Anti-diabetic potential of a novel, long-acting amylin analogue ZP8396 in ZDF rats

Jolanta Skarbaliene on behalf of the Zealand Pharma team

ADA 2022 82nd Scientific Sessions

Presenter disclosure

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Stock/shareholder: Zealand Pharma A/S

Photography allowed

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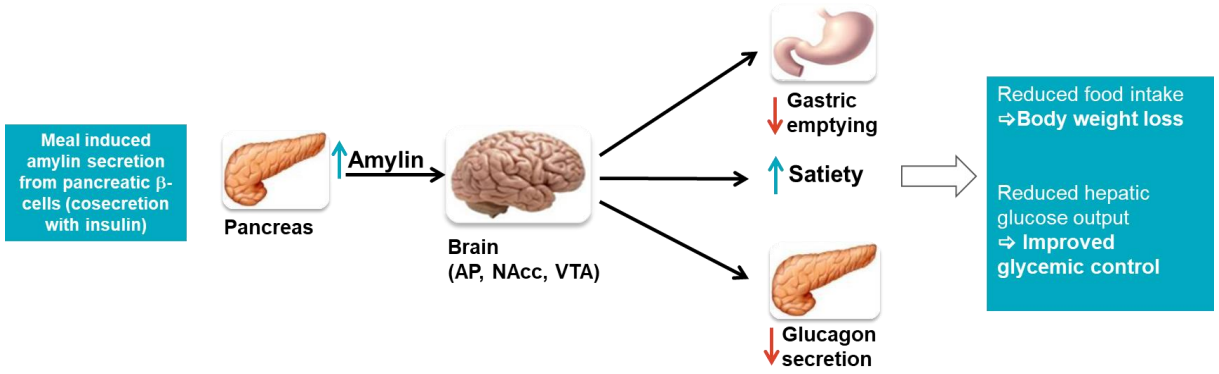
Background

Human amylin[1]

Amylin is a 37-amino acid peptide hormone mainly produced in the pancreatic beta cells and co-secreted with insulin in response to ingested nutrients

The main actions:

- Acts as a satiation signal
- Impacts reward system
- Glucose regulation (decrease glucagon)
- Delays gastric emptying



ZP8396 – amylin analogue in clinical development for weight management

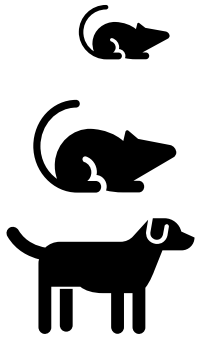
- **Long-acting, acylated human amylin analogue**
- **ZP8396 exhibits high *in vitro* potency on the human CT-R, AMY-R1 and AMY-R3**
- **Designed to improve solubility, minimize fibrillation and allow for co-formulation with other peptides, including GLP-1**
- **Significant weight loss in pre-clinical obesity models as monotherapy or in combination with GLP-1 analogues**

[1]Hay DL et al. Pharmacol Rev 2015;67(3):564-600. DOI:10.1124/pr.115.010629.

Pharmacokinetic parameters of ZP8396

- The pharmacokinetic profile of ZP8396 was fully characterized in three species.

- The plasma half-life ($T_{1/2}$) from the various species indicates that the $T_{1/2}$ in humans would be >**130 hours** and compatible with once-weekly dosing.



	SC parameters		
	$t_{½}$, (h)	T_{max} (h)	Bioavailability (%)
Mouse	26.7	8	79
Rat	33.9	24	69
Dog	>130*	48	73

* i.v. data

In vivo pharmacological evaluation of ZP8396

The aim of the studies was to investigate the anti-diabetic potential of ZP8396 in Zucker Diabetic Fatty (ZDF) rats.

