

2.0 SYNOPSIS

Name of Sponsor/Company:

CymaBay Therapeutics, Inc.

Name of Finished Product:

MBX-8025/Seladelpar

Name of Active Ingredient:

MBX-8025/Seladelpar

Title of Study:

A 12-Week, Double-Blind, Randomized, Placebo-Controlled, Phase 2 Study to Evaluate the Effects of Two Doses of MBX-8025 in Subjects with Primary Biliary Cirrhosis (PBC) and an Inadequate Response to Ursodeoxycholic acid (UDCA)

Investigators/Study Centers:

A total of 49 sites in 5 countries (Canada, Germany, Poland, the United Kingdom, and the United States) were included. Of these, 30 sites screened subjects and 22 sites in 4 countries (Canada, Germany, the United Kingdom, and the United States) randomized subjects prior to the stopping of the study.

Studied Period (Years):

(Date of First Enrollment) 02 November 2015

(Date of Last Completed) 08 July 2016

Phase of Development: 2**Objectives:**

Primary: To evaluate the effect of MBX-8025 on alkaline phosphatase (AP) levels

Secondary:

- To evaluate the safety and tolerability of MBX-8025 in subjects with primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis)
- To evaluate the effects of MBX-8025 on PBC response criteria
- To evaluate the effects of MBX-8025 on other markers of liver function, lipids, pruritus, and quality of life

Exploratory: To evaluate the effect of MBX-8025 on liver imaging results and other biochemical markers that may be relevant to the pathophysiology of PBC or the mechanism of action of the drug.

Methodology:

This was a double-blind, randomized, placebo-controlled, 12-week dose-ranging (50 mg and 200 mg/day) study in male and female subjects with PBC who had inadequate response to UDCA.

After signing an informed consent form, subjects entered a screening period (up to 4 weeks). Randomization took place after confirmation of eligibility. Subjects were centrally randomized, assigned in a 1:1:1 ratio to receive MBX-8025 50 mg/day, MBX-8025 200 mg/day, or placebo. Subjects were to be randomized within 7 days prior to the first dose of study medication at Visit 2 (Week 0/Day 1). Subjects were to take their assigned study medication orally once daily, for

12 weeks. Subjects were to attend study visits at Weeks 0 (Baseline), 2, 4, 8, and 12. In addition to the study visits, the site contacted subjects remotely over the phone at Weeks 6 and 10. After the end of treatment, subjects entered a 2-week follow-up period and completed a follow-up visit at Week 14 (or 2 weeks after the end of treatment). Subjects who discontinued participation in the study prematurely or were participating in the study when it was stopped returned for end of treatment and end of study visits. AP values remained blinded throughout the study.

Eligible subjects were to have taken UDCA for at least 12 months prior to screening and were to continue taking UDCA at approximately the same dose during the study. Subjects were allowed to receive required medication to treat new or existing medical conditions. Use of fibrates, simvastatin, colchicine, methotrexate, azathioprine and systemic steroids was prohibited during the study.

Number of Subjects (Planned and Analyzed):

A total of 75 subjects were planned (25 per treatment group) to be enrolled into the study and assigned to study treatment. At the time of study closure, a total of 41 subjects (approximately 55% of the planned 75) had been randomized (14, 13, and 14 in the MBX-8025 50 mg, MBX-8025 200 mg, and placebo groups, respectively).

Of the 41 randomized subjects, 3 were randomized but not treated. One of these subjects (randomized to 200 mg) experienced an SAE of gastro-intestinal bleeding that was considered hepatic decompensation prior to the initiation of study medication and this subject was discontinued prior to receiving any study medication. The other 2 subjects had been randomized (one to placebo and one to 50 mg) but had not received study medication at the time the study was stopped and were withdrawn prior to receiving study medication.

Of the 38 subjects who received study medication, 10 completed the study before it was stopped by the Sponsor and 9 subjects (5 subjects in the MBX-8025 groups) completed 12 weeks of treatment.

