

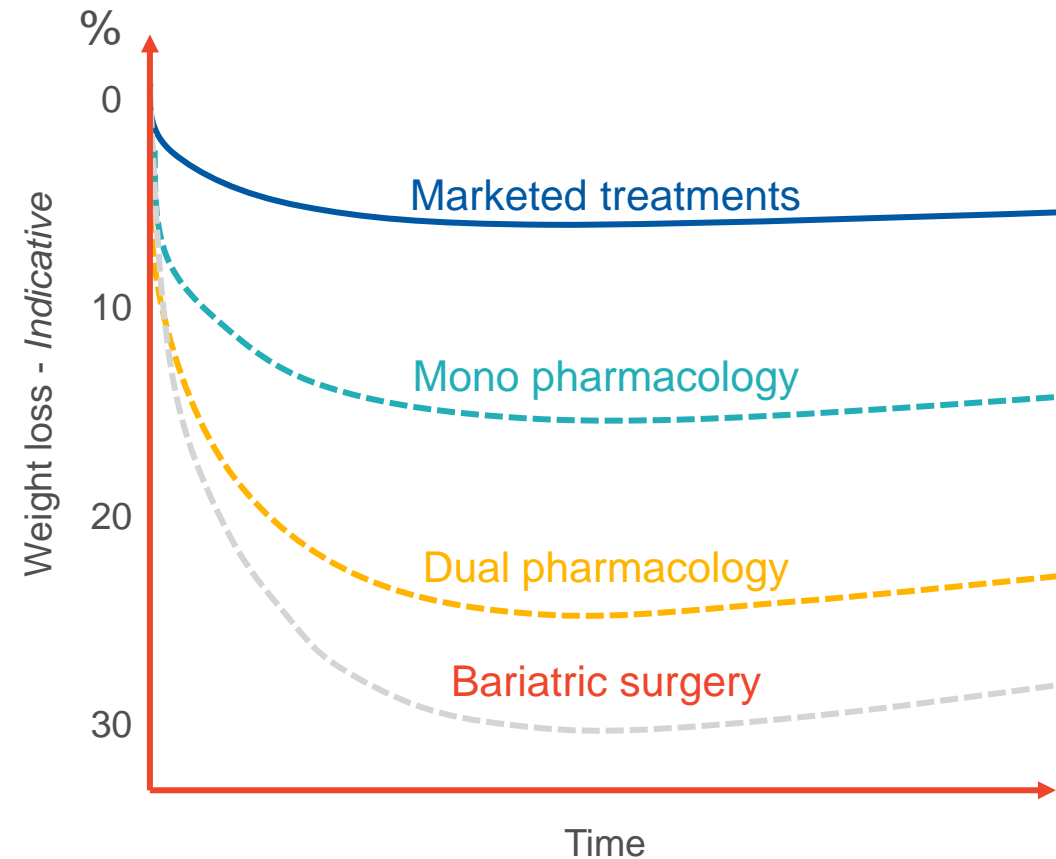
# Effect of Dapiglutide Alone and in Combination with the Amylin Analog ZP8396 in the Diet-induced Obesity Rat model

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# Background: Rational for Combination Therapies in the Treatment of Obesity

- Obesity is a complex metabolic disease modulated by several molecular pathways
- Monotherapy or single receptor agonism is generally insufficient to induce changes in line with bariatric surgery
- Targeting multiple receptor for gut/pancreatic peptides has been shown to further reduce body weight (e.g. GLP-1 in combination with Amylin, GIP or Glucagon)
- Triple agonist compounds are in early clinical development



# Background: Biology of GLP-1, Amylin and GLP-2

In this rat study we have targeted three receptors, GLP-1, GLP-2 and Amylin, to investigate the anti-obesity effect in the DIO model

## GLP-1<sup>1</sup>

- 31-mer peptide hormone
- Secreted postprandially by the intestinal enteroendocrine L cells

### Main actions:

- Improves glycemic control
- Reduces body weight

## Amylin<sup>2</sup>

- 37-mer peptide hormone
- Postprandially secreted from the pancreatic beta cells

### Main actions:

- Improved glycemic control postprandially
- Reduced body weight

## GLP-2<sup>3</sup>

- 33-amino acid peptide hormone
- Co-secreted postprandially with GLP-1 from intestinal L cells

### Main actions:

- Trophic factor for the intestine
- Delays gastric emptying and intestinal transit
- Putative effects include:
  - improved intestinal barrier
  - anti-inflammatory
  - metabolic improvements
  - improved tolerability to GLP-1 side effects