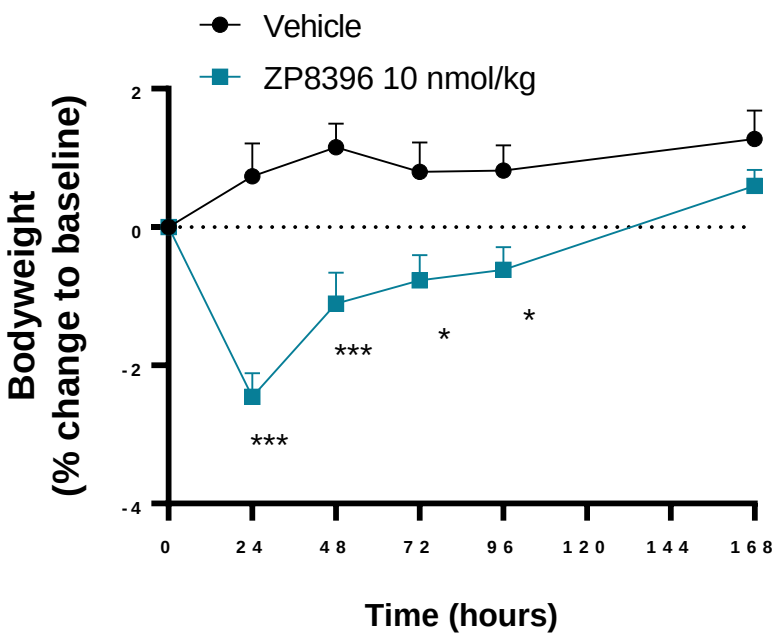
1. **Acute effects**
   The anti-diabetic potential was assessed after a single injection of ZP8396 (s.c., 10 nmol/kg) in ZDF rats

2. **Chronic effects**
   The anti-diabetic effects were assessed after a 4-weeks treatment with ZP8396 (s.c., 30 nmol/kg) in ZDF rats

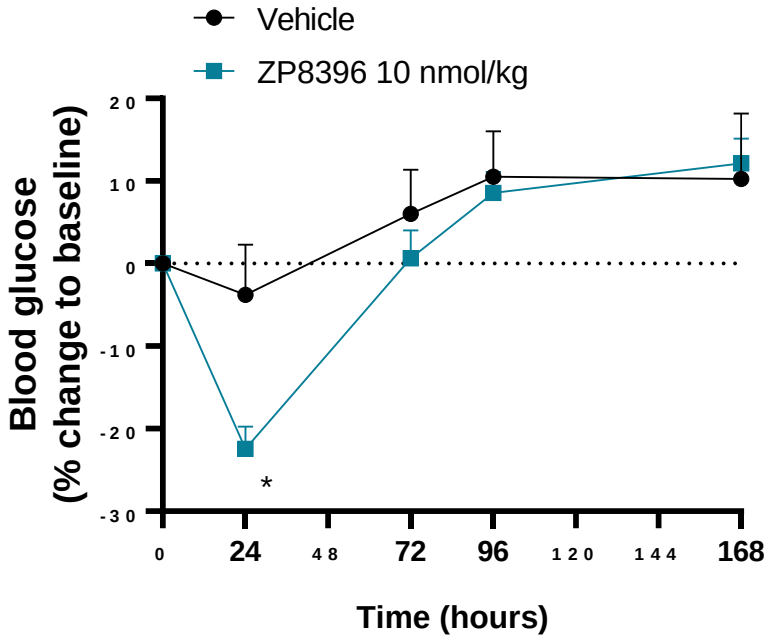
Study 1 – Anti-diabetic potential of ZP8396 in ZDF rats

ZP8396 reduces body weight, lowers blood glucose and plasma glucagon levels after a single injection

