2 SYNOPSIS

Sponsor: CymaBay Therapeutics, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
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Study Title:
Study Number CB8025-21427: A 12-week, open-label, dose-escalating, phase 2 study to evaluate the effects of MBX-8025 in patients with Homozygous Familial Hypercholesterolemia (HoFH)

Investigators and Study Centers: The Principal Investigators and their affiliated institutions were as follows:

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- Eric Bruckert, MD, PhD; Institut E3M et IHU cardiometabolique (ICAN), Hôpital Pitié Salpêtrière, Paris, France
- Dr. J de Graaf; Radboud UMC, Nijmegen, the Netherlands
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Publication:

Gaudet D, Saheb S, Bruckert E, de Graaf J, Langslet G, Tardif J-C, Bergheanu SC, Steinberg A, Choi Y-J, Martin R, McWherter C, Kastelein J, Boudes P. A pilot study of MBX-8025 in the treatment of homozygous familial hypercholesterolemia (HoFH). 84th European Atherosclerosis Society Congress, Innsbruck, Austria. May 29-June 1, 2016; Abstract EAS16-1024.

Studied Period:
11 June 2015 (first subject informed consent), to
15 February 2016 (last subject completed)

Phase of Development: 2

Objectives:
Primary
The primary objective of this study was to evaluate the effect of MBX-8025 on low-density lipoprotein-cholesterol (LDL-C).

Secondary
The secondary objectives of this study were to:

- Evaluate the effects of MBX-8025 on other lipid metabolism parameters.
- Evaluate the safety and tolerability of MBX-8025 in patients with HoFH.
- Evaluate steady-state trough plasma levels of MBX-8025 and its metabolites, M1, M2 and M3

Exploratory
To evaluate the effects of MBX-8025 on proprotein convertase subtilisin/kexin type 9 (PCSK-9) and high-sensitivity C-reactive protein (hs CRP).

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Methodology:

This was an international, multicenter study in male and female subjects with HoFH. The study had an open-label, single-arm, dose-escalating (50, 100, and 200 mg/day) design, with 3 consecutive treatment periods. Subjects had confirmed mutations in the low-density lipoprotein receptor (*LDL-R*) gene.

The screening period was a maximum of 2 weeks. All subjects had to confirm eligibility on Visit 2 (Week 0) prior to entering the run-in period. The run-in period was 14 days, Weeks 0 to 2. At the end of the run-in period, subjects entered the treatment phase, 3 periods of 4 weeks (Weeks 2 to 14), equal to 84 days. A 14-day follow-up period concluded the study (Weeks 14 to 16). The total duration per subject was a maximum of 18 weeks.

During the run-in period, subjects were treated with placebo, which was dispensed at Week 0. At the end of the run-in period, subjects were dispensed 50 mg MBX-8025 daily; treatment commenced immediately and was ongoing for 4 weeks. At the end of the 4 weeks, the Principal Investigator (PI) evaluated the available safety and tolerability data:

- In the absence of adverse events (AEs), or if AEs were mild or moderate and, according to the Principal Investigator, not related to the study drug, the subject escalated the dose of MBX-8025 to 100 mg once daily.
- If AEs were mild or moderate and deemed related to the study drug by the Principal Investigator, OR if AEs were severe, but deemed not related to the study drug, the Principal Investigator had the options to: (1) maintain the subject on 50 mg MBX-8025 once daily, OR (2) in consultation with the Data Safety Monitoring Board (DSMB), to escalate to 100 mg MBX-8025 once daily.
- If AEs were severe and drug related, the subject stopped treatment and entered the follow-up period.