<sup>1</sup> Reviewed in: Muller TD, Nature Rev Drug Dis, 21:201, 2022

<sup>2</sup> Reviewed in: Hay DL, Pharmacol Rev, 67:3, 2015

<sup>3</sup> Reviewed in: Drucker DJ, Ann Rev of Phys. 76:561, 2014

# Background: Dapiglutide and ZP8396

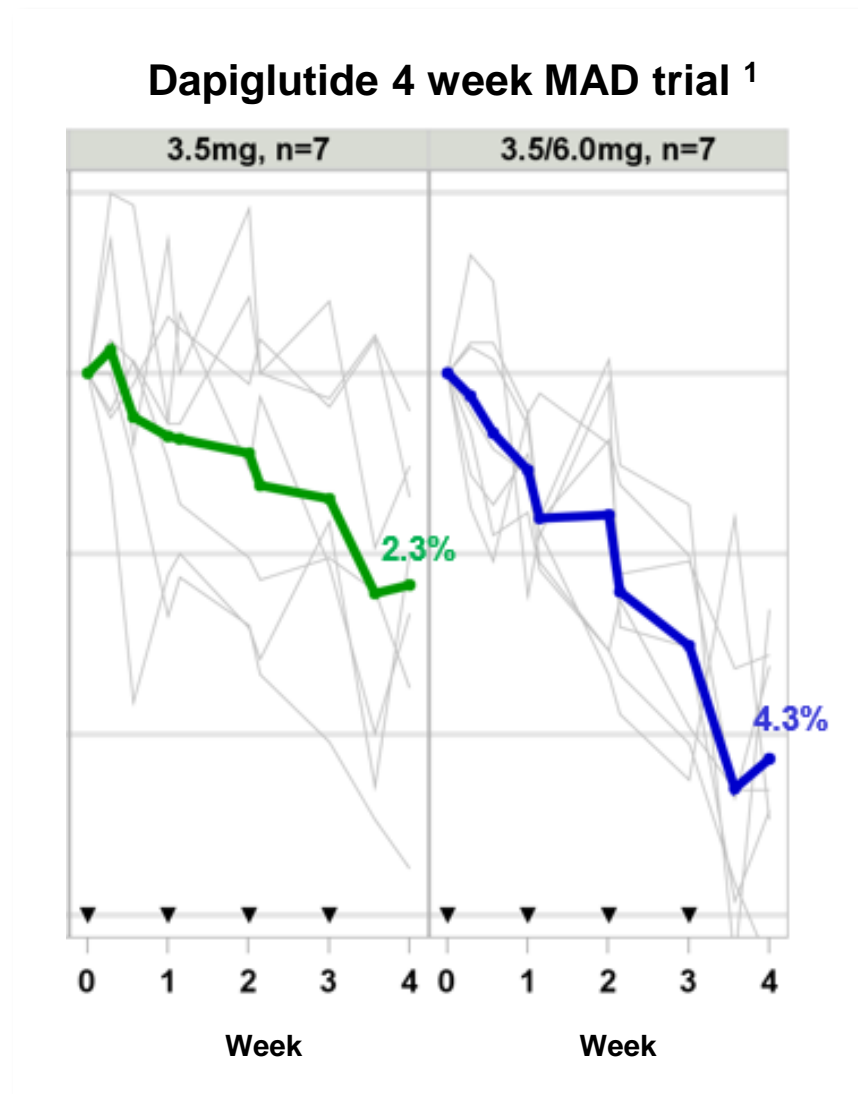
## Dapiglutide

- Long-acting, acylated GLP-1/GLP-2 dual agonist
- Completed phase 1 trials - reduction of body weight in lean subjects over 4 weeks



## ZP8396

- Long-acting, acylated human amylin analogue with high potency on human CT-R, AMY-R1 and AMY-R3
- Dose-dependent weight reduction confirmed in DIO rat
- Anti-diabetic potential demonstrated in ZDF rats
- Phase 1 clinical trials ongoing



<sup>1</sup> Agersnap et al, ADA 2022

# Combination Treatment: Diet-induced Obesity Rat Model

## Study Objective

To assess the impact of treatment with the GLP-1/GLP-2 receptor agonist dapiglutide and the long-acting amylin agonist ZP8396 alone and in combination on measures of:

- Body weight
- Food intake
- Measures of glycemia
- PK

...in a Diet-Induced Obesity (DIO) rodent model

# Study design: Combination Dapiglutide/ZP8396 in DIO Rodents

Group 1: Vehicle, sc qd

Group 2: Dapiglutide, 30 nmol/kg, sc qd

Group 3: Dapiglutide, 100 nmol/kg sc qd

Group 4: ZP8396, 10 nmol/kg, sc ev. 2<sup>nd</sup> day

Group 5: Dapiglutide 100 nmol/kg qd + ZP8396, 10 nmol/kg, sc ev. 2<sup>nd</sup> day

Body weight (daily); food intake (every other day)

