilirubin, Unconjugated Bilirubin, Bone-specific AP, aldolase, Sodium, Potassium, Chloride, Bicarbonate, BUN/Urea, Creatinine, eGFR, CK (if above upper limit of normal, CK-MM, CK-MB, and CK-BB will be measured), venous blood glucose, LDH, TG, TC, HDL-C, and LDL-C, Troponin I, Aldolase, Lipase

b) Hematology:

Erythrocyte Count (RBC), Hemoglobin, Hematocrit, Leukocyte Count (WBC), WBC Differential (absolute and percentage), Platelets, PT/INR

c) Exploratory biochemistry:

AMA, CTX, Cyctacin C, IgM, Fibrinogen, Fibroblast growth factor 19 (FGF19), Haptoglobin, hs- CRP, homocysteine, P1NP

d) Bile Acids and Sterols:

- Bile Acids: CA, CDCA, GCA, TCA, GCDCA, TCDCA, DCA, LCA, GDCA, GLCA, TDCA, TLCA, UDCA, GUDCA, TUDCA
- Sterols: DESM, LANO, LATH, 7-DHC, CSTN, COPR, SQLN; β-SITO, CAMP, STIG,
- C4 (7α-hydroxy-4-cholesten-3-one)

e) Back-Up Serum Sample:

From Visit 2 (Day 1) through Visit 15 (Week 56) or ET visit (if applicable), 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 two years following completion of the study and used to measure drug level, potential new biochemical markers, and/or to replace any missing or discarded samples.

f) Urinalysis

Spot sample will be analyzed via dip stick. Blood, Glucose, Ketones, Leukocyte Esterase, Nitrites, pH, and Protein will be measured. If positive, microscopic examination of sediments will be performed. Urine myoglobin will be measured if muscle injury is suspected.

24-hour urine collection will be analyzed for urine creatinine and creatinine clearance will be calculated. Additional details about sample collection, processing, handling and laboratory determination techniques are provided in the Laboratory Manual.

9.2.5 PK Samples for MBX-8025 level

24-hour plasma and urine concentration determination of MBX-8025 and its metabolites (M1, M2 and M3) will be performed on subjects participating in 24-hour PK testing. 24-hour blood samples will be collected at Visits 2 (Day 1) and Visit 8 (Week 12). Blood samples will be collected within 30 minutes prior to dosing, and 30 min, 1, 2, 4, 6 and 24 hrs after dosing.

24-hour urine sample will be collected over two intervals 0-6 hours and 6-24 hours.

PK trough level: Plasma concentration determination of MBX-8025 and its metabolites (M1, M2 and M3) will be collected pre-dose at Visits 4 (Week 2) and Visit 7 (Week 8).

Sample collection, processing and handling details are provided in the Laboratory Manual.

9.2.6 5D-itch Scale

The 5-D-itch scale will be used as a secondary measure for the multidimensional quantification of pruritus over time. The 5D-itch Scale is a measure of itching that has been validated in patients with chronic pruritus to detect changes over time. It is a brief, single page, multiple choice or 'check all boxes that apply' form (Elman, et al., 2015). See Appendix D for details.

The test will be performed at Visit 2 (Week 0) through Visit 15 (Week 56), and Early Termination Visit (if applicable).

9.2.7 Pruritus Visual Analog Score (VAS)

VAS will be used as a secondary measure to evaluate pruritus in subjects with PBC.

The test will be performed at Visit 2 (Week 0) through Visit 15 (Week 56), and Early Termination Visit (if applicable). See Appendix E for details.

9.2.8 PBC-40 QoL

The PBC-40 questionnaire will be used as a secondary measure to evaluate health-related QoL measures, specifically fatigue. PBC-40 is a disease-specific health related quality of life tool developed to specifically measure the psychometric profile of PBC patients. It covers six domains relevant to PBC including cognitive, social, emotional function, fatigue, itch, and other symptoms (Jacoby, et al., 2005). See Appendix F for details.