At the end at the second 4-week treatment period, the Principal Investigator again evaluated safety and tolerability data:

- In the absence of AEs, or if AEs were mild or moderate and, according to the Principal Investigator, not related to the study drug, the subject escalated the dose of MBX-8025 to 100 mg once daily if the subject was on 50 mg once daily, OR to 200 mg once daily if the subject was on 100 mg once daily.
- If AEs were mild or moderate and deemed related to the study drug by the Principal Investigator, OR if AEs were severe but deemed not related to the study drug, the Principal Investigator had the options to: (1) maintain the subject on his current dose of 50 or 100 mg MBX-8025 once daily, OR (2) decrease the dose of MBX-8025 from 100 mg to 50 mg once a day, OR (3) in consultation with the DSMB, to escalate the dose of MBX-8025 from 50 mg to 100 mg, or from 100 mg to 200 mg, once daily.
- If AEs were severe and drug related, the subject stopped treatment and entered the follow-up period.

At the end of the third 4-week treatment period, subjects entered the 2-week follow-up period.

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Number of Subjects (Planned and Analyzed):
Approximately 10 subjects were planned; 13 subjects were analyzed for safety, and 12 subjects were analyzed for efficacy.

Diagnosis and Main Criteria for Inclusion/Exclusion:

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

1. Must have given written informed consent (signed and dated) and any authorizations required by local law and have been able to comply with all study requirements.
2. Male or female with HoFH confirmed by genotype (two mutant alleles at the LDL-receptor (*LDL-R*) gene locus or double heterozygotes *LDL-R*/*apolipoprotein B* [apo B]).
3. 18 years of age or older.
4. Existing lipid lowering therapies (statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid and their combinations, LDL-C apheresis) on a stable regimen for at least four weeks before screening visit.
5. Stable lipid lowering diet compatible with a Step I diet of the AHA.
6. Fasting LDL-C ≥ 4.8 mmol/L (≥ 185.6 mg/dL) during screening.
7. For females or males of reproductive potential, use of at least one barrier contraceptive and a second effective birth control method during the study and for at least two weeks after the last dose.

Any of the following criteria excluded a subject from enrollment into the study:

1. Treatment with lomitapide or mipomersen within two months of screening.
2. Heart failure with New York Heart Association (NYHA) class III and class IV or a left ventricular ejection fraction (LVEF) of less than 30%.
3. Uncontrolled cardiac arrhythmia during the past three months of screening.
4. Myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass graft or stroke during the past three months of screening.
5. Planned cardiac surgery, or planned revascularization, in the next four months.
6. Uncontrolled hypertension.
7. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal (ULN).
8. Unexplained creatine kinase (CK) ≥ 5 times the ULN.
9. For females, pregnancy or breast-feeding.
10. Any other condition(s) that would compromise the safety of the patient or compromise the quality of the clinical study as judged by the Investigator and/or Medical Monitor.

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Test Product, Dose and Mode of Administration, Lot Number: The test product was MBX-8025 capsules (50 or 100 mg). Dosing was oral (PO), once daily, in doses of 50 (first 4-week treatment period, 100 (second 4-week treatment period), and 200 mg (third 4-week treatment period). The 50 mg MBX-8025 test product was batch number 14G059, and the 100 mg MBX-8025 test product was batch number 14G060.

The placebo treatment was administered PO once daily and only during the run-in period. The placebo was a gelatin capsule, containing all ingredients in the investigational product, except for the active pharmaceutical ingredient, MBX-8025. Only 1 batch of placebo was used: batch number 14G058.

Duration of Treatment: The planned duration of treatment for each subject was 12 weeks.

Reference Therapy, Dose and Mode of Administration, Lot Number: No reference therapy was used in this study.

Criteria for Evaluation:

Efficacy

The primary efficacy measures were absolute and percentage reduction in serum LDL-C at the visits from baseline through Week 16. For subjects receiving LDL-C apheresis, efficacy was evaluated on the basis of pre-apheresis lipid levels.

Secondary efficacy measures were absolute and percentage changes at the visits from baseline through Week 16 for the following: total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), very-low-density lipoprotein cholesterol (VLDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), remnant lipoprotein cholesterol (RLP-C), apolipoprotein B (apo B), apolipoprotein A-I (apo A-I), lipoprotein (a), serum triglycerides (TG), and apolipoprotein C-III (apo C-III).

