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Phase 1 Single and Multiple Ascending Dose Study of MBX 1416

Topline Results

January 7, 2025

Post-bariatric Hypoglycemia (PBH): a Rare, Serious and Chronic Complication of Bariatric Surgery

Estimated >90,000 patients in U.S.[1,2,3,4]

CAUSE[1,2]

Rapid transit of nutrients into intestines **stimulates excess GLP-1 and insulin secretion**; occurs after a meal

PBH presents six months to years after roux-en-Y gastric bypass and sleeve gastrectomy

SYMPTOMS

Severe Hypoglycemia

Neuroglycopenia symptoms including seizures, loss of consciousness, confusion, weakness, dizziness and blurred vision

PATIENT IMPACT

Unpredictable timing and frequency

Social isolation

Diminished quality of life, including disability

Glucagon injection may be required

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1. Fischer et al Surg Obes Relat Dis. 2021, 2. Michaels et al Obes Surg. 2017, 3. Lee et al Obesity 2015, 4. Internal Estimates

Managing PBH: No Currently Approved Pharmacotherapies

STANDARD OF CARE[1,2]

Includes restricted diet, off-label medications and surgery

Frequent, small meals and avoid/limit high glycemic index foods

- Limited efficacy and long-term adherence challenges

Off-label use of acarbose, diazoxide and octreotide

- Limited clinical data
- Side effect profiles and cost may limit patient adherence

IN DEVELOPMENT

Once-daily PBH investigational therapy

Avexitide

- GLP-1 receptor antagonist in Phase 3 development

MBX 1416

Once-weekly PBH investigational therapy

Designed to:

- Provide daily and nightly prevention of severe hypoglycemia and associated risks
- Offer convenient weekly dosing
- Improve QoL
- Eliminate need for rescue therapy (glucagon) and surgical intervention

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PBH=Post-bariatric Hypoglycemia; GLP-1=glucagon-like peptide-1; QoL=quality of life
1. Suhl E et al Surg Obes Relat Dis 2017, 2. Salehi M et al JCEM 2018

MBX 1416 Phase 1 Trial

Single and Multiple Ascending Doses of MBX 1416 in healthy adult subjects[1]

SAD (n=32) COMPLETE

- n=8 subjects/cohort (2 placebo: 6 active)
- Treatments: placebo or MBX 1416 dosed at 10, 30, 100 and 200 mg SC

MAD (n=23) COMPLETE

- n=up to 8 subject/cohort (2 placebo: 6 active)
- Treatments: placebo or MBX 1416 dosed at 10 mg, 15 mg in 2 injections, or 30 mg SC QW x 4

Endpoints

Primary:

- To evaluate safety and tolerability

Secondary:

- Pharmacokinetic (PK) profile of MBX 1416
- Pharmacodynamic (PD) – Response to Mixed Meal Tolerance Test (MAD)

A cohort (n=14) evaluated potential drug-drug interaction (DDI) of MBX 1416 on rosuvastatin exposure and on gastric emptying by using acetaminophen

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SC = subcutaneous; QW = once-weekly