Of the 28 subjects who discontinued the study early, 24 discontinued due to the stopping of the study. Of the other 4 remaining subjects, 1 withdrew their consent to participate in the study and 3 subjects discontinued treatment due to AEs.

Diagnosis and Criteria for Study Entry:

Inclusion Criteria:

For inclusion in the study, subjects must have fulfilled 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 2 of the following criteria:
 - History of AP above the ULN for at least 6 months
 - Positive antimitochondrial antibodies (AMA) titers ($>1/40$ on immunofluorescence or M2 positive by enzyme-linked immunosorbent assay) or positive PBC-specific antinuclear antibodies
 - Documented liver biopsy result consistent with PBC
4. On a stable and recommended dose of UDCA for the 12 months prior to screening
5. $AP \geq 1.67 \times ULN$. Screening AP values may have been determined using either the central

laboratory or a local laboratory.

6. Females of reproductive potential were required to use at least 1 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 were sexually active with female partners of reproductive potential were required to use barrier contraception and their female partners were required to 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 precluded full participation in the study or would confound its results (e.g., cancer on active treatment)
2. AST or ALT $> 3 \times$ ULN
3. Total bilirubin $> 2 \times$ ULN
4. Autoimmune hepatitis
5. Primary sclerosing cholangitis
6. Known history of alpha-1-Antitrypsin deficiency
7. Known history of chronic viral hepatitis
8. creatine kinase (CK) above ULN
9. Serum creatinine above ULN
10. For females, pregnancy or breast-feeding
11. Use of colchicine, methotrexate, azathioprine or systemic steroids in the 2 months preceding screening
12. Current use of fibrates, including fenofibrates, or simvastatin
13. Use of an experimental treatment for PBC
14. Use of experimental or unapproved immunosuppressant
15. 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

Test Product, Dose, Mode of Administration, and Batch Number:

MBX-8025 50 mg or 100 mg capsules taken orally once daily, dosed as follows:

50 mg: One MBX-8025 50 mg capsule and 1 identical placebo capsule

200 mg: Two MBX-8025 100 mg capsules

MBX-8025 50 mg Lot numbers 14G059 and 15G133

MBX-8025 100 mg Lot numbers 14G060 and 15G134

Reference Therapy, Dose, Mode of Administration, and Batch Number:

Two placebo capsules, identical in appearance to MBX-8025 capsules taken orally once daily.

Placebo Lot numbers 14G058 and 15G132

Duration of Study:

Up to 18 weeks, including a 4-week screening period prior to treatment, a 12-week treatment period, and a 2-week follow-up period after the end of treatment.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Measure:

Percentage change from baseline to end of treatment in AP level.

Secondary Efficacy Measures:

- Composite endpoint of AP and total bilirubin
 - $AP < 1.67 \times ULN$ and total bilirubin within normal limit and
 - $\geq 15\%$ decrease in AP
- Change from baseline to the end of treatment in the following biochemistry parameters: AST, ALT, gamma-glutamyl transferase (GGT), 5'-nucleotidase, bilirubin (total, conjugated, unconjugated), bone-specific AP, triglycerides, total cholesterol, high density lipoprotein cholesterol, and low density lipoprotein cholesterol
- Published PBC response criteria (Paris I and II, Toronto I and II)
- United Kingdom-primary biliary cirrhosis/cholangitis (UK-PBC) risk score
- 5-Dimension Itch Scale score
- Pruritus Visual Analog Scale (VAS) score
- PBC-40 quality of life questionnaire

Exploratory Efficacy Measures:

- Elastography (selected centers)
- AMA, immunoglobulin M, high-sensitivity C-reactive protein (hs-CRP), homocysteine
- Exploratory biochemistry parameters including but not limited to total bile acids, UDCA, chenodeoxycholic acid, cholic acid, lithocholic acid, deoxycholic acid, and bile acid precursor C4 (7α -hydroxy-4-cholesten-3-one)

Safety:

- Adverse events and treatment-emergent adverse events (TEAEs): The severity of AEs was graded by Investigators using the NCI CTCAE, Version 4.
- Vital signs
- Physical examination
- Laboratory tests (biochemistry and hematology)
- Electrocardiography
- Use of concomitant medications

Subjects with CK elevations were to have their dose of study medication adjusted or be discontinued from treatment.