Exploratory efficacy measures were absolute and percentage change at the visits from baseline through Week 16 for PCSK-9 and hs-CRP.

Safety

The safety and tolerability endpoints were assessed by evaluating AEs, vital signs, physical examinations, clinical laboratory tests (blood chemistry and hematology), electrocardiograms (ECGs), and use of concomitant medications. Any laboratory abnormality deemed clinically significant by the Investigator was considered an AE. Adverse events were recorded at any time after the time of signed informed consent and captured until the End-of-Study (EOS) visit (Week 16). Adverse events were classified according to seriousness, expectedness, relationship to MBX-8025, severity, duration, and action taken with MBX-8025.

Any laboratory abnormality that the Investigator deemed clinically significant was considered an AE.

Pharmacokinetics

Blood samples for the plasma concentrations of MBX-8025 and its metabolites (M1, M2, and M3) were collected pre-dose at Visits 4 (Week 4), 5 (Week 6), 6 (Week 8), 7 (Week 10), 8 (Week 12), and 9 (Week 14).

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Statistical Methods:

Efficacy/Pharmacodynamic: The efficacy population was the population of interest for the efficacy and pharmacodynamic data. For each lipid parameter, the following values were calculated using all the data recorded while a subject received a particular dose level of MBX-8025, generally through Week 14:

- Minimum value for the dose level for all tests, except HDL-C and apo A-I; for HDL-C and apo A-I, the maximum value was used.
- Last value for the dose level.
- Mean of all values for the dose level.

The changes and percentage changes from Baseline were calculated for these parameters and were summarized for each MBX-8025 dose level and by apheresis status (apheresis or no apheresis subgroups). Baseline 1 values were defined as Visit 3 (Week 2) values, or most recent value obtained during the screening and run-in periods prior to the first dose of MBX-8025. Other definitions of baseline were exploratory.

The numbers and percentages of subjects with at least a 15%, 20%, 25%, or 30% reduction in LDL-C were summarized for each dose level and by apheresis status. The percentage change in LDL-C was used to classify subjects as responders or non-responders. As exploratory analyses, response rates in the apheresis subgroup were compared with the non-apheresis subgroup using Fisher's exact test within each dose level.

Safety: Adverse event terms were mapped to preferred terms (PTs) and assigned to a system organ class (SOC) using the *Medical Dictionary for Regulatory Activities* (MedDRA). A treatment-emergent adverse event (TEAE) was defined as an adverse event with an onset or an increase in severity level after the initial dose of MBX-8025. TEAEs were summarized based on the number of subjects who experienced events. The denominator for these percentages was based on the number of subjects in the safety population. Summaries were provided for each dose level for all subjects and by apheresis subgroup. The MBX-8025 dose that a subject was receiving at AE onset was used for the summaries.

Summaries displayed by SOC and PT were ordered by decreasing incidence. Summaries of TEAEs and treatment-related AEs were also provided. Listings were provided for deaths, serious adverse events (SAEs), and AEs/TEAEs leading to discontinuation of MBX-8025; narratives were presented for SAEs, MBX-8025 discontinuation, and study discontinuation due to AEs.

Pharmacokinetics: The plasma concentrations of MBX-8025 and its metabolites (M1, M2, and M3) were summarized at Visits 4 (Week 4), 5 (Week 6), 6 (Week 8), 7 (Week 10), 8 (Week 12), and 9 (Week 14).

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Summary of Results:

Subject Disposition

A total of 13 subjects were enrolled, received treatment, and completed this study. Thirteen subjects were in the safety population, and 12 subjects were in the efficacy population. Subject 440-01, in the apheresis subgroup, was excluded from the efficacy population, because he missed multiple apheresis sessions during the study that resulted in marked LDL-C fluctuations.