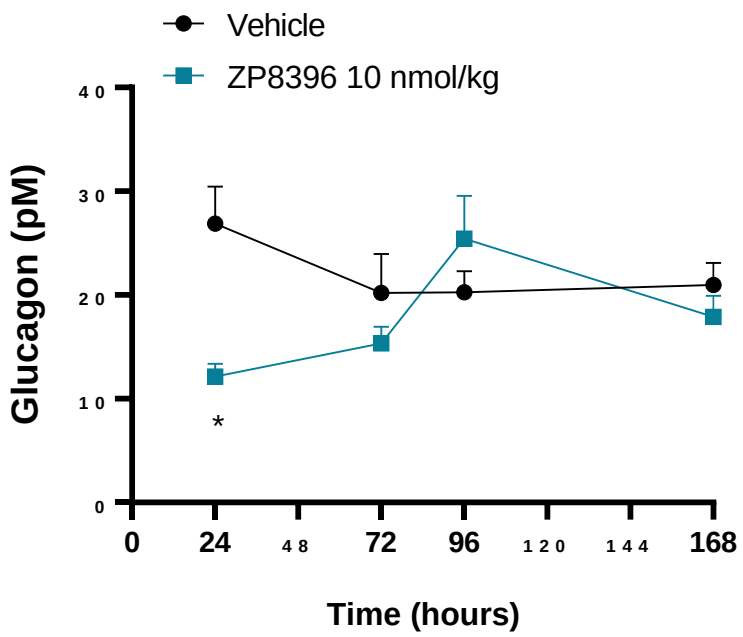
Body weight



Glucose



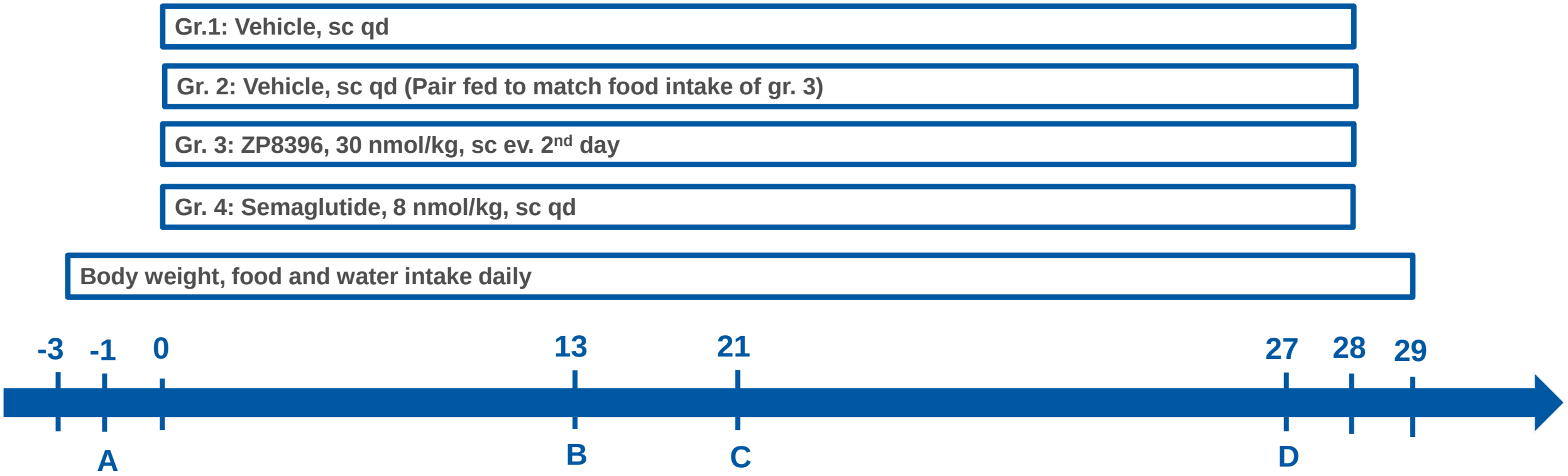
Glucagon



****p<0.001, *p<0.05 vs. vehicle. Two-way ANOVA followed by Sidak multiple comparison post-tests. Data are means ± SEM. n =10.*