It will be performed at Visit 2 (Day 1), Visit 5 (Week 4), and Visit 7 (Week 8) though Visit 15 (Week 56), and ET Visit (if applicable). The questionnaire will be evaluated by the site personnel and the investigator will react to any evidence of deterioration.

10. ADVERSE EVENTS

10.1 GENERAL

10.1.1 Definition of Adverse Events (AEs)

An adverse event (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.

10.1.2 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

10.1.3 AE Severity

The severity of an AE will be graded from 1 to 5 according to the CTCAE version 4.0 criteria (v4.03, June 14, 2010) and appendix F.

10.1.4 Relationship to Treatment

The relationship or association of the AE to a study treatment will be characterized as "**unrelated**", "**unlikely/remote**," "**possible**," or "**related**".

- **Unrelated**: indicates that the AE can be explained by known characteristics of the subject's clinical state or other modes of therapy administered to the subject or it does not follow a reasonable temporal sequence from administration of the study treatment
- **Unlikely/Remote:** an event for which an alternative explanation is more likely (e.g. concomitant medications or ongoing medical conditions) or the temporal relationship to study drug administration and/or exposure suggests that a causal relationship is unlikely
- **Possible:** the event cannot be explained by the subject's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and study drug administration
- **Related:** there is clear evidence that the event is related to the use of the study treatment (e.g. confirmation by positive re-challenge test)

10.1.5 Action Taken With Study Medication

As a consequence of an AE, the action taken with the MBX-8025 can be:

- None: no changes were made to MBX-8025 administration or dose
- Permanently discontinued: MBX-8025 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
- Not applicable: e.g. in case the AE occurred after signing the ICF but before the administration of MBX-8025 was commenced
- Specific subject withdrawal criteria and dose adjustments are mentioned in Section 10.5.

10.2 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 CRF, 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 end-of-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 intercurrent 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 CRF. 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 the course of this study will be supplied to the Sponsor and recorded in the CRF.

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- AE Persists: Subject terminates from the trial and the AE continues
- Recovered: Subject recovered completely from the AE
- Became Serious: The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- Change in Severity (if applicable): AE severity changed

10.2.1 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 to the end-of-study evaluation, regardless of relationship to the study treatment, must be reported immediately (no later than 24 hours) by the Investigator to the Sponsor's representative (Contract Research Organization (CRO)) 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 event

All criteria, which are applicable for same subject, should be entered. The outcome for the event will be listed on the SAE Report Form as follows:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

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

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 end-of-study. If the event of death occurs after the end-of-study, the death will not have to be reported as a Serious Adverse Event.

The Investigator will document all available information regarding the SAE on the SAE 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 MBX-8025 administrations
- 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 counter-measures 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 in CRF 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.

10.2.2 Follow-up of Reported AEs

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

After EOS Visit (Visit 12), 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.

10.3 DISTRIBUTION OF RESPONSIBILITIES

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

10.4 SAFETY MONITORING CRITERIA, DOSE ADJUSTMENT, AND WITHDRAWAL CRITERIA,

10.4.1 Safety Monitoring and Dose Adjustment

Enrolled subjects with the following lab abnormalities should be monitored closely and may be discontinued from MBX-8025 or go through MBX-8025 dose adjustment if criteria are met:

10.4.1.1. Liver Safety Monitoring

I. Elevation of ALT/AST

Normal ALT/AST at baseline

- ALT/AST > 5× ULN AND Total bilirubin is < 1.5 × ULN or < 2 mg/dL: interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
- ALT/AST > 5 × ULN AND Total bilirubin is ≥ 1.5 × ULN or ≥ 2 mg/dL: stop MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B).

Elevated ALT/AST at baseline:

- ALT/AST > 3 × baseline AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice)/ INR < 1.5 × ULN: MBX- 8025 can be continued. Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B) and discuss results with Medical Monitor to determine MBX-8025 intake.