All 13 subjects completed the MBX-8025 dosing periods at 50 and 100 mg, and 10 subjects completed the 200 mg MBX-8205 dosing period. Of the 13 subjects in the safety population, 8 subjects underwent apheresis, and 5 did not undergo apheresis. Eight subjects in the apheresis group and 5 in the non-apheresis group were treated with 50 mg and 100 mg MBX-8025; 6 subjects in the apheresis group and 4 in the non-apheresis group were treated with 200 mg MBX-8025.

Study completion was defined as completion of the 2-week follow-up period, and all 13 subjects completed the study. Three of 13 subjects discontinued MBX-8025 due to a TEAE; 2/8 subjects were in the apheresis group and 1/5 was in the non-apheresis group. The TEAEs of joint pain and right shoulder pain were in the apheresis group, and the worsening of stable angina pectoris was in the non-apheresis group.

Subject Demographics and Baseline Characteristics

There were 8 male and 5 female subjects. The subjects' mean age was 41.2 years. Their mean height was 171.5 cm, mean weight was 79.6 kg, and mean body mass index (BMI) was 26.5 kg/m^2.

In the apheresis subgroup, 5/8 subjects were male and 3/8 were female, and the mean age in this group was 33.6 years. In the non-apheresis subgroup, 3/5 subjects were male and 2/5 were female; the mean age was 53.2 years.

In the apheresis group, 6 subjects received apheresis on a biweekly schedule, and 2 subjects received weekly apheresis.

All enrolled subjects had confirmed HoFH, 12 subjects had functionally defective mutations, and 2 subjects had functionally negative mutations in the *LDL-R* gene. Furthermore, 12 of 13 subjects had cardiovascular pathology. All subjects were taking stable lipid-lowering therapy and receiving maximum tolerated doses of statins and ezetimibe. No subjects were treated with lomitapide, mipomersen, or PCSK-9 inhibitors.

Despite all subjects' being treated with maximum tolerated doses of conventional lipid-lowering therapy prior to this study, their mean Baseline 1 LDL-C was 374.5 mg/dL, with a range of 273.0 to 522.0 mg/dL (normal range 50 to 130 mg/dL). The mean baseline LDL-C was 395.9 mg/dL for the apheresis group and 344.6 mg/dL for the non-apheresis group.

Efficacy

Primary Efficacy Outcome: The study accomplished its primary objective—to evaluate the activity of MBX-8025 on LDL-C in subjects with HoFH. Per-protocol analyses were performed on 12/12 subjects in the efficacy population; 7/12 subjects were receiving concomitant apheresis.

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For all subjects on MBX-8025 treatment, the mean maximum decrease in LDL-C was -18.7%; the overall mean decrease from Baseline 1 was -9.6%; and the mean last value decrease on treatment for LDL-C was -8.7%.

The mean maximum decrease in LDL-C from Baseline 1 by MBX-8025 dose was -13.2% for subjects taking 50 mg MBX-8025, -10.5% for those taking 100 mg, and -10.7% for those taking 200 mg. The mean decrease was -8.7% in subjects taking 50 mg MBX-8025, -8.9% in subjects taking 100 mg, and -6.2% in subjects taking 200 mg.

The apheresis group had a mean Baseline 1 LDL-C of 395.9 mg/dL; for the non-apheresis group, the mean Baseline 1 LDL-C was 344.6 mg/dL. The mean maximum percentage LDL-C decrease was -21.0% for the apheresis group and -15.5% for the non-apheresis group.

Three of 12 subjects had a ≥ 30% decrease in LDL-C. Five of 12 subjects had a ≥ 20% decrease, including 1 subject who was LDL-R negative, and 7/12 subjects had a ≥ 15% decrease. Five of 12 subjects had a < 15% decrease in LDL-C. For the subjects with a ≥ 15% decrease, the corresponding absolute mean decrease in LDL-C was -109 mg/dL.