Study 2 – Chronic anti-diabetic effects of ZP8396 in ZDF rats

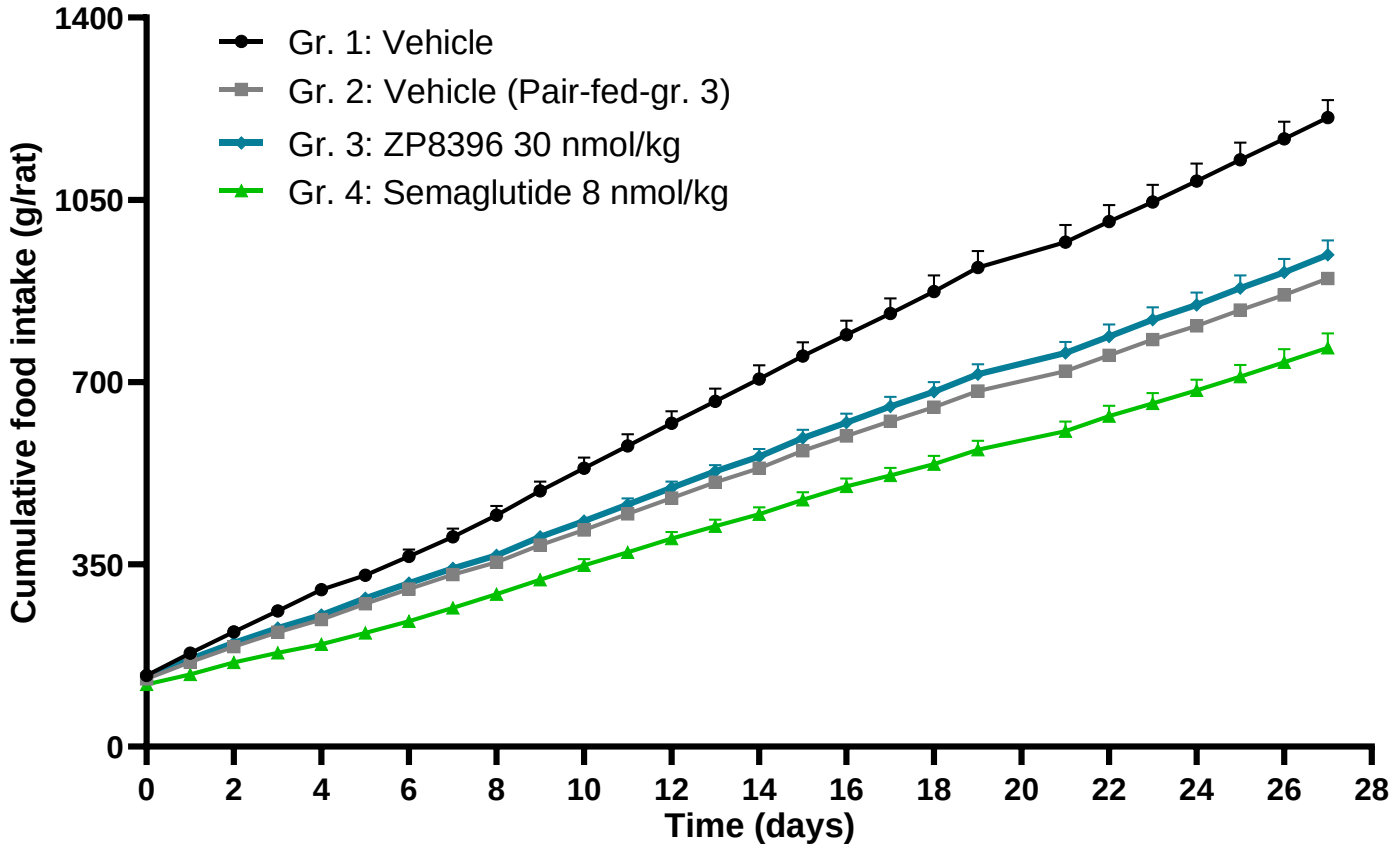
Study design



A: Baseline characterization (fasting state)
B: Blood glucose (non fasting state)
C: IPGTT (fasting state)
D: Pre-termination characterization (fasting state)

Study 2 – Anti-diabetic effects of 4-weeks treatment with ZP8396 in ZDF rats

ZP8396 is effective in lowering cumulative food intake



Gr. 2: Vehicle (Pair-fed-gr.3)
Gr. 3: ZP8396 30 nmol/kg
Gr. 4: Semaglutide 8 nmol/kg