II. Symptoms of clinical hepatitis (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) AND ALT/AST > 3 × baseline (irrespective of baseline levels): interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

III. Elevation of total bilirubin (> 2 × ULN or > 1.5 × baseline), regardless of ALT or AST levels, and indicators of immunological reaction (e.g., rash, eosinophilia > 5%), or symptom of clinical hepatitis (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): interrupt MBX-8025. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B). Study medication

can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

IV. Hepatic decompensation (eg., progression to cirrhosis, gastro-esophageal variceal bleeding, ascites) during the trial: stop MBX-8025.

V. Close monitoring of a subject is not possible: stop MBX-8025 (see Appendix B for more details).

10.4.1.2. Muscle Safety Monitoring

I. CK > 5 × ULN with musculoskeletal symptoms: stopped MBX-8025. Repeat the test within 3 days. Follow the subject weekly until resolution or stabilization.

II. CK > 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If on repeat test CK is > 2.5 × ULN, stop MBX-8025. Follow the subject weekly until the event resolution or stabilization.

III. CK > 2.5 × ULN and ≤ 5 × ULN with musculoskeletal symptoms: interrupt MBX-8025. Repeat the test within 3 days. Follow the subject weekly until the event resolution or stabilization. MBX-8025 might be resumed at a decreased dose after event resolution.

IV. CK > 2.5 × ULN and ≤ 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If the test is confirmed, MBX-8025 will be continued at a decreased dose.

10.4.1.3. Serum Creatinine Monitoring

I. Serum creatinine > 2.0 × ULN: stop MBX-8025. The subject should be monitored weekly until resolution or stabilization.

II. Serum Creatinine > 1.5 × ULN and ≤ 2.0 × ULN: interrupt MBX-8025. Repeat the test within 72 hours. If the test is confirmed and no alternative etiology is identified, stop MBX- 8025. If alternative etiology is identified, MBX-8025 may be restarted after serum creatinine returns to baseline values. The subject should be monitored weekly until event resolution.

10.4.1.4. Pancreatic Safety Monitoring

I. Amylase > 3 × ULN and/or lipase > 3 × ULN without clinical symptoms of acute pancreatitis: repeat the test within 3 days. If the test confirms suspicion, interrupt MBX- 8025. Abdominal imaging is to be performed to exclude an alternative cause for the event. MBX-8025 might be restarted only if a firm competing etiology of acute pancreatitis is identified.

II. Amylase > 3 × ULN and/or lipase > 3 × ULN with clinical symptoms of acute pancreatitis: interrupt MBX-8025. Abdominal imaging is to be performed to exclude an alternative cause for the event and repeat amylase/lipase within 3 days. MBX-8025 might be restarted only if a firm competing etiology of acute pancreatitis is identified.

10.4.2. Dose adjustment for extension periods

- Unless otherwise specified, subjects will continue into the extension on their originally assigned dose.
- During the extension, the subject's dose might be re-adjusted for safety or efficacy reasons.

- For individual subjects in the 2 mg, 5 mg, and 10 mg treatment groups, an ongoing safety and efficacy review will determine the dose to be used (1 mg, 2 mg, 5 mg, 10 mg, 15 mg, or 20 mg).
- Dose up-titration to 15 mg can be performed only within 26-week treatment period. Beyond Week 26 (Visit 11), the highest dose will be 10 mg.

10.4.3 Additional Withdrawal Criteria and Replacement of Subjects

Subjects must 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 successfully complete the end-of-study Visit 12 (Week 30).

If a subject withdraws from the study, he/she may be replaced.

10.5 DATA SAFETY AND MONITORING BOARD

There is no DSMB in the study. It is an open label study. The Investigator, the subject and the Sponsor will know the study drug assessment. The Sponsor will be reviewing safety and efficacy data in the ongoing manner to determine if the individual subject dose needs to be adjusted.