1. ClinicalTrials.gov Identifier: NCT06036784;

MBX 1416 Phase 1 Results: Safety Data

Summary of Subject Demographics

	Part A - SAD						Part B - MAD					Part C - DDI
	MBX 1416 10 mg (N=6)	MBX 1416 30 mg (N=6)	MBX 1416 100 mg (N=6)	MBX 1416 200 mg (N=6)	Placebo (N=8)	All SAD Subjects (N=32)	MBX 1416 10 mg (N=6)	MBX 1416 30 mg (N=6)	MBX 1416 30 mg [R] (N=6)	Placebo (N=5)	All MAD Subjects (N=23)	MBX 1416 45 mg (N=14)
Age (years)												
Mean (SD)	36.3 (6.0)	51.8 (10.6)	35.7 (15.2)	40.3 (7.7)	44.4 (7.7)	41.9 (10.9)	38.3 (8.9)	39.3 (18.3)	36.0 (7.9)	47.0 (9.1)	39.9 (11.8)	35.9 (12.0)
Sex, (n %)												
Male	3 (50.0%)	4 (66.7%)	3 (50.0%)	1 (16.7%)	4 (50.0%)	15 (46.9%)	5 (83.3%)	4 (66.7%)	4 (66.7%)	5 (100.0%)	18 (78.3%)	8 (57.1%)
Female	3 (50.0%)	2 (33.3%)	3 (50.0%)	5 (83.3%)	4 (50.0%)	17 (53.1%)	1 (16.7%)	2 (33.3%)	2 (33.3%)	--	5 (21.7%)	6 (42.9%)
Race, (n %)												
Asian	1 (16.7%)	--	--	1 (16.7%)	--	2 (6.3%)	--	--	3 (50.0%)	2 (40.0%)	5 (21.7%)	--
Black or African American	1 (16.7%)	--	--	--	2 (25.0%)	3 (9.4%)	--	--	1 (16.7%)	--	1 (4.3%)	2 (14.3%)
Native Hawaiian or Other Pacific Islander	--	--	--	--	--	--	--	--	1 (16.7%)	--	1 (4.3%)	--
White	2 (33.3%)	6 (100.0%)	6 (100.0%)	4 (66.7%)	6 (75.0%)	24 (75.0%)	6 (100.0%)	6 (100.0%)	1 (16.7%)	3 (60.0%)	16 (69.6%)	12 (85.7%)
Other	2 (33.3%)	--	--	1 (16.7%)	--	3 (9.4%)	--	--	--	--	--	--
Ethnicity, (n %)												
Hispanic or Latino	3 (50.0%)	1 (16.7%)	4 (66.7%)	4 (66.7%)	2 (25.0%)	14 (43.8%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	2 (40.0%)	8 (34.8%)	5 (35.7%)
Not Hispanic or Latino	3 (50.0%)	5 (83.3%)	2 (33.3%)	2 (33.3%)	6 (75.0%)	18 (56.3%)	3 (50.0%)	4 (66.7%)	5 (83.3%)	3 (60.0%)	15 (65.2%)	9 (64.3%)
Weight (kg)												
Mean (SD)	71.6 (13.6)	76.1 (15.8)	58.0 (5.2)	63.6 (12.2)	71.0 (7.2)	68.3 (12.3)	77.4 (9.1)	67.6 (4.4)	71.5 (8.0)	77.7 (6.9)	73.4 (8.1)	75.6 (11.6)
BMI (kg/m^2)												
Mean (SD)	25.4 (3.2)	24.9 (3.3)	21.9 (1.6)	23.4 (4.0)	23.8 (2.0)	23.9 (2.9)	24.4 (2.3)	24.3 (2.1)	24.4 (1.9)	25.9 (2.6)	24.7 (2.2)	26.4 (2.5)

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SAD = single ascending dose; MAD = multiple ascending dose; DDI = drug-drug interaction; SD = standard deviation

Overall Summary of Adverse Events

No serious AEs and no Grade 4 AEs observed

	SAD		MAD		DDI	
	MBX 1416 (N=24)	Placebo (N=8)	MBX 1416 (N=18)	Placebo (N=5)	Rosuvastatin + Acetaminophen (N=14)	MBX 1416 45 mg + Rosuvastatin + Acetaminophen (N=14)
Number of Subjects with any TEAEs	10 (41.7%)	4 (50.0%)	13 (72.2%)	3 (60.0%)	2 (14.3%)	2 (14.3%)
Grade 3	--	--	5 (27.8%)	--	--	--
Grade 4	--	--	--	--	--	--
Treatment-related[1]	3 (12.5%)	--	13 (72.2%)	1 (20.0%)	--	1 (7.1%)
With Any Serious TEAE	--	--	--	--	--	--
Leading to Treatment Discontinuation	--	--	3 (16.7%)	--	--	--

- **Single dose cohorts (SAD and DDI):** No Grade 3 or 4 AEs
- **Multiple dose cohorts (MAD):** No Grade 4 AEs; 5 subjects (4 subjects in the 30 mg and 1 subject in the 10 mg cohorts) experienced a total of 6 Grade 3 AEs (all ISRs), based on erythema at the injection site >10 cm
  - In all 5 subjects, Grade 3 erythema occurred after the 3rd or 4th dose
- Except for AEs related to ISRs, no pattern or imbalance between MBX 1416 and placebo were observed for any AE