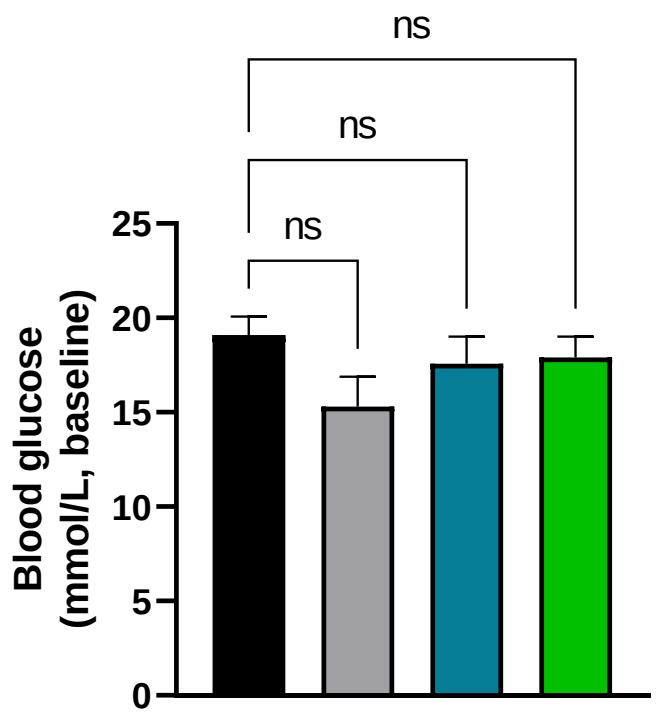
0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
ns	ns	*	*	**	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*		**	**	**	**	**	**	**
ns	ns	ns	*	**	*	ns	ns	*	*	*	*	*	*	*	*	**	**	**	**		**	**	**	**	**	**	**
ns	**	**	**	**	***	**	**	**	**	**	**	**	**	**	**	***	**	***	***		***	***	***	***	***	***	***

**p<0.05, **p<0.01, ***p<0.001, vs. vehicle. Two-way ANOVA followed by Dunnett's multiple comparison test. Data are means ± SEM. n =6-8.*

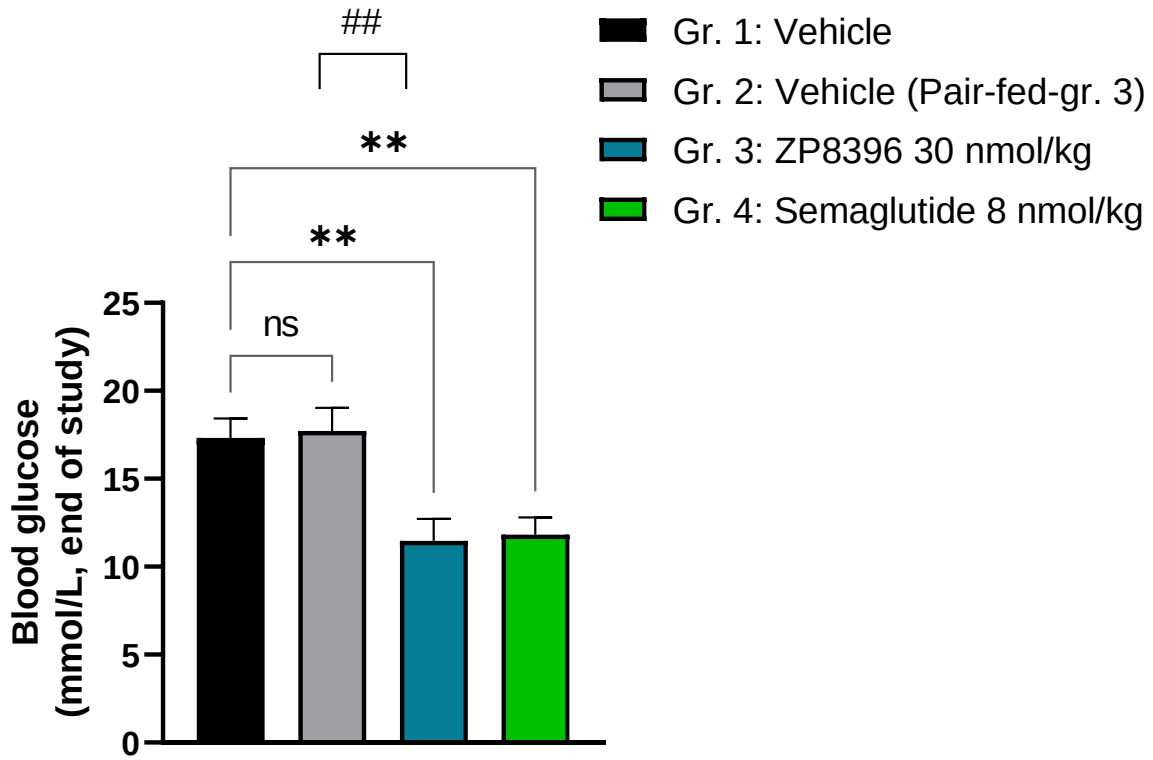
Study 2 – Anti-diabetic effects of 4-weeks treatment with ZP8396 in ZDF rats

