Sustained Exposure of MBX 6180, a Novel Triple GLP-1/GIP/Glucagon Receptor Agonist Prodrug, in Nonhuman Primates

Jessica E Saulls, PhD, DABT[1]; John Lee, MS[1]; Porsha Howell, PhD[1]; Vasily Gelfanov, PhD[1]; Elisa Fabbrini, MD, PhD[1]; Jessica Pellman, PhD[1]; Michael Hackett, PhD, DABT[1]; Fa Zhang, PhD[2]; Richard D DiMarchi, PhD[2]
[1]MBX Biosciences, Inc., Carmel, IN, USA; [2]Department of Chemistry, Indiana University, Bloomington, IN, USA

OBJECTIVE

- To assess the preclinical efficacy and time action of MBX 6180, a novel triple glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), and glucagon receptor agonist prodrug, at elevated doses suitable for safety assessment

INTRODUCTION

- Peptide therapeutics targeting GLP-1, GIP, and glucagon receptors can effectively reduce body weight in patients with obesity[1–3]
- However, the use of current peptide therapeutics targeting GLP-1 and GIP receptors for the treatment of obesity is limited by poor gastrointestinal tolerability, which may result from rapid increases in post-dose concentrations (burst effect) and short half-lives that can lead to fluctuations in plasma exposure[4,5]
- Moreover, due to their short half-lives, current therapeutics require frequent dosing,[6,7] which can be burdensome for some patients[8]
- MBX 6180 is a novel, investigational triple GLP-1, GIP, and glucagon receptor agonist fatty acylated prodrug designed to bind plasma albumin, which extends the circulating residence time and gradually releases the bioactive peptide (MBX 6181) over time
- The design is intended to provide sustained exposure and reduce peak-to-trough fluctuations in plasma concentrations associated with current peptide therapies
- Preclinical in vitro studies and range finding studies in healthy rats and nonhuman primates were conducted to evaluate the pharmacodynamic and pharmacokinetic (PK) profile of MBX 6180 and to determine doses for the pivotal Investigational New Drug (IND) application-enabling studies

METHODS

In vitro potency

- Maximum response and half-maximal effective concentration (EC_{50}) values were determined from concentration-response curves generated with a cAMP-responsive luciferase reporter assay after HEK293 cells overexpressing the human glucagon, GLP-1, or GIP receptors were incubated with serial dilutions of native agonists, MBX 6180, MBX 6181, or retatrutide for 5 hours

PK, body weight, and food consumption assessments in rats

- Sprague Dawley rats received subcutaneous (SC) doses of MBX 6180 in 2 phases:
  - Phase 1: Single dose of SC MBX 6180 (50, 500, or 5000 nmol/kg; n = 3 per group); body weight was recorded at baseline, day 3, and day 8; food consumption was measured daily
  - Phase 2: Once-weekly SC MBX 6180 (1500 nmol/kg; n = 6) or vehicle (n = 3) for 2 weeks; concentrations of MBX 6180 and the bioactive peptide were assayed through 168 hours after each dose using liquid chromatography-tandem mass spectrometry (LC-MS/MS); PK parameters were determined using noncompartmental methods
    - Body weight was assessed at baseline and twice weekly in a separate cohort of rats receiving once-weekly doses of SC MBX 6180 (1500 nmol/kg; n = 5) or vehicle (n = 5) for 2 weeks

Single-dose PK assessment in cynomolgus monkeys

- Cynomolgus monkeys (n = 2) received 1 SC dose of MBX 6180 or the bioactive peptide (MBX 6181) at 50 nmol/kg
- Plasma concentrations of MBX 6180 and the bioactive peptide were assayed using LC-MS/MS at 4, 8, 12, and 24 hours after dosing, daily through day 7, and every other day through day 21; PK parameters were determined using noncompartmental methods using Phoenix WinNonlin (Certara, Princeton, NJ)
- For the bioactive peptide (MBX 6181) dosed directly, measurements were collected at the same time points but truncated at day 7