AE = adverse event; TEAE = treatment emergent adverse event; ISR = injection site reaction; SAD = single ascending dose; MAD = multiple ascending dose; DDI = drug-drug interaction
1. Adverse events whose relationship to study drug was 'related', 'probably related', or 'possibly related'

Injection Site Reactions (ISRs) Assessment Summary

ISRs were common and mostly mild/moderate

- Given injectable peptides are known to cause ISRs, we proactively collected all ISRs, including mild reactions, using a dedicated form and the FDA Toxicity Grading Scale
- ISRs were observed in 73% of subjects who received MBX 1416 compared to 0% in the placebo group
  - In 88% of these subjects, ISRs were mild or moderate, predominantly characterized by:
    - Erythema (95% of subjects with an ISR)
    - Minimal or no pain
    - Resolution generally within ~7 days
- No systemic clinical manifestations were observed in association with ISRs
- Histological characterization of a Grade 3 ISR[1] that developed in a subject from a MAD 30 mg cohort suggests a commonly observed reaction with peptide therapeutics, i.e., delayed-type hypersensitivity ISR

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1. Grade 3 erythema defined based on size >10 cm

Laboratory Values, Vital Signs, and ECG Findings

No clinically meaningful changes

- Body Weight and Vital Signs
  - No meaningful changes in body weight were observed across the study
  - Mean changes in vital signs from baseline were generally small and not dose-related
- Laboratory Parameters
  - Mean changes from baseline in clinical chemistry, including glucose, and hematology values were generally small with no apparent pattern of dose-dependency
  - Mostly isolated and transient reductions in hemoglobin were noted in a few subjects from both the SAD and MAD cohorts in both active and placebo groups.
    - These were not deemed clinically significant by the investigator and were not reported as AEs
- Electrocardiogram (ECG)
  - Mean changes from baseline in ECG parameters were generally small and not dose-related
  - No clinically meaningful changes in QTc were observed

