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# Melanocortin Receptor 4 Agonist PL8905 in Combination With Glucagon-Like Peptide 1 Produces Synergistic Weight Loss, Reduced food Intake, and Greater Glucose Control in Diet-Induced Obese Rats

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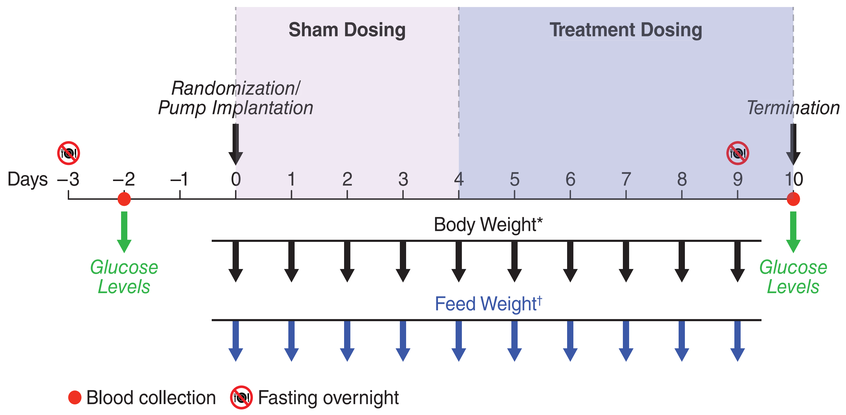
## Introduction

- Obesity, a complex multifactorial disorder with genetic and environmental factors leading to increased morbidity and mortality, is a major health problem worldwide[1]
- Glucagon-like peptide 1 (GLP-1) agonists such as liraglutide, tirzepatide, and semaglutide are approved for chronic weight management and type-2 diabetes[2-4]
- The melanocortin pathway regulates energy balance and the melanocortin-4 receptor (MC4R) gene is the most commonly associated gene found in childhood obesity[5]
- Melanocortin receptor 4 (MC4R) plays an important role in food intake behavior and energy homeostasis via the binding of its endogenous agonist α-melanocyte-stimulating hormone, whose release is stimulated by leptin[5,6]
- Setmelanotide, an MC4R agonist, was approved by the FDA in 2020 for the indication of chronic weight management in adults and pediatrics 6 years of age with genetically-linked obesity. It acts on the MC4R pathway to reverse hyperphagia and promote weight loss through decreased caloric intake and increased energy expenditure[7-9]
- There is, therefore, the potential that activating the MC4R pathway may be treatment option for general obesity[9,10]
- Here we present studies that investigated the synergistic or additive effects of PL8905, a novel, selective MC4R agonist, in combination with GLP-1 in diet-induced obese (DIO) rats

## Methods

- Subcutaneous treatment with PL8905 0.3, 1, and 3 mg/kg alone and in combination with continuous infusion of GLP-1 1 mg/kg/d was investigated in DIO rats (n=100) (**Figure 1**)
- Sham dosing with saline (2 mL/kg) on days 0–3 was used to acclimate the rats to treatment
- On days 5–9 animals were dosed subcutaneously with PL8905 twice daily, infused with GLP-1, or both
- Vehicle was 3.2% mannitol dissolved in 50 mM Tris pH 7.4
- Body and feed weight was measured on days 0–9; glucose levels on days –2 and 10
  - For the glucose tolerance test, glucose was administered PO at 1 g/kg. Glucose levels were taken at baseline (prior to glucose administration) and at 15, 30, 60, 90, and 120 min post glucose administration

### Figure 1. Study Design



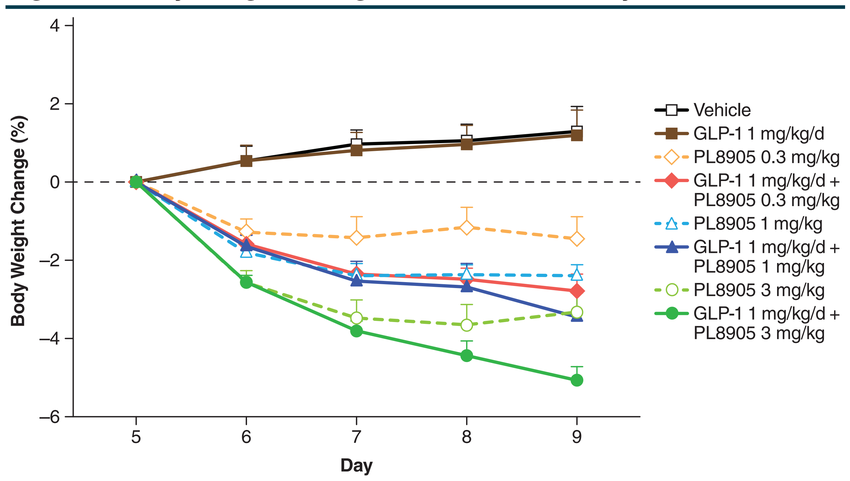

*Taken at t=0 hours.
†Taken at 0 hours and 24 hours after lights out on days 0–9, and at 0, 2, 6, and 24 hours after lights out on days 5–9.