-3 -1 0

28 29

A B

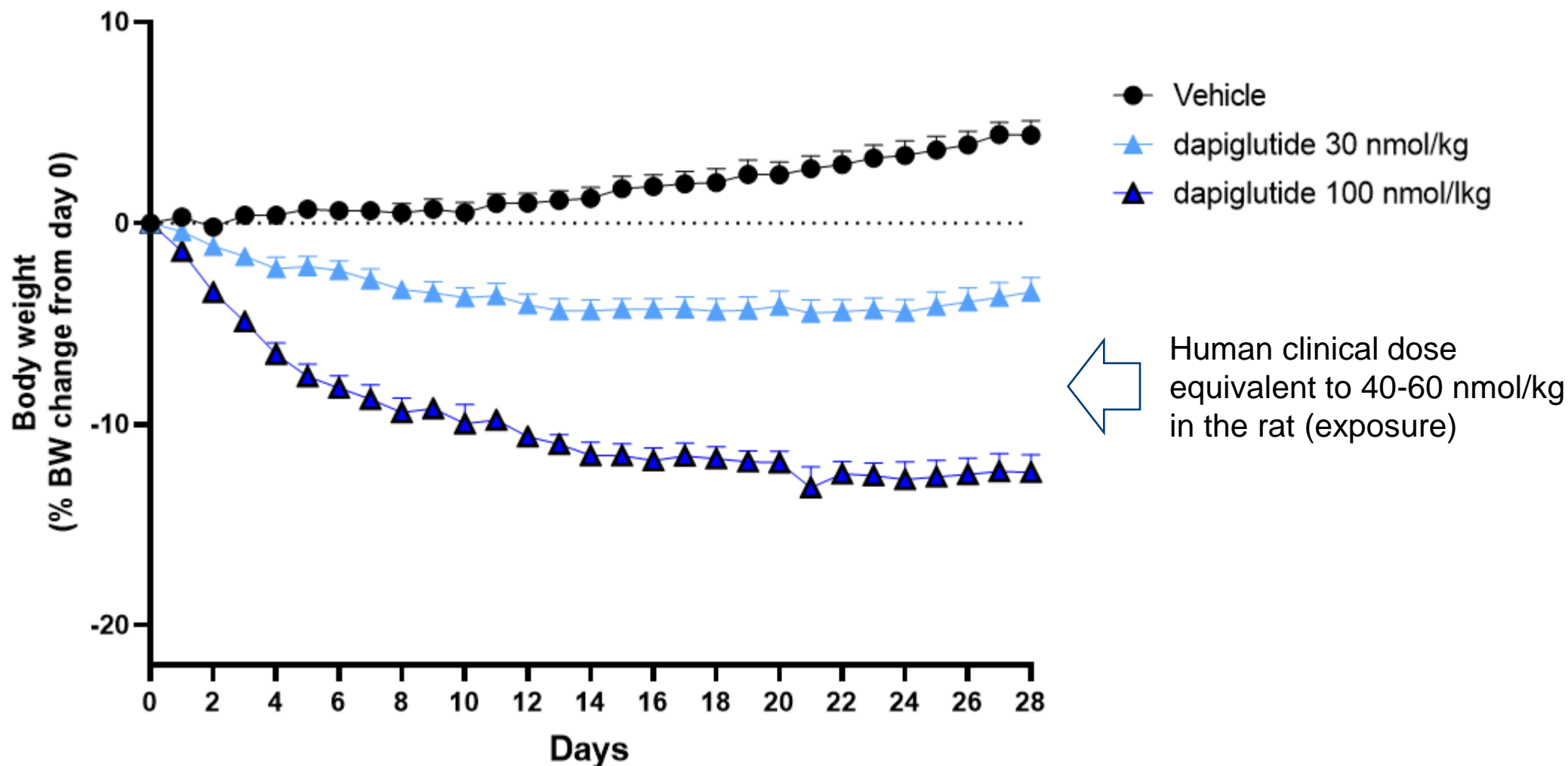
C

**A** Stratification, group allocation

**B** Baseline characterisation; fasted blood glucose

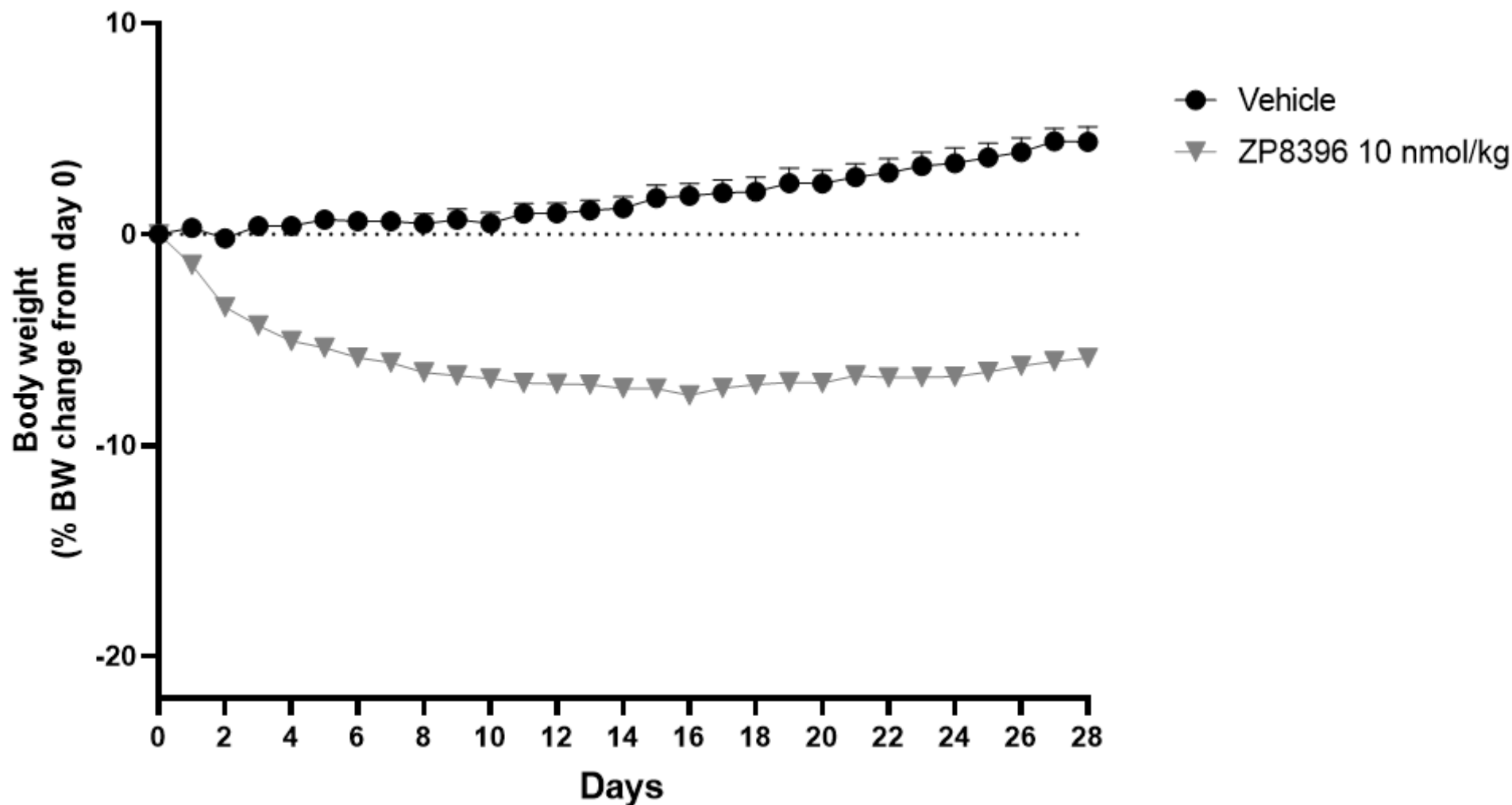
**C** Termination; fasted blood glucose, peptide exposure