PK and body weight assessment with once-weekly dosing in cynomolgus monkeys

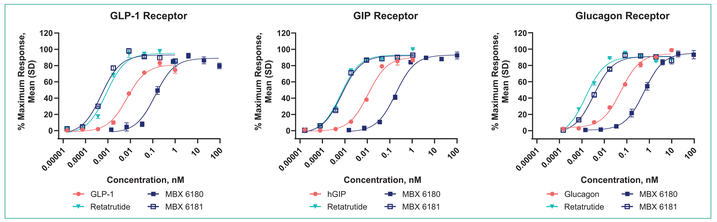
- Cynomolgus monkeys received SC doses of MBX 6180 (200 nmol/kg, n = 3; 500 nmol/kg, n = 3) once weekly for 3 weeks
- Body weight was recorded at baseline and twice weekly throughout the study; after doses 1 and 3, concentrations of MBX 6180 and the bioactive peptide were measured at 4, 8, and 24 hours postdose and daily through 7 days, with an additional assessment 10 days after dose 3

RESULTS

MBX 6180 activates human GLP-1, GIP, and glucagon receptors in vitro

- The bioactive peptide (MBX 6181) demonstrated robust activation of GLP-1, GIP, and glucagon receptors similar to retatrutide; the prodrug (MBX 6180) had significantly reduced potency **(Figure 1)**
- Conversion of MBX 6180 to MBX 6181 increased potency across GLP-1, GIP, and glucagon receptors **(Table 1)**

Figure 1. Dose Response of MBX 6180 and MBX 6181 at Human GLP-1, GIP, and Glucagon Receptors



GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MBX 6180, prodrug; MBX 6181, bioactive peptide; hGIP, human gastric inhibitory polypeptide.

Table 1. In Vitro Potency and Relative Activity of MBX 6180 and MBX 6181 at Human GLP-1, GIP, and Glucagon Receptors

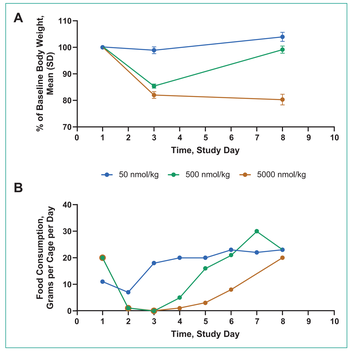
Receptor	Compound	EC_{50}, nM	% of Native Ligand Activity
GLP-1 receptor	GLP-1	0.0066	100
	MBX 6180	0.1249	5
	MBX 6181	0.0005	1300
	Retatrutide	0.0008	800
GIP receptor	GIP	0.0095	100
	MBX 6180	0.1709	6
	MBX 6181	0.0006	1500
	Retatrutide	0.0005	1900
Glucagon receptor	Glucagon	0.0526	100
	MBX 6180	0.5827	9
	MBX 6181	0.0031	1600
	Retatrutide	0.0013	4000

EC_{50}, half-maximal effective concentration; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; MBX 6180, prodrug; MBX 6181, bioactive peptide.

Single-dose MBX 6180 reduced body weight in rats

- A single SC dose of MBX 6180 (50, 500, or 5000 nmol/kg) led to dose-dependent reductions in mean body weight relative to baseline **(Figure 2A)**, which was accompanied by dose-dependent reductions in food consumption **(Figure 2B)**

Figure 2. Effect of Single-Dose SC MBX 6180 on (A) Body Weight and (B) Food Consumption in Healthy Rats

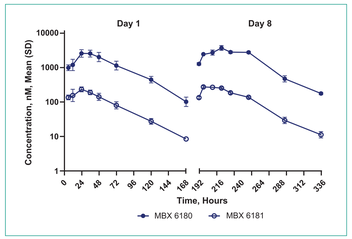


SC, subcutaneous.