- If a subject had a CK level $> 2.5 \times ULN$ and $\leq 5 \times ULN$ with musculoskeletal symptoms: study drug was to be interrupted until resolution. The subject was to be monitored weekly until resolution. Study drug could be resumed at a decreased dose after the event resolution.
- If a subject had a CK level $> 2.5 \times$ the upper limit of normal (ULN) and $\leq 5 \times ULN$ during treatment without musculoskeletal symptoms, the test was to be repeated within 72 hours. If the test was confirmed, study drug was to be continued at a decreased dose.
- If a subject was found to have a CK level $> 5 \times ULN$ without musculoskeletal symptoms, the test was to be repeated within 48 hours. If the on-repeat test CK was above ULN, study medication was to be discontinued and the subject was to be withdrawn from the study. The subject was then to be monitored weekly until resolution or stabilization of their CK level.

- If a subject was found to have a CK level $>5 \times$ ULN with musculoskeletal symptoms, the study drug was to be discontinued and the subject was to be monitored weekly until resolution or stabilization.

Safety data were periodically reviewed by a data safety and monitoring board (DSMB) to protect subject welfare and identify potential safety signals. The severity of adverse events (AEs) was graded by Investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0. If any of the 3 study stopping criteria below were met, the study was to be paused and evaluated for safety by the DSMB:

- ≥ 3 NCI CTCAE Grade 3 AEs in the same category
- ≥ 2 NCI CTCAE Grade 4 AEs in the same category
- ≥ 1 NCI CTCAE Grade 5 AE

The study could continue if the DSMB determined that causality was not associated with the study drug.

Statistical Methods:

Study Populations:

Safety: Any randomized subject who received at least 1 dose of medication.

Modified intent-to-treat (mITT): Any randomized subject who received at least 1 dose of medication and had at least 1 on-treatment postbaseline AP evaluation.

Per-protocol (PP): Any randomized subject who received at least 1 dose of medication, had at least 1 postbaseline AP evaluation, and did not have a protocol violation that was deemed to impact the efficacy analysis.

Analysis:

Efficacy analysis was conducted on the mITT population and the PP population. The mITT population was used for the primary efficacy analysis. Safety analysis was conducted on the Safety Population.

Baseline 1 was defined as the mean between assessments at Visit 1 (Week -4 to Week 0) and Visit 2 (Week 0). Baseline 2 was defined as the last non-missing assessments/values prior to or on the date of the first study dose.

Baseline 1 and Baseline 2 were used to derive the primary variable (AP). Baseline 1 was considered primary and Baseline 2 was considered supportive. Baseline 2 was used to derive all other assessments.

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

For missing postbaseline data, the last non-missing postbaseline value on treatment was carried forward (last observation carried forward).

The primary efficacy analysis compared the mean percentage change from Baseline 1 and Baseline 2 to end of treatment in AP levels between the MBX-8025 200 mg treatment group and the placebo group. If this analysis was statistically significant, the next comparison was between the MBX-8025 50 mg treatment group and the placebo group.

Sample Size and Power:

It was assumed that the mean percentage decrease from baseline in AP would be no more than 5% in the placebo group and at least 25% in the MBX-8025 groups. Additionally, the standard deviation of the percentage change from baseline to end of treatment was assumed to be 20%.

Based on these assumptions, and on the use of a 2-sided 2-sample comparison of means at the $\alpha = 0.05$ level of significance and a sample size of 23 subjects per group, the study had 90% power to detect a difference of 20 percentage points between the active and placebo groups. To account for up to 2 subjects per group who might be excluded from the mITT population, the planned sample size was 25 subjects per group (75 total subjects).