10.6 PRECAUTIONS

10.6.1 Pregnancy

No specific studies have been performed to determine the reproductive and developmental toxicity of MBX-8025. As a precaution, women of child bearing potential receiving MBX-8025 must use one barrier contraceptive and a second effective birth control method during the study and for at least 90 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.

Acceptable methods of birth control include consistent use of an approved oral contraceptive (birth control pill), an implantable contraceptive (such as Norplant), an injectable contraceptive (Depo-Provera), a double-barrier method (diaphragm with spermicide, condom with spermicide), or

abstinence. Oral, implantable, or injectable contraceptives are only considered effective if used properly and started at least 60-90 days prior to the screening visit.

11. STUDY TERMINATION

CymaBay Therapeutics, Inc. reserves the right to discontinue the study if it becomes aware of information concerning the quality, 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, EC, 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 Principal 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.

12. DATA MANAGEMENT AND STATISTICAL ANALYSES

12.1 DATA MANAGEMENT

12.1.1 Processing of Electronic Case Report Forms

Electronic CRFs will be completed for all study subjects enrolled in the study. At scheduled monitoring visits, eCRFs will be 100% verified against source documentation. Upon completion of this review, finalized eCRFs will be submitted to the Sponsor's designated CRO. Any subsequent changes to the eCRFs will be performed in accordance with the CRO's Standard Operating Procedures (SOP) for editing and clarifying CRFs.

12.1.2 Database

Data entry will be performed through username and password protected access to a secure database. All data will be entered using electronic Case Report Form (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 MedDRA coding thesaurus will be used to classify AEs and Medical History, and the WHO Drug classification will be used to code medications.

12.1.3 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.

12.2 STATISTICAL ANALYSIS

12.2.1 Sample Size Estimation

It is assumed that the 5 mg and 10 mg treatment groups will have at least 10% difference in the mean AP percent change with a 15 % standard deviation. Based on this assumption, and on the use of two-sided, two-sample t-test at the alpha =0.05 level of significance, a study sample size of 49 subjects per group will have a 90% power to detect a 10% mean difference between 5 mg and 10 mg treatment groups.

There is no formal sample size justification for 2 mg treatment group.

12.2.2 Study Population

Approximately 116 subjects from 18 to 75 (inclusive) old will receive MBX-8025 according to the protocol.

12.2.2.1 Safety population

The safety population is defined by any subject who receives at least one dose of medication. Subjects will be included in the group based on treatment received, if this should differ from the treatment assignment. All safety analyses will be completed using the safety population.

12.2.2.2 Modified intent to treat population (mITT)

The mITT population is defined as any subject who receives at least one dose of medication and has at least one post baseline AP evaluation on treatment. The mITT population is the primary analysis population for all efficacy analyses. Subjects will be included in the treatment group to which they were assigned.

12.2.2.3 Per-protocol population (PP)

The PP population is defined as any subject who receives at least one dose of medication, has at least one post baseline AP evaluation, and does not have a protocol violation that is deemed to impact the efficacy analysis. Supportive efficacy analyses will be completed using the PP population.

12.2.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics (medical histories, physical examinations, and concomitant medications) will be summarized using descriptive statistics for continuous variables and frequency distributions for discrete variables.

12.2.4 Efficacy Analysis

12.2.4.1. Primary Efficacy Analysis

Efficacy analysis will be conducted on the mITT population and the PP population. The mITT population will be used for the primary efficacy analysis.

Descriptive statistics such as means, medians and measures of dispersion will be presented.

Baseline will be defined as the mean assessments between V1 and V2 (Week-2 and Day 1, baseline 1) for the primary analysis and composite endpoint, and as V2 (Day 1, baseline 2) values for other analyses.

The last observation carried forward (LOCF) approach will be used for missing laboratory data.