No clear dose response was seen for LDL-C. Also, none of the 12 subjects taking 50 mg MXB-8025, 2/12 taking 100 mg, and 1/9 taking 200 mg had a ≥ 30% decrease in LDL-C. Three of 12 subjects taking 50 mg MBX-8025, 2/12 taking 100 mg, and 2/9 taking 200 mg had a ≥ 20% decrease in LDL-C. Five of 12 subjects taking 50 mg MBX-8025, 4/12 taking 100 mg, and 3/9 taking 200 mg had a ≥ 15% reduction in LDL-C.

Two of 7 subjects in the apheresis group and 1/5 subject in the non-apheresis group had a ≥ 30% decrease in LDL-C. Four of 7 subjects in the apheresis group and 1/5 subject in the non-apheresis group had a ≥ 20% decrease; 5/7 subjects in the apheresis group and 2/5 in the non-apheresis group had a ≥ 15% decrease. Two of 7 subjects in the apheresis group and 3/5 in the non-apheresis group had a < 15% decrease in LDL-C level. The mean maximum decreases were -21.0% for subjects in the apheresis group and -15.5% in the non-apheresis group. The mean decrease in LDL-C was -11.7% for subjects in the apheresis group and -6.6% in the non-apheresis group. No clear response difference was seen between the apheresis and the non-apheresis groups.

Selected Secondary Efficacy Outcomes

Total Cholesterol

Overall, subjects had a mean Baseline 1 TC of 439.8 mg/dL, with a range of 319.0 to 576.0 mg/dL (normal range, 100 to 200 mg/dL).

For all subjects on MBX-8025 treatment, the mean maximum decrease in TC was -18.0%; the overall mean decrease from Baseline 1 was -9.0%; and the mean last value TC decrease was -9.9%.

The mean maximum decrease in TC from Baseline 1 by MBX-8025 dose was -11.8% for subjects taking 50 mg, -10.3%, for those taking 100 mg, and -9.7%, for those taking 200 mg. The mean decrease was -7.8% in subjects taking 50 mg MBX-8025, -8.7% in subjects taking 100 mg, and -6.6% in subjects taking 200 mg.

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The apheresis group had a mean baseline TC, using Baseline 1, of 395.9 mg/dL; for the non-apheresis group, the mean baseline TC was 344.6 mg/dL. The mean maximum percentage TC decrease was -20.0% for the apheresis group and -15.1% for the non-apheresis group.

HDL-C

Overall, subjects had a mean Baseline 1 HDL-C of 37.8 mg/dL (normal range, 35 to 60 mg/dL), with a range of 21.0 to 49.0 mg/dL.

For all subjects on MBX-8025 treatment, the mean maximum increase in HDL-C was 6.6%; the overall mean decrease from Baseline 1 was -7.4%; and the mean last value decrease on treatment for HDL-C was -17.0%.

By MBX-8025 dose, the mean maximum increase in HDL-C from Baseline 1 was 5.4% for subjects taking 50 mg; the mean maximum decrease was -4.8%, for those taking 100 mg and -13.6% for those taking 200 mg. The mean change was 0.0% in subjects taking 50 mg MBX-8025; the mean decrease was -10.5% in subjects taking 100 mg and -15.2% in subjects taking 200 mg.

The apheresis group had a mean baseline HDL-C, using Baseline 1, of 36.0 mg/dL; for the non-apheresis group, the mean baseline HDL-C was 40.4 mg/dL. The mean maximum percentage increase in HDL-C was 7.9% for the apheresis group and 4.9% for the non-apheresis group.

Apolipoprotein B

Overall, subjects had a mean Baseline 1 apo B of 232.8 mg/dL, with a range of 156.0 to 311.0 mg/dL (normal range, 55 to 105 mg/dL).

For all subjects on MBX-8025 treatment, the mean maximum decrease in apo B was -17.9%; the overall mean decrease from Baseline 1 was -9.0%; and the mean last value decrease on treatment for apo B was -9.1%.