## Results

### Body Weight Changes

- Treatment with vehicle or GLP-1 alone resulted in a slight increase in body weight at day 9 (normalized to day 5) when compared to baseline (**Figure 2**)
- PL8905 alone produced significant declines of ~1.6%–3.4% ($P$<0.01 vs vehicle, two-way ANOVA followed by Dunnett's multiple comparisons)
- PL8905 combined with GLP-1 produced greater declines of ~2.9%–5.1% ($P$<0.01)

### Figure 2. Body Weight Changes Normalized to Day 5

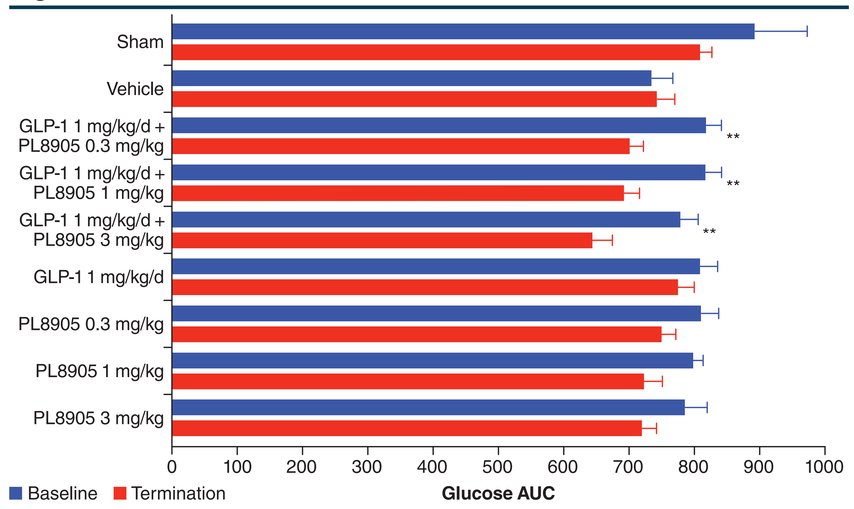



n=8 for each treatment group. Error bars are SEM. GLP-1, glucagon-like peptide 1.

### Blood Glucose Levels

- PL8905/GLP-1 groups showed significant ($P$<0.01) reduction of blood glucose AUC when comparing termination values with baseline
- PL8905 or GLP-1 treatment alone showed trends towards lower glucose AUC, but did not reach significance.

### Figure 3. Glucose Tolerance Test: Baseline and Terminal Levels

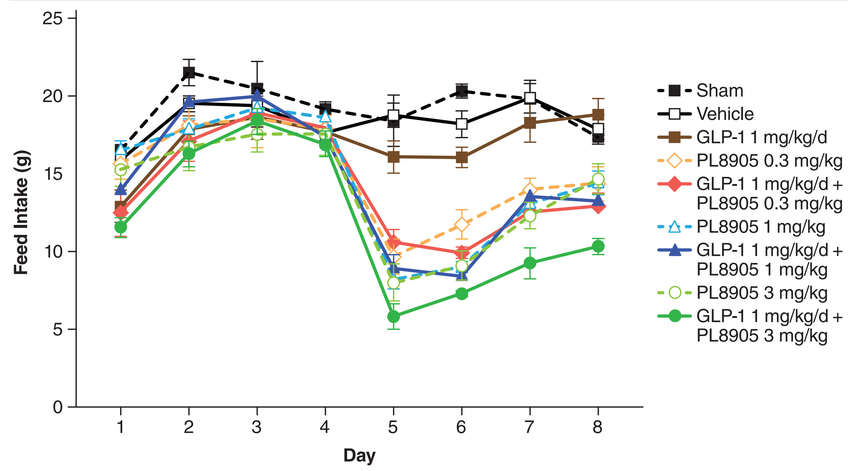



AUC glucose was from baseline to 120 min post glucose administration. **$P$<0.01 vs. baseline using two-way ANOVA followed by Dunnett's multiple comparisons. AUC, area under the concentration time curve.

### Feed Intake

- Feed intake in PL8905 groups and PL8905/GLP-1 combination groups decreased vs vehicle, although it recovered on day 9 for PL8905 groups (**Figure 4**)

### Figure 4. Feed Intake at 24 Hours for Days 1–8




n=8 for each treatment group (sham n=4). Error bars are SEM. GLP-1, glucagon-like peptide 1. Sham is saline solution. Vehicle (placebo) is the solvent for the active treatments.

## Conclusions

- 1 mg/kg/day GLP-1 had little effect on food intake, body weight, or blood glucose in DIO rats
- PL8905 0.3–3 mg/kg when combined with 1 mg/kg/d GLP-1 showed significantly greater weight loss and glucose control in DIO rats than PL8905 monotherapy, GLP-1, or vehicle
- Combination treatment with MC4R agonist and GLP-1 agonist may be a more effective therapy for diabetes and obesity

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***Disclosures*** John H. Dodd and Carl Spana are employees of and own stock in Palatin Technologies, Inc. Marie Makhlina and Wei H. Yang are former employees and may own stock in Palatin Technologies, Inc.

***References*** **1.** Mahmoud R, et al. *Int J Mol Sci.* 2022;23(19) **2.** Baggio LL and Drucker DJ. *Mol Metab.* 2021;46:101090. **3.** Collins L and Costello RA. *Glucagon-like peptide-1 receptor agonists.* StatPearls Publishing; 2023. **4.** Popoviciu MS, et al. *Int J Mol Sci.* 2023;24(13) **5.** Yang Y and Xu Y. *J Mol Cell Biol.* 2020;12(10):785-797. **6.** Tao YX. *Endocr Rev.* 2010;31(4):506-543. **7.** Clement K, et al. *Nat Med.* 2018;24(5):551-555. **8.** Clement K, et al. *Lancet Diabetes Endocrinol.* 2020;8(12):960-970. **9.** Collet TH, et al. *Mol Metab.* 2017;6(10):1321-1329. **10.** Yeo GSH, et al. *Mol Metab.* 2021;48:101206.