# Change in Body Weight with Dapiglutide treatment Alone



Data are mean values with SEM (n= 9/group).

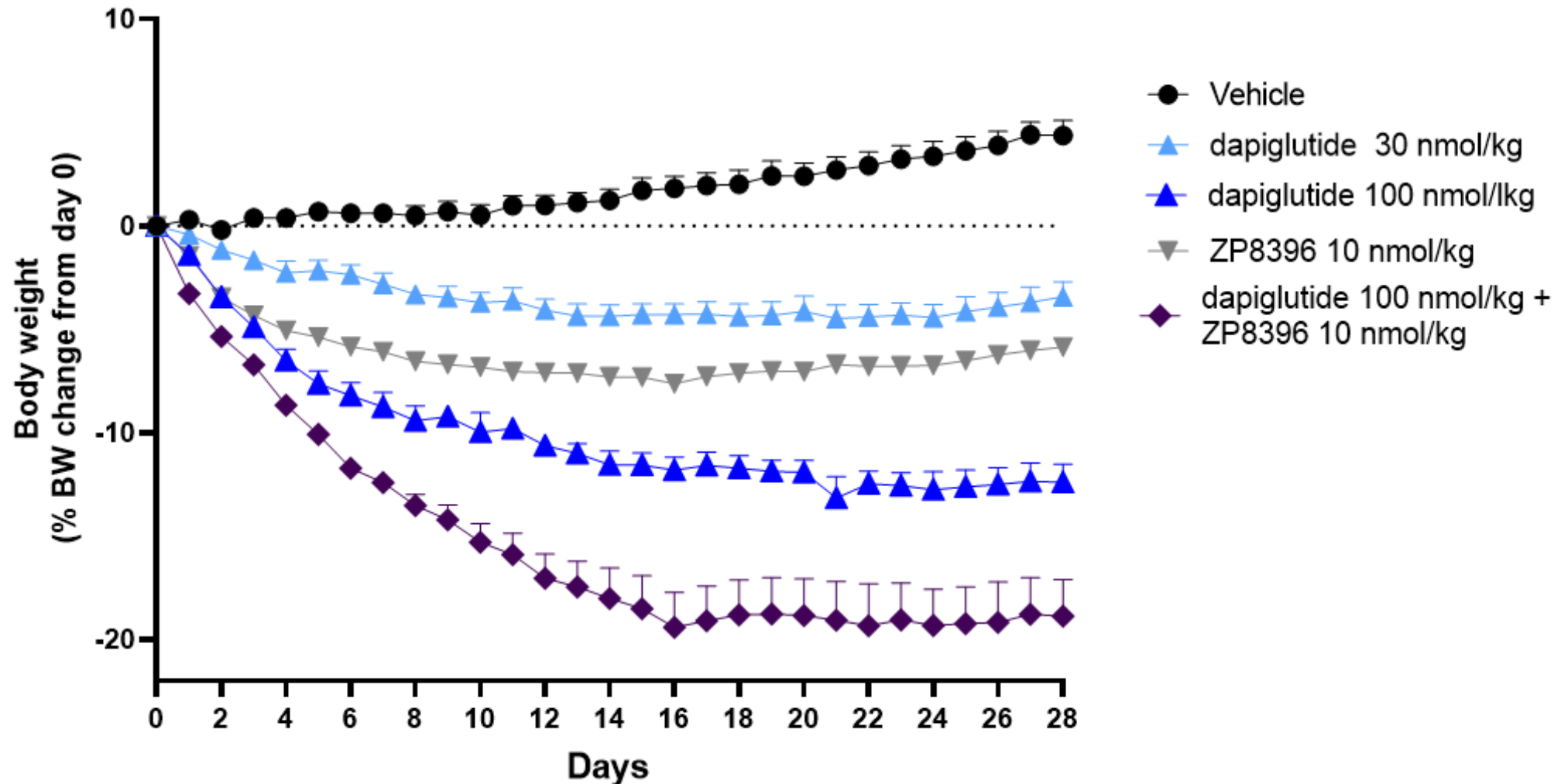
# Change in Body Weight with ZP8396 Treatment Alone