Once-weekly administration of MBX 6180 in rats demonstrated sustained exposure of prodrug and bioactive peptide

- After both the first and the second SC dose of once-weekly MBX 6180 1500 nmol/kg, plasma concentrations of both MBX 6180 and the bioactive peptide rose through 24 hours post dose and remained quantifiable through the end of the dosing interval (168 hours post dose); no accumulation was noted **(Figure 3)**

Figure 3. Concentration-Time Profile of MBX 6180 and Bioactive Peptide in Healthy Rats With Once-Weekly SC Administration of MBX 6180 at 1500 nmol/kg

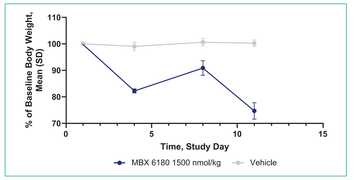


MBX 6180, prodrug; MBX 6181, bioactive peptide; SC, subcutaneous.

Once-Weekly MBX 6180 led to reductions in body weight in rats

- Once-weekly administration of MBX 6180 at 1500 nmol/kg for 2 weeks led to a mean reduction in body weight of 25.3% at day 11 **(Figure 4)**

Figure 4. Effect of Once-Weekly SC Administration of MBX 6180 at 1500 nmol/kg on Body Weight in Rats

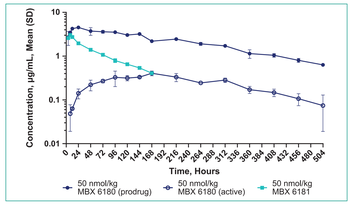


MBX 6180, prodrug; SC, subcutaneous.

MBX 6180 generated gradually increasing and sustained exposure to the bioactive peptide in cynomolgus monkeys

- After 1 dose of SC MBX 6180 50 nmol/kg, concentrations of MBX 6180 increased at the first measurement after injection and peaked at a mean (range) time to maximum concentration (T_{max}) of 24 (24–24) hours **(Figure 5, Table 2)**
- The concentration of the bioactive peptide increased more gradually, with a mean (range) T_{max} of 132 (96–168) hours, compared with a direct SC injection of the bioactive peptide for which T_{max} was ~8 hours and concentration dropped by 10-fold over the first week
- Consistent with prolonged exposure, both MBX 6180 and the bioactive peptide remained quantifiable throughout the 21-day sampling period, with mean (range) half-lives of 5.85 (4.72–6.99) and 5.83 (4.26–7.40) days, respectively

Figure 5. Concentration-Time Profile of MBX 6180 and Bioactive Peptide After SC Administration in Healthy Cynomolgus Monkeys



MBX 6180, prodrug; MBX 6181, bioactive peptide; SC, subcutaneous.

MBX 6180 led to reductions in body weight in cynomolgus monkeys

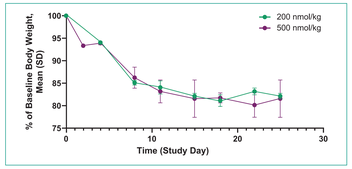
- At day 25 after initiation of once-weekly MBX 6180 administration in monkeys, body weight decreased from baseline by a mean of 17.9% in the 200-nmol/kg group and 18.4% in the 500-nmol/kg group **(Figure 6)**

Table 2. PK Profile of MBX 6180 and Bioactive Peptide After SC Administration in Healthy Cynomolgus Monkeys

Parameter	MBX 6180 (Prodrug)	MBX 6180 (Active)	MBX 6181
T_{max}, hours	24 (24–24)	132 (96–168)	8 (8–8)
C_{max}, µg/mL	4.51 (4.47–4.55)	0.429 (0.417–0.441)	3.02 (2.93–3.11)
T_{last}, days	21 (21–21)	21 (21–21)	7 (7–7)
AUC_{inf}, day•µg/mL	50.3 (50.1–50.6)	5.57 (4.63–6.51)	9.58 (9.35–9.81)
$t_{1/2}$, days	5.85 (4.72–6.99)	5.83 (4.26–7.40)	2.74 (2.67–2.81)
CL/F, mL/day/kg	5.86 (5.84–5.89)	—	25.7 (25.1–26.3)
V_z/F, mL/kg	49.5 (40.1–58.9)	—	101 (101–102)

AUC_{inf}, area under the concentration-time curve from 0 extrapolated to infinity; CL/F, total apparent clearance; C_{max}, maximum observed concentration; MBX 6180, prodrug; MBX 6181, bioactive peptide; PK, pharmacokinetic; SC, subcutaneous; $t_{1/2}$, half-life of the terminal phase; T_{last}, time to the last measurable concentration; T_{max}, time to observed C_{max}; V_z/F, apparent volume of distribution.
All values are presented as mean (range).