ZP8396 is effective in lowering fasting blood glucose levels

Glucose (Baseline)



Glucose (End of study)

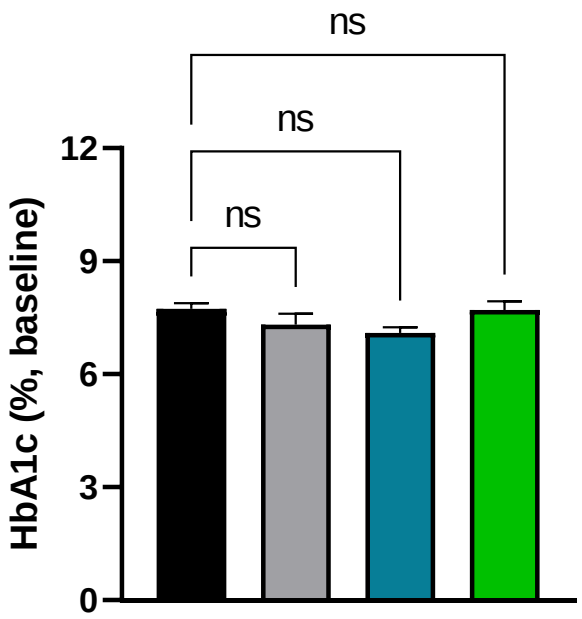


***p<0.01 vs. vehicle. One-way ANOVA followed by Dunnett's multiple comparison test or by unpaired, two tailed t-test, ##p < 0.01 vs. vehicle. Data are means ± SEM. n =7-8.*