The primary efficacy analysis will compare the mean percentage change from baseline to end of 8-week treatment in AP levels. The primary efficacy analysis will compare the mean percentage change to end-of treatment with AP levels using an analysis of covariance (ANCOVA) model with treatment group as the factor and the baseline AP level as a covariate. Pairwise comparisons between the MBX-8025 2 mg, 5 mg, and 10 mg treatment groups will be tested.

12.2.4.2. Secondary Efficacy Analysis

The secondary efficacy analysis will compare the mean percentage change in AP levels from baseline to Week 12, from baseline to Week 26, and from baseline to the end of extension (52-week treatment). An additional secondary analysis will use the absolute AP change from baseline to end of 8-week treatment, from baseline to end of 12-week treatment, from baseline to end of 26-week treatment, and from baseline to end of extension (52-week treatment). These analyses will be completed using the same type of ANCOVA model as described for the primary analysis. Pairwise comparisons between the MBX-8025 2 mg, 5 mg, and 10 mg treatment groups will again be tested.

The secondary efficacy analysis will analyze the responder rate with a composite endpoint of AP and Total Bilirubin (AP < 1.67 × upper limit of normal (ULN), Total Bilirubin within normal limit, and at least 15% decrease in AP).

Published PBC response criteria (Barcelona, Paris I and II; Toronto I and II), UK-PBC risk score, 5D-itch scale, pruritus VAS, and PBC-40 QoL will be used as secondary measures to assess subject's treatment response. In order to determine the biochemical response, parameters available from biochemistry (i.e. AP, AST, ALT, albumin, total bilirubin) and hematology (i.e. platelet count) will be used (Carbone, et al., 2015; Hirschfield, et al., 2014).

Primary and secondary analyses will be carried out using two-sided tests at the alpha=0.05 level of significance.

12.2.4.3. Exploratory Efficacy Analysis

The exploratory efficacy analysis will be performed on bile acids, sterols, C4, and additional biochemistry measurements (AMA, CTX, cystatin C, IgM, fibrinogen, FGF19, haptoglobin, hs- CRP, homocysteine, microRNA-122, and P1NP). Descriptive summaries will be used for this analysis.

Please see the Statistical Analysis Plan (SAP) for more details.

12.2.5 Pharmacokinetic Analyses

PK parameters for MBX-8025 and metabolites (M1, M2 and M3) will be summarized using descriptive statistics. Pharmacokinetic modeling may also be performed on the data generated from the study. Dose proportionality may be examined using graphical methods. 24-hour urinary excretion of MBX-8025 and metabolites will be analyzed. Other statistical analyses will be added in the SAP.

12.2.6 Safety Analysis

Safety analysis will be conducted on the safety population.

The safety measures will be incidence rate of adverse events (AE) and Treatment Emergent Adverse Events (TEAEs), ECG, biochemistry, hematology, and urinalysis (NCI CTCAE Version 4.0)

Safety data will be summarized by dose level. Baseline values for laboratory tests, vital signs, and electrocardiograms will be defined as the last evaluation performed prior to administration of MBX-8025.

12.2.6.1 Adverse Events

The subset of AEs occurred after the first dose of MBX-8025 will be considered to be TEAEs. The incidence of AEs and TEAEs will be tabulated.

12.2.6.2 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 time. Vital signs collected at all study time points will be recorded in the eCRF and analyzed.

12.2.6.3. Physical Examination

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

12.2.6.3 Laboratory Tests

Descriptive statistics and mean or median change from baseline will be determined for each measure of laboratory tests, at each assessment time. Abnormal laboratory values will be graded by the investigator as: "clinically significant" or "not clinically significant", where available, and all laboratory values will be reported. 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.

The last observation carried forward (LOCF) will be used for missing laboratory data.