Figure 6. Effect of Once-Weekly SC MBX 6180 on Body Weight in Healthy Cynomolgus Monkeys

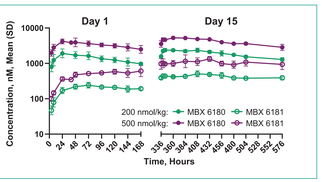


MBX 6180, prodrug; SC, subcutaneous.

Steady-state exposure was observed by the third dosing interval of once-weekly SC administration of MBX 6180 in monkeys, with moderate accumulation

- During weekly SC administration of MBX 6180, concentrations of the bioactive peptide increased continuously through the first dosing interval and were nearly constant throughout the third dosing interval **(Figure 7)**
- At day 15, moderate accumulation (approximately 2-fold) of the bioactive peptide was observed with comparable pre-dose and 168-hour post-dose concentrations, suggesting that steady state had been achieved

Figure 7. Concentration-Time Profile of MBX 6180 and Bioactive Peptide in Healthy Cynomolgus Monkeys With Once-Weekly Dosing of MBX 6180



MBX 6180, prodrug; MBX 6181, bioactive peptide.

CONCLUSIONS

- MBX 6181 had potent agonist activity comparable to retatrutide at the human GLP-1, GIP, and glucagon receptors, while the prodrug MBX 6180 had weak activity at all receptors
- Administration of single SC doses of MBX 6180 yielded an infusion-like profile for the bioactive peptide with the potential to support monthly dosing
- Range finding studies in rats and nonhuman primates met their intended endpoint, allowing MBX 6180 to proceed into IND-enabling toxicology studies

DISCLOSURES AND ACKNOWLEDGMENTS

This study was funded by MBX Biosciences. All authors had access to the data; participated in the development, review, and approval of the abstract; and agreed to submit this abstract to ObesityWeek 2026 for consideration as an oral presentation or poster. Medical writing support was provided by Jake Wilmot, PhD, and Emily J Farrar, PhD, of JB Ashtin, and was funded by MBX Biosciences, Inc.

JES, JL, PH, VG, EF, and **MH** are full-time employees of MBX Biosciences, Inc., and may hold MBX Biosciences, Inc. stock or stock options. **FZ** is an employee of Indiana University, which has research and patent licensing agreements with MBX Biosciences, Inc. **RDD** is a co-founder of MBX Biosciences, Inc., and an employee of Indiana University, which has research and patent licensing agreements with MBX Biosciences, Inc.

References

1. Wilding JPH, et al. *N Engl J Med*. 2021;384(11):989–1002.
2. Jastreboff AM, et al. *N Engl J Med*. 2022;387(3):205–16.
3. Jastreboff AM, et al. *N Engl J Med*. 2023;389(6):514–26.
4. Jalleh RJ, et al. *J Clin Invest*. 2026;136(4):e194740.
5. Huthmacher JA, et al. *Diabetes Care*. 2020;43(9):2303–12.
6. WEGOVY. Prescribing information. Novo Nordisk; 2026. Accessed October 19, 2026. https://www.novo-pi.com/wegovy.pdf
7. ZEPBOUND. Prescribing information. Eli Lilly; 2026. Accessed October 19, 2026. https://uspl.lilly.com/zepbound/zepbound.html#pi
8. Thieu VT, et al. *Patient Prefer Adherence*. 2019;13:561–76.

MBX Biosciences