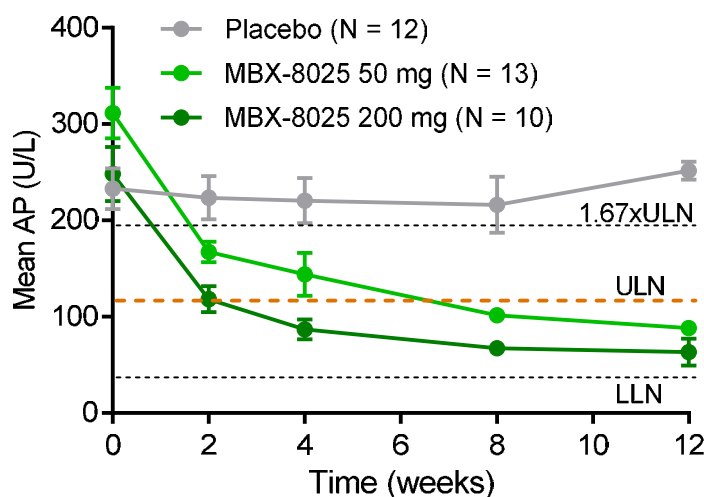
Summary – Conclusions

On 23 May 2016, a total of 3 subjects had experienced Grade 3 alanine aminotransferase (ALT) elevations. The study drug was unblinded for these cases and all 3 subjects were receiving MBX-8025 (1 receiving 50 mg and 2 receiving 200 mg). At the same time, based on concomitant decreases in GGT and 5' nucleotidase observed in the study overall (AP values were blinded during study), the proof-of-concept efficacy was demonstrated. As such, the Sponsor determined that there was no justification for continuing to expose subjects to MBX-8025, and stopped and unblinded the study. An ad hoc DSMB meeting was held on 26-May-2016, at which the Sponsor informed the DSMB that the study had been stopped.

On 27-May-2016, all active subjects were instructed to continue treatment with study medication until their next planned study visit. The last dose of study drug would be the day prior to this visit, and this visit was considered the end of treatment visit. Subjects were then to proceed, as planned in the original protocol, to a follow-up (off treatment) end of study visit, 2 weeks later.

Efficacy Results:

Both MBX-8025 treatment groups showed significantly greater LSmean percentage reductions from Baseline 1 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 group versus placebo; and LSmean difference 60.99%, $p < 0.0001$ for the MBX-8025 200 mg group versus placebo). The reductions from Baseline 1 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. Change in AP from Baseline 2 were consistent with and supported the results using Baseline 1 as did results of analyses of change in AP levels from Baseline 1 and Baseline 2 using a mixed model for repeated measures to impute missing values at each time point. All MBX-8025-treated subjects that completed 12-week treatment had normalized (i.e., within the ULN) AP levels.

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

ULN = upper limit of normal; LLN=lower limit of normal
Error bars are \pm the standard error of the mean

A composite endpoint was also analyzed defining responders as having an AP level of $<1.67 \times \text{ULN}$ that had decreased at least 15% from their Baseline 2 level and a total bilirubin value within the normal range. Results for the composite endpoint of AP and total bilirubin supported those for the primary study endpoint. 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 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).

Both MBX-8025 treatment groups showed significantly greater LSmean percentage reductions from Baseline 2 in GGT levels at the end of treatment than did the placebo group. The MBX-8025 200 mg group had an LSmean reduction 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). The MBX-8025 treatment groups had comparable LSmean percentage reductions from Baseline 2 in GGT levels (LSmean difference 4.56%, $p = 0.7155$). These results support and confirm results for 5' nucleotidase levels.

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 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 did not achieve statistical significance (LSmean difference 12.00%, $p = 0.1459$). The LSmean percentage change from Baseline 2 in the MBX-8025 50 mg treatment groups at the end of treatment was significantly

different from that in the MBX-8025 200 mg group (LSmean difference 18.19%, $p = 0.0407$).