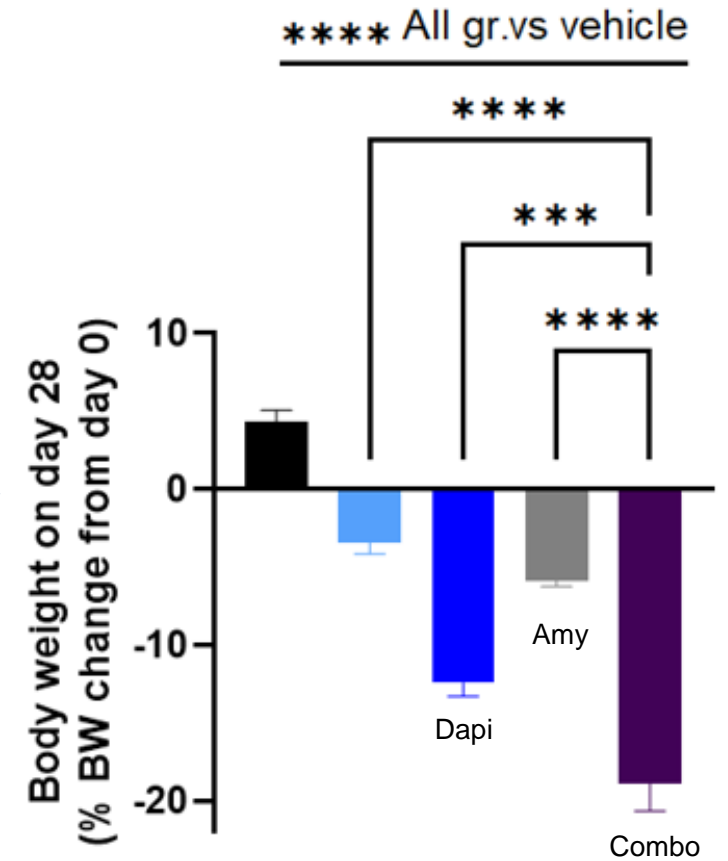
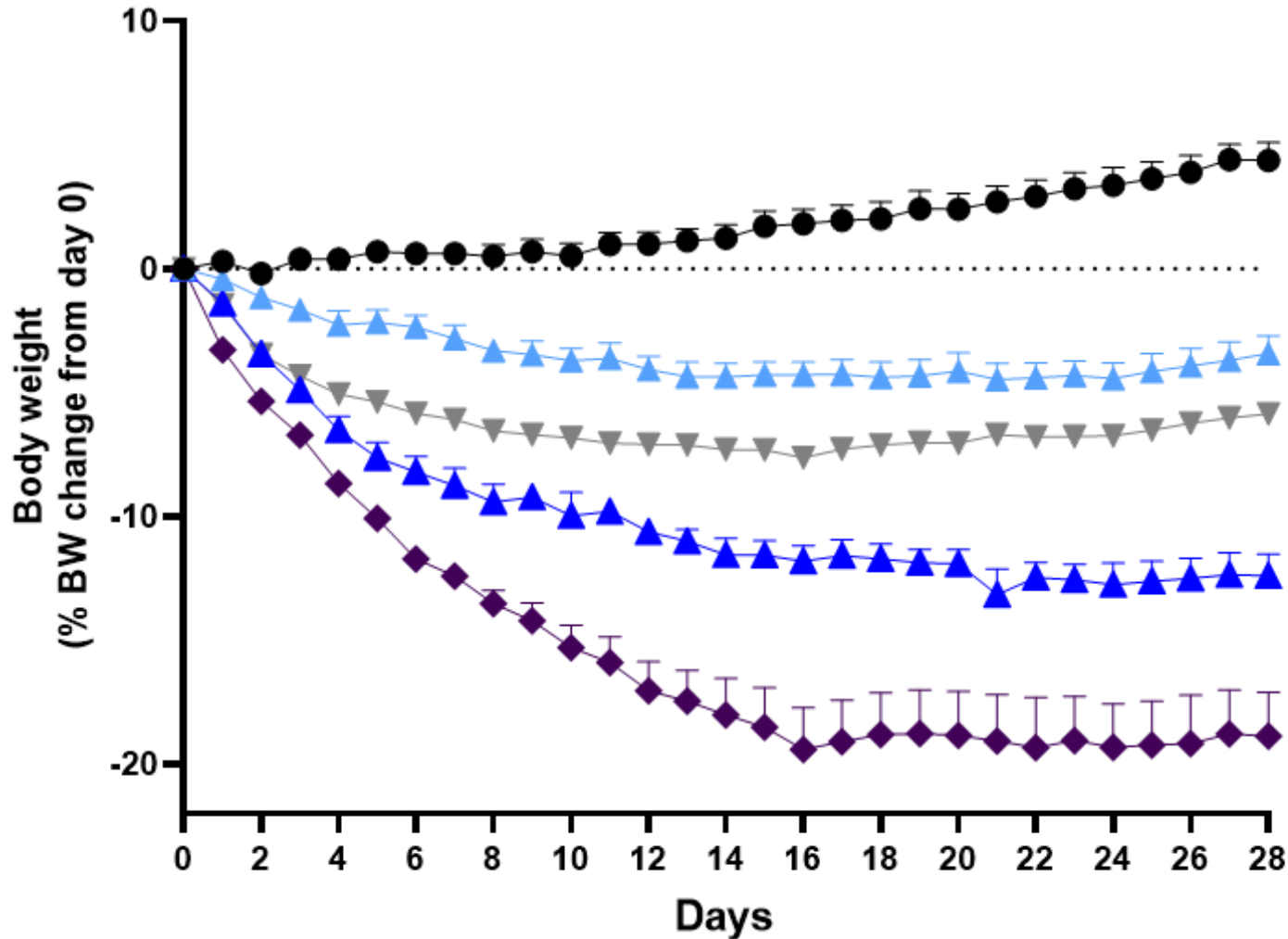
Data are mean values with SEM (n= 9/group).