12.2.6.5 Electrocardiograms

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

12.2.6.5 Concomitant Medications

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

12.2.7 Timing of the Analysis

After the 24th subject in the 5 mg and 10 mg treatment groups was enrolled, a safety and efficacy data review was performed.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1 STUDY MONITORING

The Investigators and institution(s) will permit trial-related monitoring of the eCase Report Form 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 100% 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.

13.2 AUDITS AND INSPECTIONS

Regulatory authorities, the Ethics Committee (EC), and/or CymaBay Therapeutics Inc. or its designee(s) may request access to all source documents, electronic Case Report Form 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.

13.3 ETHICS COMMITTEEs

The Investigators will provide ECs with all information impacting the risk profile of the drug. The trial will not commence until written EC 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.

14. 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 adverse events 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.

15. ETHICS

15.1 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 ICH requirements for composition, documentation, and operational procedures.

15.2 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.

15.3 WRITTEN INFORMED CONSENT

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 both the Investigator and the subject. The original will be retained by the Investigator and filed in the Investigator's Site File. A copy of the original must be provided to the study subject.

16. 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 fifteen (15) years after completion of the study, or notification from the Sponsor that the data can be destroyed, whichever comes first.

17. 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.

18. 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 – LABORATORY EVALUATIONS

Biochemistry			
AP	Total Bilirubin	Chloride	LDH
AST	Conjugated Bilirubin	Bicarbonate	TG
ALT	Troponin I	BUN/Urea	Total Cholesterol
GGT	Unconjugated Bilirubin	Serum Creatinine	HDL-C
5' nucleotidase	Bone-specific AP	eGFR	LDL-C
Protein	Aldolase	CK (if ULN, CK-MM, CK-MB, and CK-BB)	Amylase
Albumin	Sodium	Venous Glucose	Lipase
	Potassium		
Hematology	**Exploratory Biochemistry**	**Urinalysis**	**Other Tests**
RBC	AMA	Blood	Serum Pregnancy Test
Hemoglobin	CTX	Glucose	24 hour PK Blood Samples
Hematocrit	Cystatin C	Ketones	24-hour PK Urine Samples
WBC	IgM	Leukocyte Esterase	PK trough level
WBC differentials (abs and %)	Fibrinogen	Nitrite	24-hour Urine Creatinine
Platelets	FGF19	pH	Creatinine Clearance
PT/INR	Haptoglobin	Protein	Back-up Sample
	hs-CRP	Microscopic examination of sediments (if positive)	
	Homocysteine	Urine Myoglobin (if muscle injury is suspected)	
	P1NP		
	microRNA-122		
Bile Acids and Sterols			
Bile Acids: CA, CDCA, GCA, TCA, GCDCA, TCDCA DCA, LCA, GDCA, GLCA, TDCA, TLCA UDCA, GUDCA, TUDCA TC			
Sterols: DESM, LANO, LATH, 7-DHC, CSTN, COPR, SQLN β-SITO, CAMP, STIG 7 α HC C4			

APPENDIX B – CLOSE OBSERVATION CRITERIA

The "close observation" will be performed on subjects meeting liver safety monitoring criteria per Section 10.4.1.1. If "close observation" is not feasible, MBX-8025 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, loss of appetite, dark urine, or jaundice)
    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 INR within 3 days
    b. Monitor the subject every 3 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. NASH
    d. Hypoxic/ischemic hepatopathy
    e. Biliary Tract Disease besides PBC

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.

The NCI CTCAE may also be accessed here:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX D – 5D-ITCH SCALE