Both MBX-8025 treatment groups also showed LSmean increases from Baseline 2 in ALT levels at the end of treatment, while LSmean ALT was reduced in the placebo group. The MBX-8025 200 mg group had an LSmean increase of 181.11% (SE 77.864) at the end of treatment and the MBX-8025 50 mg group had an LSmean increase of 111.83% (SE 68.061). There was an LSmean reduction of 4.67% (SE 69.632) in the placebo group. Although the LSmean percentage changes from Baseline 2 were numerically larger in the MBX-8025 treatment groups at the end of treatment compared with the placebo group, these differences did not achieve statistical significance (LSmean difference 116.50%, $p = 0.2409$ for the MBX-8025 50 mg group and LSmean difference 185.5%, $p = 0.0849$ for the MBX-8025 200 mg group compared to placebo). The LSmean percentage change from Baseline 2 in the MBX-8025 200 mg group was also numerically larger than that in the MBX-8025 50 mg group, the difference did not achieve statistical significance (LSmean difference 69.28%, $p = 0.5154$).

Both MBX-8025 treatment groups also showed LSmean increases from Baseline 2 in AST levels at the end of treatment, while LSmean AST was reduced in the placebo group. The MBX-8025 200 mg group had an LSmean increase of 232.69% (SE 77.049) at the end of treatment and the MBX-8025 50 mg group had an LSmean increase of 130.81% (SE 66.933). There was an LSmean reduction of 2.02% (SE 69.364) in the placebo group. Although the LSmean percentage changes from Baseline 2 were numerically larger in both MBX-8025 treatment groups at the end of treatment compared with the placebo group, only the difference between the MBX-8025 200 mg group and the placebo group achieved statistical significance (LSmean difference 234.71%, $p = 0.0322$). The LSmean percentage change from Baseline 2 in the MBX-8025 200 mg group was also numerically larger than that in the MBX-8025 50 mg group, although the difference did not achieve statistical significance (LSmean difference 101.88%, $p = 0.3326$).

It is notable that the mean increases in transaminases in the MBX-8025 groups were driven upward by 3 subjects who had NCI CTCAE Grade 3 transaminase increases (2 in the MBX-8025 200 mg group and 1 in the MBX-8025 50 mg group).

Both MBX-8025 treatment groups had LSmean reductions from Baseline 2 in TG at the end of treatment. The MBX-8025 200 mg group had an LSmean reduction of 7.11% (SE 9.415), the MBX-8025 50 mg group had an LSmean reduction of 30.27% (SE 8.243). The placebo group had an LSmean increase at the end of treatment of 7.04% (SE 8.617). The LSmean percentage change in TG at the end of treatment in the MBX-8025 50 mg group was significantly greater than that in the placebo group (LSmean difference 37.31%, $p = 0.0039$). Although the LSmean percentage change in the MBX-8025 200 mg group was numerically larger than that in the placebo group, this between-group difference did not achieve statistical significance (LSmean difference 14.15%, $p = 0.2777$). LSmean percentage changes were not significantly different between the MBX-8025 treatment groups (LSmean difference 23.16%, $p = 0.0734$).

Both MBX-8025 treatment groups showed greater LSmean percentage reductions from Baseline 2 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 LSmean percent reduction from Baseline 2 in LDL-C was significantly greater for the MBX-8025 200 mg group at the end of treatment than that for the placebo group (LSmean difference 14.85%, $p = 0.0186$). The LSmean percent reduction from Baseline 2 in LDL-C was numerically greater for the MBX-8025 50 mg group at the end of treatment than that

for the placebo group, but the difference did not achieve statistical significance (LSmean difference 10.06%, $p = 0.0745$). The LSmean percent reduction from Baseline 2 in LDL-C was also numerically greater for the MBX-8025 200 mg group at the end of treatment than that for the MBX-8025 50 mg group, but the difference did not achieve statistical significance (LSmean difference 4.80%, $p = 0.4131$).

hs-CRP levels were reduced in response to MBX-8025 treatment. Median Baseline 2 hs-CRP values were 2.650 mg/mL, 3.700 mg/mL, and 4.850 mg/mL in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively. Median percentage changes from Baseline 2 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-8025 50 mg and MBX-8025 200 mg groups, respectively.