# Change in Body Weight with Dapiglutide, ZP8396 Alone and in Combination

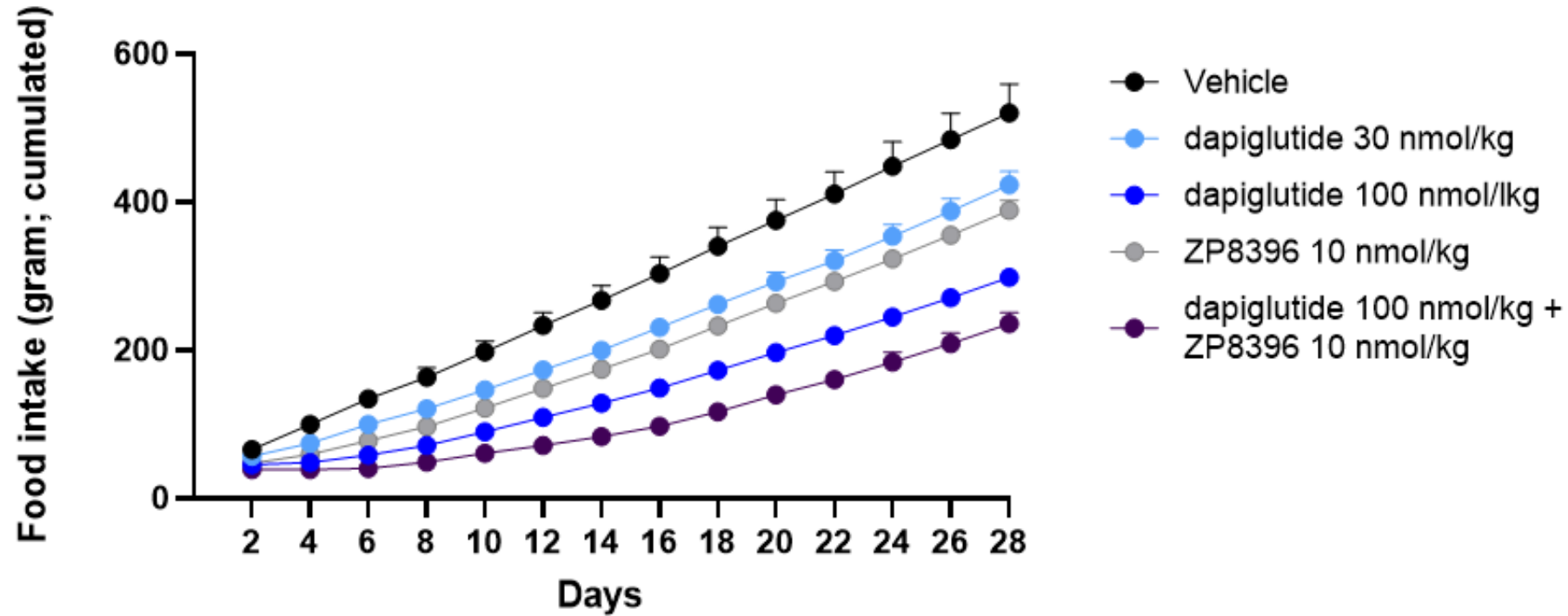


# Change in Body Weight with Dapiglutide, ZP8396 Alone and in Combination

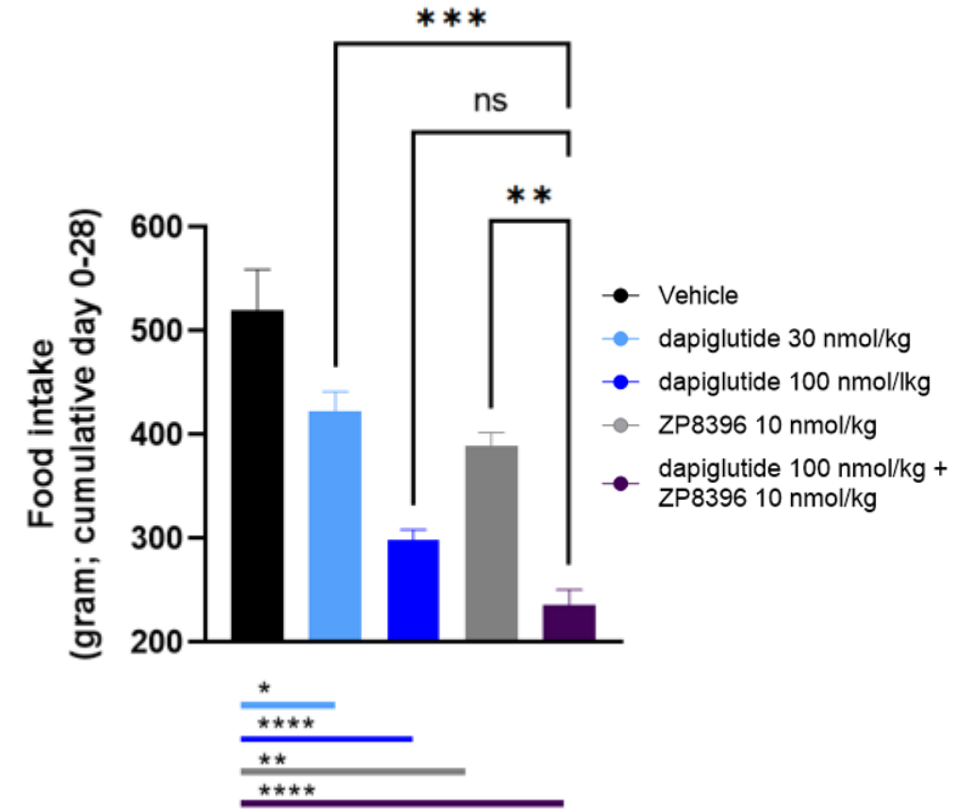