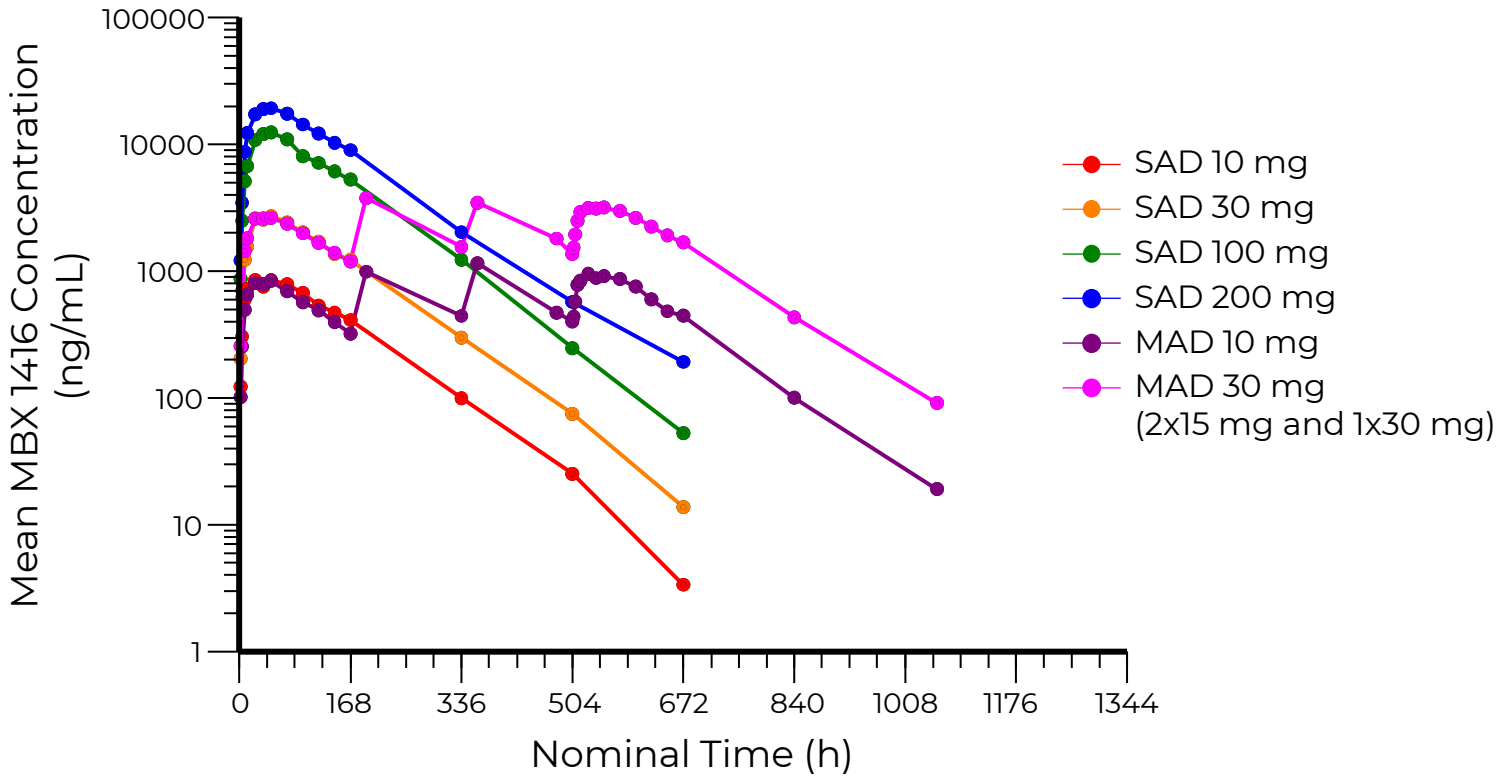
QTc = corrected QT interval

MBX 1416 Phase 1 Results: Pharmacokinetics & Pharmacodynamics

Pharmacokinetics of Single and Multiple Doses of MBX 1416

MBX 1416 exposures were reproduceable and increased dose-proportionally

- MBX 1416 concentrations increased dose-proportionally over the 10 to 200 mg dose range
- Steady-state achieved by the third dose
- Median t_{max} of 36-48 hours at steady state
- Some accumulation (≤1.31) observed for 10 mg and 30 mg dose levels
- Peak-to-trough ratio ~2.5
- Low inter-subject variability