By MBX-8025 dose, the mean maximum decrease in apo B from Baseline 1 was -11.5% for subjects on 50 mg MBX-8025, -10.6%, for those on 100 mg, and -11.6%, for those on 200 mg. The mean decrease was -8.0% in subjects on 50 mg MBX-8025, -8.1% in subjects on 100 mg, and -6.7% in subjects on 200 mg.

The apheresis group had a mean Baseline 1 apo B of 245.9 mg/dL; for the non-apheresis group, the mean Baseline 1 apo B was 214.6 mg/dL. The mean maximum percentage decrease in apo B was -21.3% for the apheresis group and -13.0% for the non-apheresis group.

Apolipoprotein A-I

Overall, subjects had a mean Baseline 1 apo A-I of 109.5 mg/dL, with a range of 73.0 to 132.0 mg/dL (normal laboratory values for apo A-I range from 125 to 215 mg/dL for females, and 110 to 205 mg/dL for males).

For all subjects on MBX-8025 treatment, the mean maximum increase in apo A-I was 8.4%; the overall mean decrease from Baseline 1 was -6.1%; and the mean last value decrease on treatment for apo A-I was -13.5%.

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The mean maximum increase in apo A-I from Baseline 1 by MBX-8025 dose was 6.9% for subjects taking 50 mg; the mean maximum decrease was -3.0%, for those taking 100 mg and -11.2% for those taking 200 mg. The mean increase was 1.3% in subjects taking 50 mg MBX-8025; the mean decrease was -9.7% in subjects taking 100 mg and -13.6% in subjects taking 200 mg.

The apheresis group had a mean Baseline 1 apo A-I of 101.9 mg/dL; for the non-apheresis group, the mean Baseline 1 apo A-I was 120.2 mg/dL. The mean maximum percentage apo A-I increase was 9.6% for the apheresis group and 6.8% for the non-apheresis group.

Exploratory Outcomes

Overall, subjects had a mean baseline PCSK-9 of 550.7 ng/mL, with a range from 261.9 to 708.0 ng/mL (normal range, 177.0 to 460.0 ng/mL).

PCSK-9 increased during MBX-8025 treatment: the mean maximum increase was 383.9 ng/mL, or 76.6%, and the mean increase was 214.7 ng/mL, or 42.6%.

The mean maximum increase was 263.7 ng/mL, or 47.7%, for subjects on 50 mg MBX-8025; 252.1 ng/mL, or 55.1%, for subjects on 100 mg; and 310.5 ng/mL, or 76.3%, for subjects on 200 mg. The mean increases were 189.6 ng/mL, or 34.9%, for subjects on 50 mg; 185.7 ng/mL, or 40.3%, for subjects on 100 mg; and 244.1 ng/mL, or 62.4%, for subjects on 200 mg MBX-8025. These PCSK-9 changes could suggest a dose response.

Using Baseline 1, the mean PCSK-9 was 506.5 ng/mL in the apheresis group and 612.6 ng/mL in the non-apheresis group. The mean maximum increase was 427.3 ng/mL, or 93.2%, in the apheresis group and 323.2 ng/mL, or 53.4%, in the non-apheresis group. The mean increase was 260.7 ng/mL, or 55.4%, in the apheresis group and 150.4 ng/mL, or 24.7%, in the non-apheresis group.

Safety

No deaths occurred during the study.

Three SAEs were reported during the study; an SAE of chest pain occurred in Subject 420-04 prior to his receiving study drug; SAEs of angina pectoris occurred in Subject 440-01 during study drug administration (serious TEAEs), and both were judged by the PI to have an unlikely relationship to study drug; an SAE of apheresis shunt occlusion in Subject 460-01, which occurred during MBX-8025 administration, was judged by the PI as having an unlikely relationship to MBX-8025.