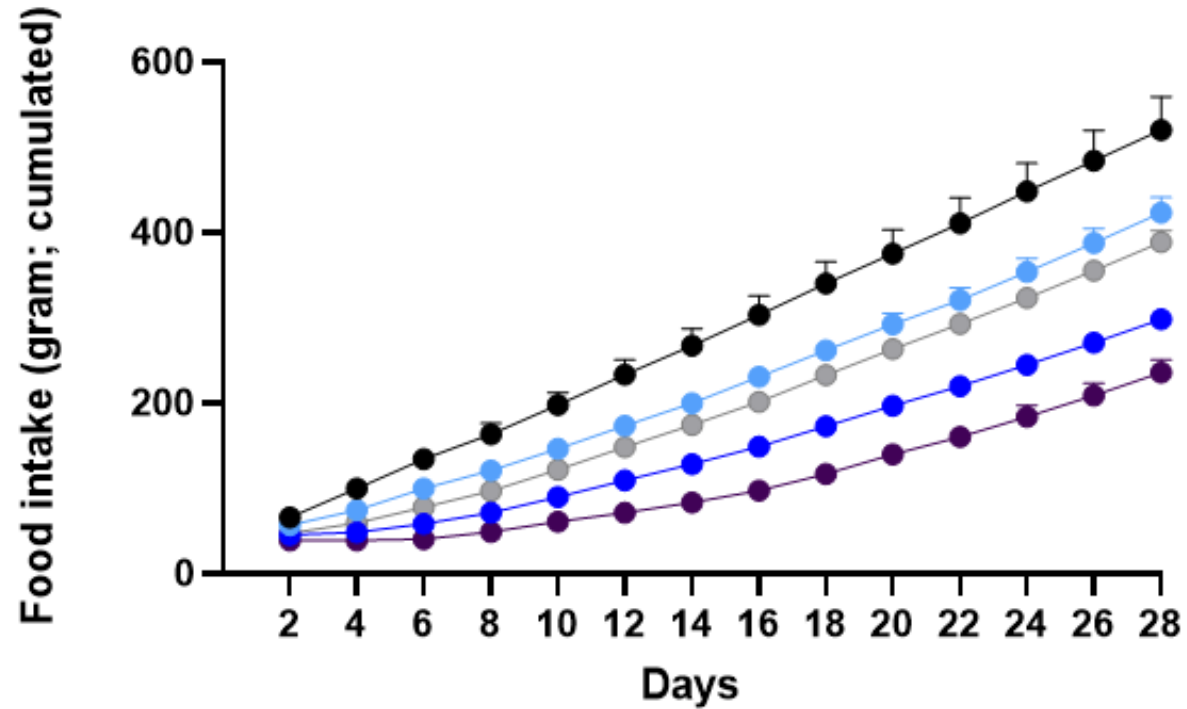


\*\*\*\*  $p < 0.0001$ , \*\*\*  $p < 0.0005$  One-way ANOVA, Bonferroni multiple comparisons test. Mean with SEM.  $n = 9/\text{group}$ .