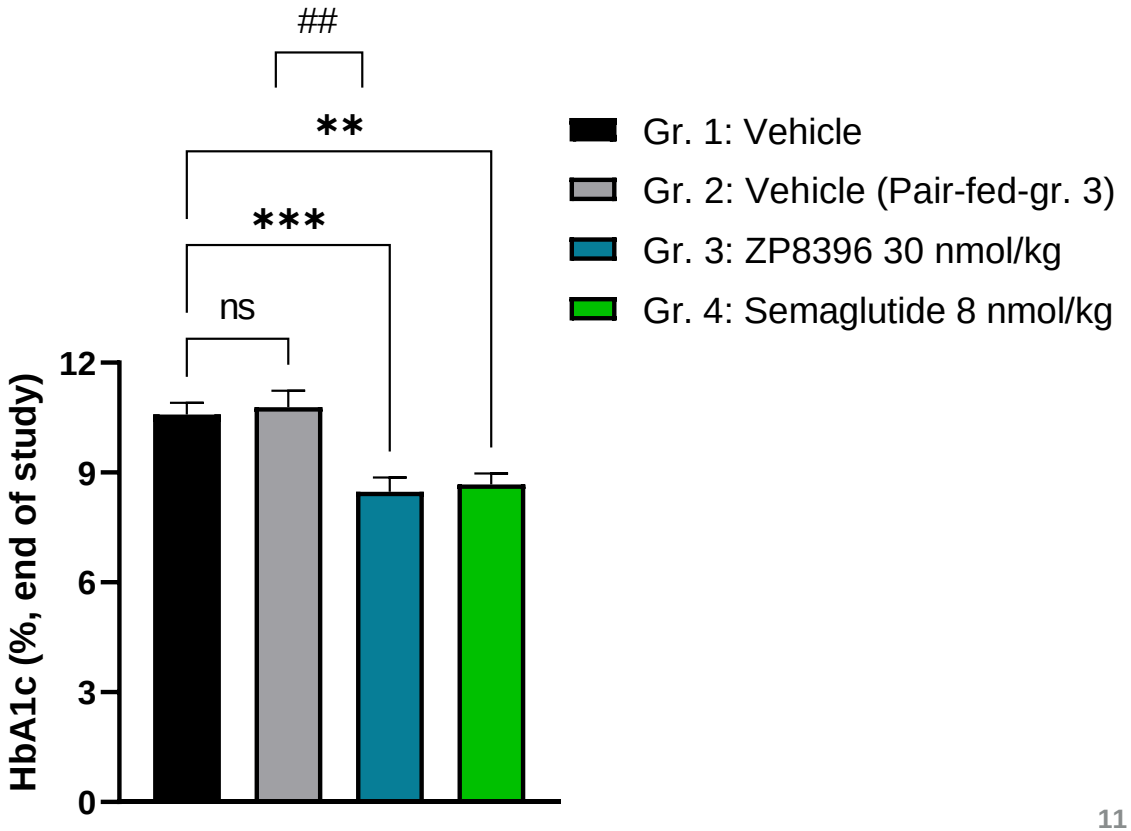
Study 2 – Anti-diabetic effects of 4-weeks treatment with ZP8396 in ZDF rats

ZP8396 effectively reduces glycated hemoglobin (HbA1c) levels in diabetic rats

HbA1c (Baseline)



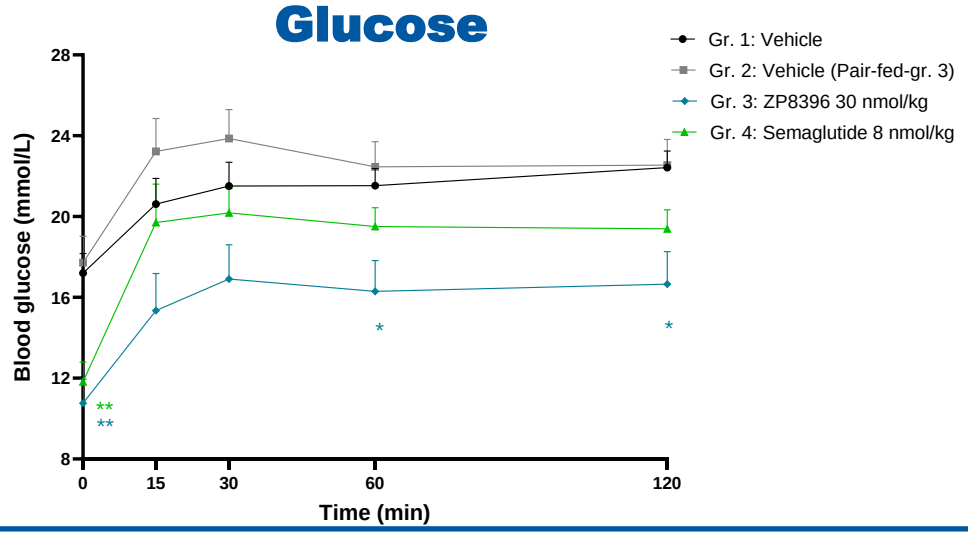
HbA1c (End of study)