Half-life of approximately 90 hours, supporting once-weekly dosing

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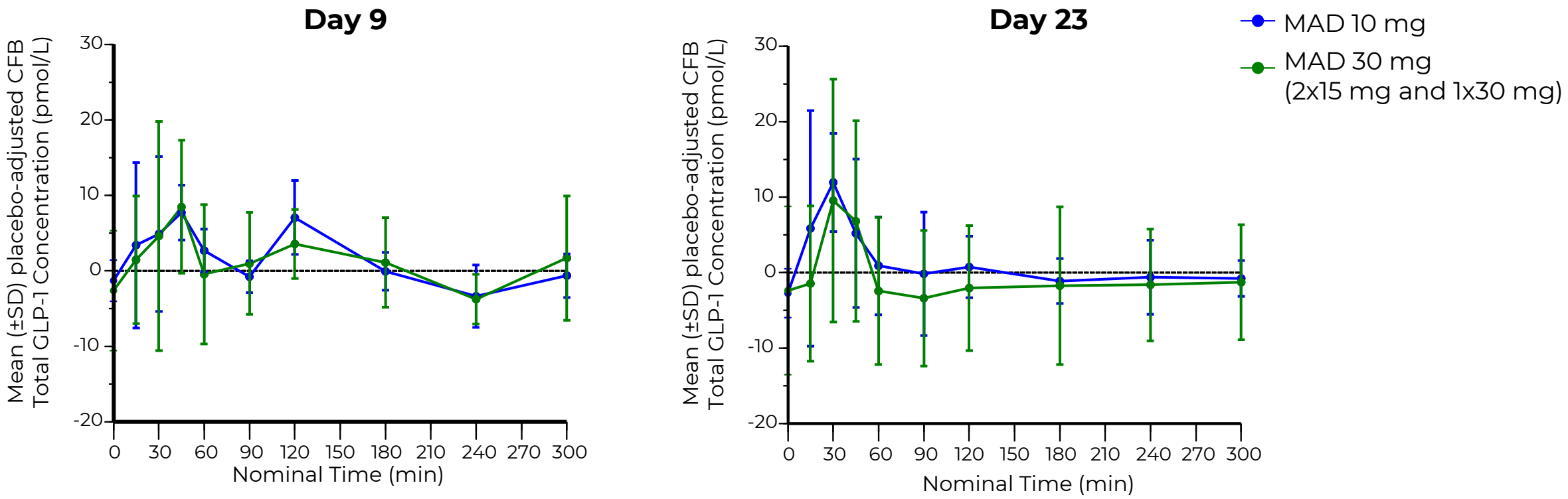
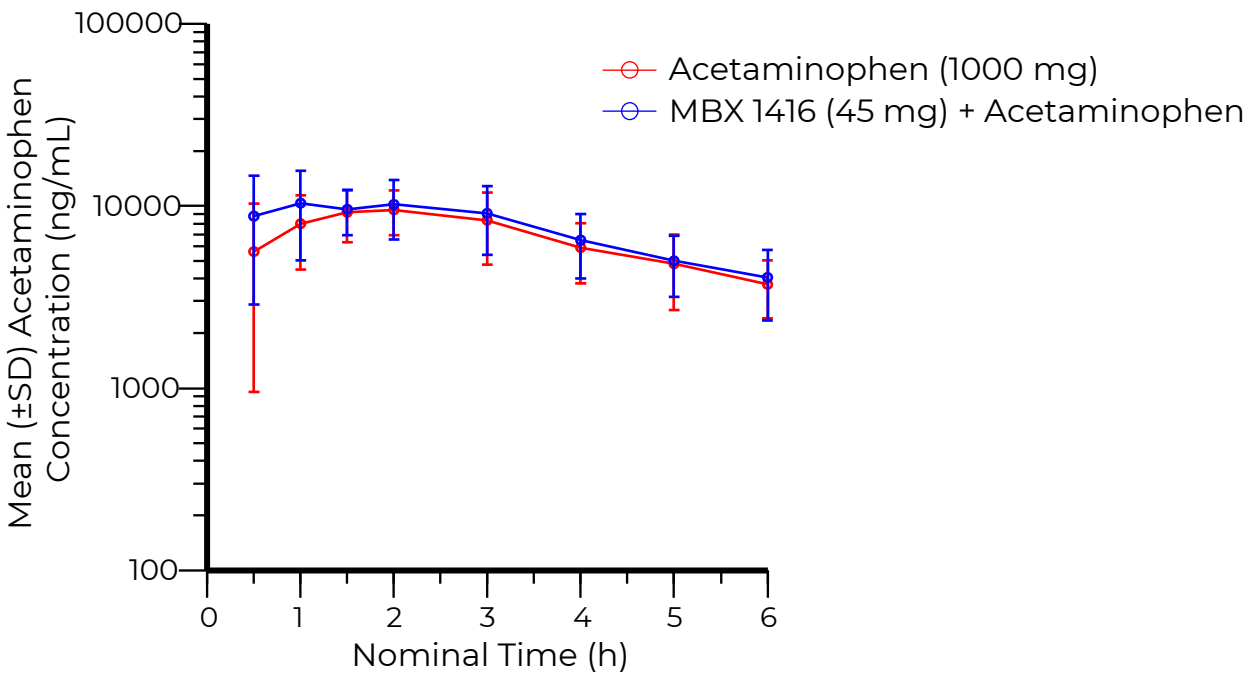
Pharmacodynamic Effect of MBX 1416 Observed During MMTT