# Food Intake During Treatment with Dapiglutide and ZP8396 Alone and in Combination

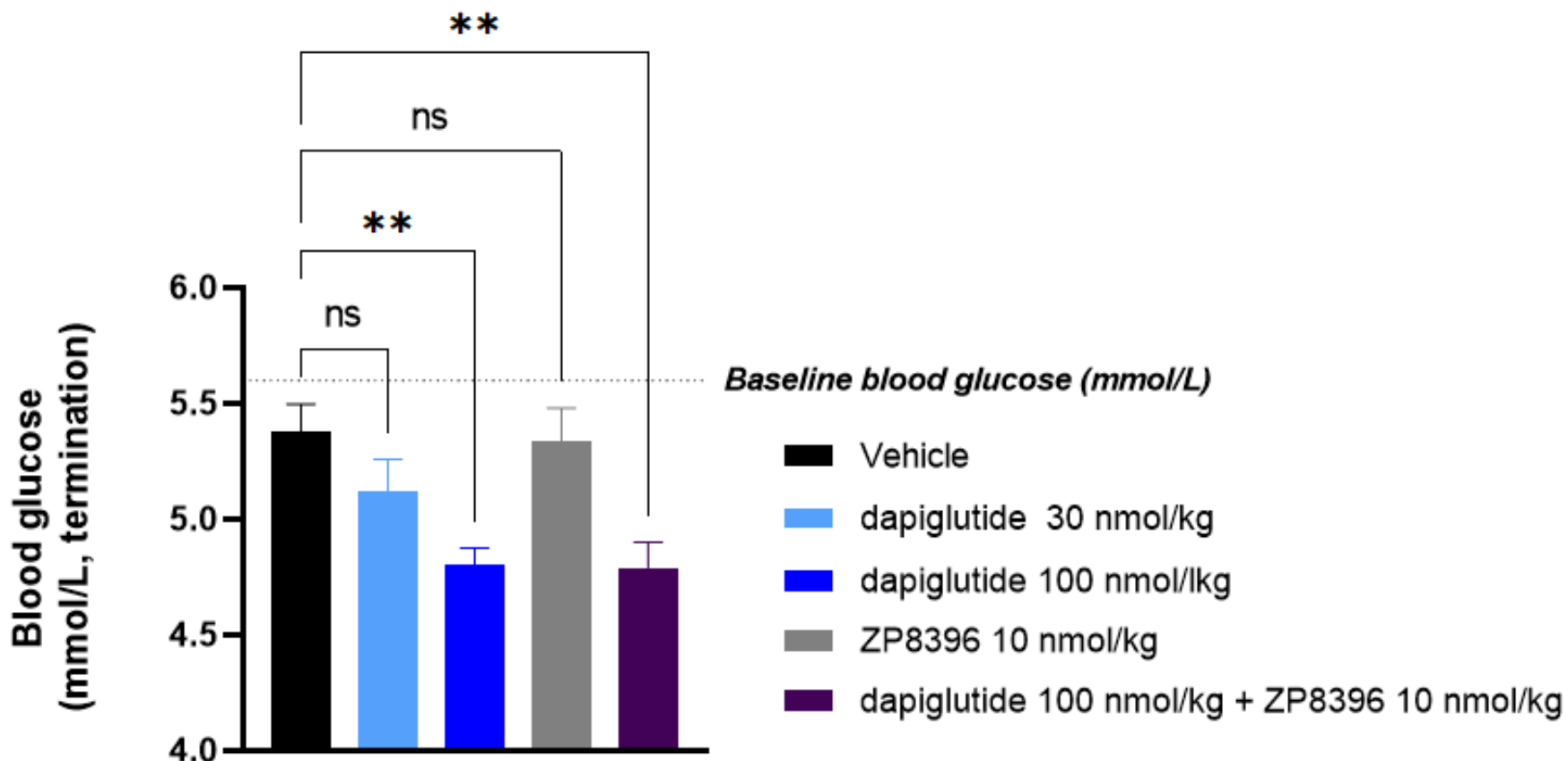


# Food Intake During Treatment with Dapiglutide and ZP8396 Alone and in Combination



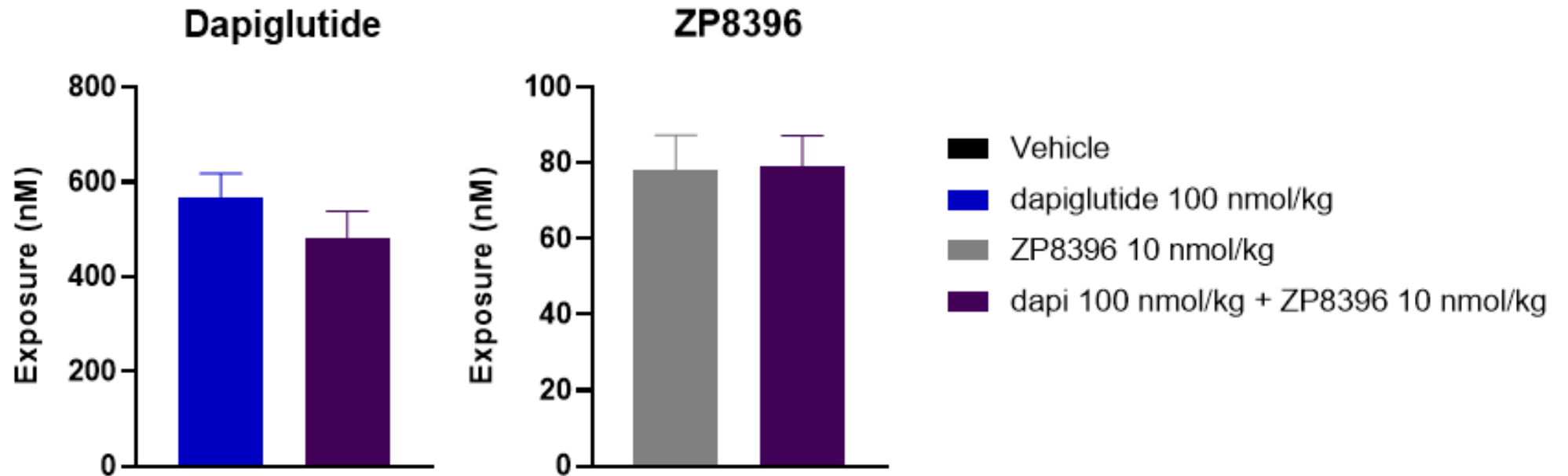
\*\*\*\*  $p < 0.0001$ , \*\*\*  $p < 0.0005$  One-way ANOVA, Bonferroni multiple comparisons test. Mean with SEM.  $n = 9/\text{group}$ .

# Impact of Treatment on Fasting Blood Glucose



\*\* $p < 0.01$  vs. vehicle. One-way ANOVA followed by Dunnett's multiple comparison test. Data are means with SEM,  $n = 9$ /group.

# Impact of Co-administration on Exposure of Dapiglutide or ZP8396



# Key Findings and Conclusions

## Key findings from the DIO rat model

- Dose-dependent body weight reduction with dapiglutide alone
- Additive effect on body weight when dapiglutide was combined with ZP8396
- Anti-obesity effects correlate with reduced food intake
- Treatment with dapiglutide also improved glycemia

## Conclusions

- Dapiglutide is a novel GLP-1/GLP-2 dual agonist with **body weight lowering effect as demonstrated in rodents and humans**
- **ZP8396** is a novel amylin analog, currently in phase 1, that has demonstrated **body weight lowering effect and anti-diabetic potential** in rodents
- In rodents, dapiglutide and ZP8396 can be **combined for additive effect on body weight**

**THANK YOU**  
**for your attention**