Three subjects reported TEAEs that led to study drug discontinuation. In the non-apheresis group, Subject 300-01 was discontinued from 100 mg MBX-8025 due to worsening of stable angina pectoris. The subject had a history of multiple myocardial infarctions, cardiac arrhythmia, hypertension, and preexisting angina pectoris. The subject was treated and recovered; the PI assessed the event as moderate in severity, with a possible relationship to MBX-8025. Two subjects in the apheresis group had TEAEs that led to study drug discontinuation: (1) Subject 420-01 was discontinued from 100 mg MBX-8025 due to arthralgia and musculoskeletal pain. No additional treatment was given, and the subject recovered. The PI assessed the event as moderate in severity, with a possible relationship to MBX-8025. (2) Subject 420-02 was discontinued from 200 mg MBX-8025 due to musculoskeletal pain. No additional treatment was given, and the subject recovered. The PI assessed the event as mild in severity, with a possible relationship to MBX-8025.

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The most commonly reported TEAE was nasopharyngitis (5/13 subjects).

Two severe TEAEs (viral gastroenteritis and apheresis shunt occlusion) were judged by the investigator as having an unlikely relationship to MBX-8025. The apheresis shunt occlusion event was also listed as an SAE for Subject 460-01; it occurred during MBX-8025 administration and the PI judged the event as having an unlikely relationship to MBX-8025.

For all subjects, there was a mean -24.3% decrease in ALT, and a mean 5.3% increase in AST. No increase in ALT or AST > 3 × ULN was observed. Other liver function mean changes included a -28.6% decrease in AP, a -28.3% decrease in GGT, and a -18.4% decrease in TB.

Muscle toxicity was carefully monitored during the study, notably because all subjects were receiving concomitant maximum tolerated doses of statins. Two subjects discontinued MBX-8025 due to muscle-related AEs: Subject 420-01 had arthralgia and musculoskeletal pain, and Subject 420-02 had musculoskeletal pain. However, no increase was observed in CK or aldolase, and the origin of the pain could have been purely from articular joints. Both events were judged as having a possible relationship to MBX-8025.

Overall, no significant changes were seen in CK and aldolase. Among all doses, and regardless of apheresis status, the mean CK increase was 3.0%, and the mean aldolase increase was 2.9%.

A dose-related increase was documented for serum creatinine: the mean increase in creatinine was 9.0% for subjects on 50 mg MBX-8025, 12.1% for subjects on 100 mg, and 19.1% for subjects on 200 mg. Shifts in serum creatinine were generally within normal values. Subject 300-01, an 81-year-old female, had a known chronic renal insufficiency with an elevated serum creatinine from Screening through the entire study (levels ranged from 1.2 to 1.9 mg/dL [normal range for females, 0.5 to 1.1 mg/dL]); while taking 100 mg MBX-8025, she had a maximum increase from Baseline 1 of 0.5 mg/dL (1.7 × ULN).

CONCLUSIONS

Efficacy conclusions:

- MBX-8205 treatment led to an LDL-C-lowering effect for some subjects: 7/12 subjects had a ≥ 15% decrease in LDL-C levels, and 3/12 subjects had a ≥ 30% decrease.
- No clear dose-response was observed with MBX-8025 treatment, and no factors were identified that could help to predict why a subject was a responder.
- MBX-8025 treatment increased the mean PCSK-9 concentration by 43% during treatment. This effect was not previously documented and may have attenuated the LDL-C-lowering effect, whether or not subjects had a response to MBX-8025.

Safety conclusions:

- In subjects with HoFH in whom daily doses were escalated from 50 mg to up to 200 mg, no consistent safety signal was elicited. Three subjects discontinued MBX-8025, due to TEAEs that were mild or moderate in intensity, and that had a possible relationship to MBX-8025.

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- No deaths or SAEs related to MBX-8025 occurred during the study.
- HDL-C decreased in a total of 9 subjects and was reported as a TEAE in 2 subjects. A causal relationship with MBX-8025 administration appeared possible. The clinical significance of this finding is uncertain.
- No other changes were identified in vital signs, physical examinations, ECG findings, or laboratory values that might possibly be related to MBX-8025 treatment.

Final Report Date: 12 January 2017