LSmean changes from Baseline 2 to the end of treatment in Pruritus VAS scale scores were not significantly greater in the MBX-8025 groups than in the placebo group (LSmean difference 9.0, $p = 0.3236$ for the MBX-8025 50 mg group compared with placebo and LSmean difference 7.4, $p = 0.4674$ for the MBX-8025 200 mg group compared with placebo). The LSmean increases in the MBX-8025 treatment groups were comparable (LSmean difference 1.6, $p = 0.8723$). There was variation in mean Pruritus VAS scores values in all treatment groups over the course of the study visits, but significant differences were not observed between the treatment groups. LSmean changes from baseline in 5-D Itch Scale score from Baseline 2 to the end of treatment were not significantly different in the MBX-8025 groups than in the placebo group. LSmean changes from baseline in PBC-40 Itch score from Baseline 2 to the end of treatment were not significantly different in the MBX-8025 groups than in the placebo group. Similarly, neither MBX-8025 treatment group showed a significantly different LSmean change in 5-D Itch Scale or PBC-40 Itch domain scores than 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 7α -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).

Median percentage changes in cholic acid from Baseline 2 at the last observation on treatment were an increase of 47.88% in the placebo group and decreases of 11.97% and 38.01% in the MBX-8025 50 mg and MBX-8025 200 mg groups, respectively. Median percentage changes in chenodeoxycholic acid from Baseline 2 at the last observation on treatment were decreases of 16.45%, 5.85%, and 23.78% in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively. The median percentage changes from Baseline 2 in deoxycholic acid at the end of treatment were decreases of 10.4%, 40.83%, and 71.54% in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively. Median lithocholic acid level also appeared to decrease. Median percentage changes in lithocholic acid from Baseline 2 at the last observation on treatment were decreases of 13.06% and 31.22% in the MBX-8025 50 mg and MBX-8025 200 mg groups, respectively. There was no median increase or decrease in the placebo group.

Overall, total bile acid levels were not substantially affected by MBX-8025 treatment. Median percentage changes in total bile acids from Baseline 2 at the last observation on treatment were

increases of 0.47% and 15.14% in the placebo and MBX-08025 50 mg groups, respectively, and a decrease of 4.94% in the MBX-8025 200 mg group.

Safety Results:

There were no deaths or treatment-emergent serious adverse events (SAEs) during the study.

Four subjects were discontinued from treatment due to TEAEs; all were in the MBX-8025 treatment groups.

Three subjects developed NCI CTCAE Grade 3 liver transaminase elevations (ALT >3.0-20.0xULN) and discontinued treatment. The first subject had a repeat transaminase evaluation while on treatment and as ALT were not decreasing blinded treatment was discontinued. The other 2 subjects had their blinded treatment immediately discontinued upon the documentation of ALT elevations. Of these subjects with Grade 3 transaminases elevation, 2 were receiving MBX-8025 200 mg (one case was considered drug related and the other possibly drug related). One subject was receiving MBX-8025 50 mg (considered possibly study medication related). For these 3 subjects, the clinical picture was similar. The transaminases elevations were documented at the first active treatment planned protocol visit, after 2 weeks of treatment. The transaminases elevations were asymptomatic, not associated with an abnormal increase in bilirubin, and fully reversible upon treatment discontinuation. Of note, the transaminases elevations were associated with a decrease in biochemical markers of cholestasis (AP and GGT).

One subject discontinued treatment because of an AE of myopathy. The subject was taking MBX-8025 200 mg. The subject had liver cirrhosis documented with a liver biopsy more than 10 years before being enrolled in the study and was on multiple concomitant medications including propranolol, spironolactone, torsemide and pantoprazole. The AE was characterized by acute muscle pain that started 8 days after initiating treatment and was associated with an elevation of muscle enzymes (peak CK 4,062 U/L, 19.3-fold ULN). The AE was reversible upon treatment discontinuation and was considered possibly related to treatment.