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

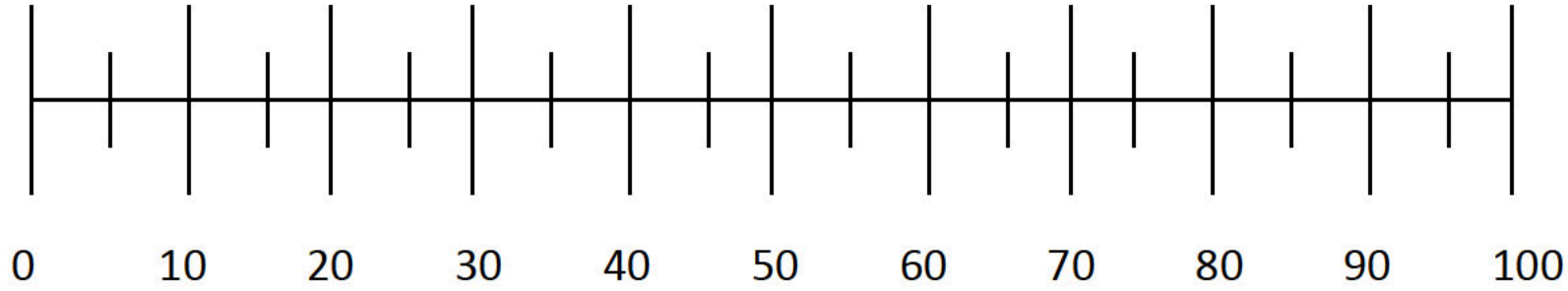
	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

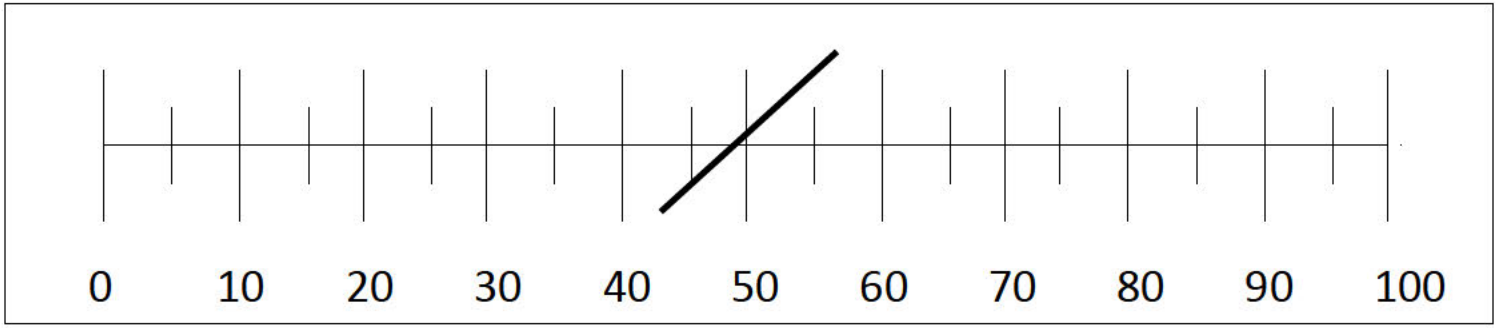
	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

APPENDIX E – PRURITUS VAS

No itching Worst possible itching



Example:



APPENDIX F – PBC-40 QoL

For each statement, please circle the response that comes closest to how you feel. If any of the statements do not apply to you please circle 'does not apply'.

Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?

1	I was able to eat what I liked	Never	Rarely	Sometimes	Most of the time	Always	
2	I ate or drank only a small amount, and still felt bloated	Never	Rarely	Sometimes	Most of the time	Always	
3	I felt unwell when I drank alcohol	Never	Rarely	Sometimes	Most of the time	Always	Did not apply / never drink alcohol

And IN THE LAST FOUR WEEKS, how often did you experience any of the following?

4	I had discomfort in my right side	Never	Rarely	Sometimes	Most of the time	Always	
5	I had dry eyes	Never	Rarely	Sometimes	Most of the time	Always	
6	My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
7	I had aches in the long bones of my arms and legs	Never	Rarely	Sometimes	Most of the time	Always	

Some people with PBC experience itching. How often did you experience itching IN THE LAST FOUR WEEKS? If you did not itch, please circle 'does not apply'

8	Itching disturbed my sleep	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/ no itch
9	I scratched so much I made my skin raw	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch
10	I felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Did not apply/no itch

Fatigue can also be a problem for many people with PBC. How often did the following statements apply to you IN THE LAST FOUR WEEKS?