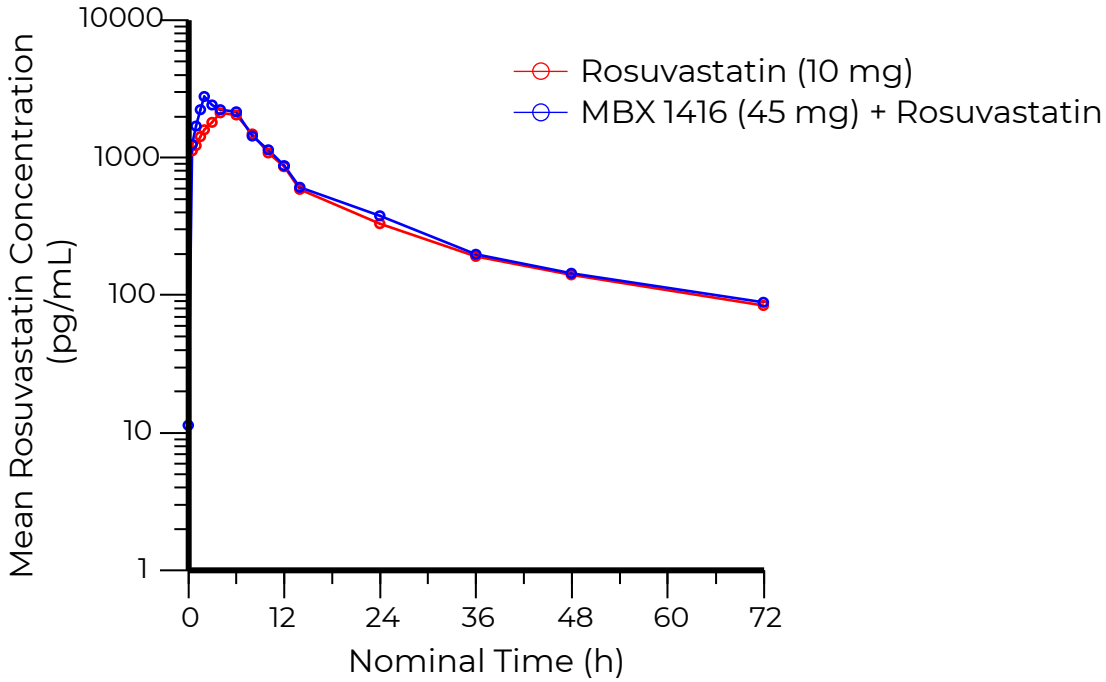
Increase in placebo-adjusted GLP-1 peak from baseline during first 60 mins of MMTT conducted 1 day after 2nd and 4th doses



GLP-1=glucagon-like peptide-1; MMTT = mixed meal tolerance test; CFB = change from baseline

MBX 1416 Demonstrated Expected Effect on Gastric Emptying and no Meaningful Effect on Rosuvastatin Exposure





- Consistent with the expected effect of GLP-1 antagonism, MBX 1416 appeared to slightly accelerate first hour gastric emptying, as demonstrated by an increase in acetaminophen exposure in the presence of MBX 1416 compared to acetaminophen alone
- Rosuvastatin exposure increased only slightly in the absorption phase in the presence of MBX 1416 compared to rosuvastatin administration alone
- Small effect on rosuvastatin likely due to accelerated gastric emptying, rather than a direct inhibitory effect of MBX 1416 on the transporters that mediate rosuvastatin cellular uptake, ie, OATP1B1 and OATP1B3

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Key Highlights from Phase 1 Study of MBX 1416

- MBX 1416 was generally well tolerated with a favorable safety profile
- No MBX 1416 dose-related serious adverse events were observed, and the majority of TEAEs were mild or moderate injection site reactions
- MBX 1416 concentrations increased dose-proportionally in both the SAD and MAD cohorts
- PK profile supportive of weekly administration:
  - In the MAD, MBX 1416 median half-life was approximately 90 hours
  - Median T_{max} of MBX 1416 at steady state was between 36 and 48 hours post-dose
- Consistent with known GLP-1 antagonism effect on gastric motility, a slight acceleration of gastric emptying was observed with MBX 1416 based on acetaminophen exposure
- In the DDI portion, MBX 1416 had no meaningful effect on rosuvastatin exposure, a commonly prescribed statin
- In mixed meal tolerance test, MBX 1416 appeared to increase GLP-1 within 60 mins suggesting a PD effect in healthy volunteers that may translate into a therapeutic benefit in PBH patients; no meaningful changes observed in other parameters (glucose, insulin, c-peptide), as expected in healthy volunteers

TEAE = treatment emergent adverse event; ISR = injection site reaction; SAD = single ascending dose; MAD = multiple ascending dose; DDI = drug-drug interaction
T_{max} = time to reach maximum concentration

Substantial Value Inflection Opportunities in 2025

PROGRAM	MILESTONE	ANTICIPATED TIMING
MBX 2109	Avail™ (Phase 2) Enrollment Completion	Q1 2025
	Avail™ (Phase 2) Topline Results	Q3 2025
MBX 1416	Phase 1 Topline Results	Complete
	End of Phase 1 Meeting	Mid-2025
	Phase 2 Initiation	2H 2025
MBX 4291	IND Submission	Q2 2025
	Phase 1 Initiation	2H 2025

Q&A

Thank you