Apart from the events previously described, there were no other AEs of NCI CTCAE grade 3 or above.

The most common AEs were pruritus (occurring in 1 [7.7%], 4 [30.8%], and 1 [8.3%] subjects in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively), nausea (occurring in 1 [7.7%], 3 [23.1%], and 1 [8.3%] subjects in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively), and diarrhea (occurring in 2 [15.4%], 3 [23.1%], and 1 [8.3%] subjects in the placebo, MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively). Dyspepsia, muscle spasms, myalgia, and dizziness each occurred in 3 subjects (7.9%) across all groups. There were no apparent differences in the distribution of AEs apart from muscle related AEs myalgia/muscle spasms/musculoskeletal pain when grouped together. One of these AEs occurred in one subject in the placebo group, one subject in the MBX-8025 50 mg group, and in four subjects in MBX-8025 200 mg group (including the subject who discontinued due to myopathy).

Of the 20 subjects with TEAEs considered possibly related or related to study medication, 3 had drug-related pruritus. Of these, 1 was in the placebo group and 2 were in the MBX-8025 50 mg group. No subject in the MBX-8025 200 mg group had pruritus considered related to study medication.

MBX-8025 was associated with dose-dependent elevation of serum homocysteine and serum

creatinine. The mean percentage changes from Baseline 2 to Visit 6 (Week 12) in serum creatinine were a decrease of 4.39% (SD 7.529, SE 3.764, n = 4) for the placebo and increases of 1.89% (SD 10.786, SE 4.823, n = 5) and 23.47% (SD 21.719, SE 15.358, n = 2) MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively.

Three subjects developed serum creatinine above normal range, 2 in the MBX-8025 200 mg group and 1 in the MBX-8025 50 mg group:

- One subject in the MBX-8025 200 mg group had an increase in serum creatinine from 0.85 mg/dL to 1.18 mg/dL (ULN 1.12 mg/dL) at Week 2.
- Another subject in the MBX-8025 200 mg group had an increase in serum creatinine from 0.93 mg/dL to 1.49 mg/dL (ULN 1.12 mg/dL) concomitant with an NCI CTCAE Grade 3 ALT elevation. The Investigator considered this elevation as an AE of acute kidney injury that was possibly related to treatment. In all cases, the serum creatinine returned to normal upon treatment discontinuation.
- One subject in the MBX-8025 50 mg group had an increase in serum creatinine from 0.99 mg/dL to 1.19 mg/dL (ULN 1.12 mg/dL) at Week 2. The subject's creatinine levels were within the normal range for the remainder of the study.

The mean percentage changes from Baseline 2 in serum homocysteine at the end of treatment were a decrease of 7.78% (SD 7.111, SE 2.370) for the placebo and increases of 30.91% (SD 17.653, SE 5.884) and 77.00% (SD 43.815, SE 17.888), MBX-8025 50 mg, and MBX-8025 200 mg groups, respectively.

There were no clinically significant differences between the treatment groups in hematology, ECG, or physical examination results.

Conclusions:

- MBX-8025 treatment, at both doses evaluated, reduces biochemical markers of cholestasis, including AP, GGT, and 5'-nucleotidase. All subjects treated for 12 weeks achieved AP levels within the normal range.
- The anticholestatic activity of MBX-8025 treatment is at least partly attributable to a suppression of bile acid synthesis.
- MBX-8025 treatment was associated with a dose-dependent elevation in transaminases. This signal was not observed in prior clinical studies in other subject populations with normal hepatic function.
- Besides elevation in transaminases, MBX-8025 was generally well tolerated. There is no evidence that MBX-8025 induces or worsens pruritus.
- Based on the high levels of efficacy and the absence of dose response between the MBX-8025 50 mg and 200 mg groups, the MBX-8025 doses tested may have been higher than necessary to achieve optimal efficacy and safety.

Date of Report: 26 April 2017