11	I had to force myself to get out of bed	Never	Rarely	Sometimes	Most of the time	Always
12	I had to have a sleep during the day	Never	Rarely	Sometimes	Most of the time	Always
13	Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always
14	I felt worn out	Never	Rarely	Sometimes	Most of the time	Always
15	I felt so tired, I had to force myself to do the things I needed	Never	Rarely	Sometimes	Most of the time	Always
16	I felt so tired, I had to go to bed early	Never	Rarely	Sometimes	Most of the time	Always
17	Fatigue just suddenly hit me	Never	Rarely	Sometimes	Most of the time	Always

18	PBC drained every ounce of energy out of me	Never	Rarely	Sometimes	Most of the time	Always	

The next section is about the effort and planning that can be involved in living with PBC. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

19	Some days it took me a long time to do anything	Never	Rarely	Sometimes	Most of the time	Always	
20	If I was busy one day I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always	
21	I had to pace myself for day-to-day things	Never	Rarely	Sometimes	Most of the time	Always	

The following statements are about the effects that PBC may have on things like memory and concentration. Thinking about THE LAST FOUR WEEKS, how often did the following statements apply to you?

22	Because of PBC I had to make a lot of effort to remember things	Never	Rarely	Sometimes	Most of the time	Always	
23	Because of PBC I had difficulty remembering things from one day to the next	Never	Rarely	Sometimes	Most of the time	Always	
24	My concentration span was short because of PBC	Never	Rarely	Sometimes	Most of the time	Always	
25	Because of PBC, I had difficulty keeping up with conversations	Never	Rarely	Sometimes	Most of the time	Always	
26	Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
27	Because of PBC, I found it difficult to remember what I wanted to do	Never	Rarely	Sometimes	Most of the time	Always	

Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?

28	Because of PBC, I get more stressed about things than I used	Not at all	A little	Somewhat	Quite a bit	Very much	
29	My sex life has been affected because of PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
30	Having PBC gets me down	Not at all	A little	Somewhat	Quite a	Very	
31	I feel I neglect my family because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Does not apply
32	I feel guilty that I can't do what I used to do because of having	Not at all	A little	Somewhat	Quite a bit	Very much	
33	I worry about how my PBC will be in the future	Not at all	A little	Somewhat	Quite a bit	Very much	

These statements relate to the possible effects of PBC on your social life. Thinking of your own situation, how much do you agree or disagree with them?

34	I sometimes feel frustrated that I can't go out and enjoy myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	
35	I tend to keep the fact that I have PBC to myself	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	
36	I can't plan holidays because of having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	

37	My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next section is about the impact that PBC may be having on your life overall. How much do you agree or disagree with the following statements?

38	Everything in my life is affected by PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
39	PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
40	I can still lead a normal life, despite having PBC	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree

The next few questions are about your general health and well being:

A	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor
B	And how would you have rated it before you had PBC?	Excellent	Very good	Good	Fair	Poor
C	COMPARED TO ONE YEAR AGO, how would you rate your health in general now?	Much better	Somewhat better	About the same	Somewhat worse	Much worse

APPENDIX G – INVESTIGATOR'S PROTOCOL SIGNATURE PAGE

CB8025-21629

An 8-week, dose ranging, open label, randomized, Phase 2 study with a 44-week extension, to evaluate the safety and efficacy of MBX-8025 in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response to or intolerance to ursodeoxycholic acid (UDCA)

PROTOCOL VERSION NUMBER: Version 4.2

DATE OF PROTOCOL: 20-JUL-2017

SPONSOR: CymaBay Therapeutics, Inc.
7999 Gateway Blvd, Suite 130
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/MMM/YYYY): _____

Site Address: _____

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