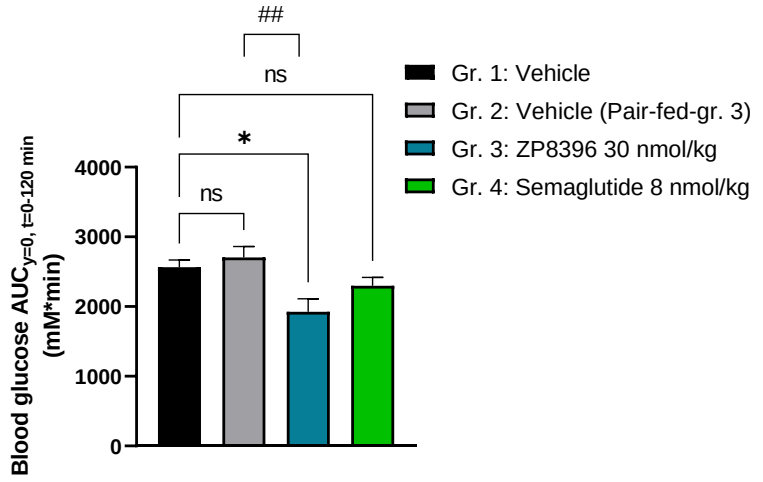


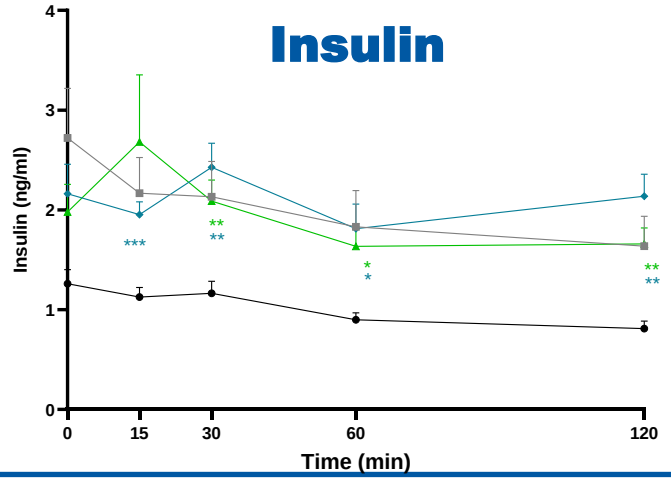
*p<0.05, **p<0.01, ***p<0.001, vs. vehicle. One-way ANOVA followed by Dunnett's multiple comparison test or by unpaired, two tailed t-test, ##p < 0.01 vs. vehicle. Data are means ± SEM. n =6-8.

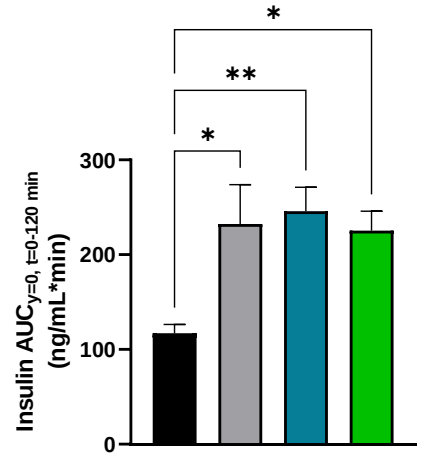
Study 2 – Anti-diabetic effects of 4-weeks treatment with ZP8396 in ZDF rats

ZP8396 improves glucose tolerance in diabetic rats during IPGTT









*p<0.05, **p<0.01, ***p<0.001, vs. vehicle. One-way or two-way ANOVA followed by Dunnett's multiple comparison test or by unpaired, two tailed t-test, ##p < 0.01 vs. vehicle. Data are means ± SEM. n =6-8.

Summary:
Effects of a novel amylin analogue (ZP8396) in ZDF rats

Single injection of ZP8396

- Reduced body weight
- Lowered blood glucose and plasma glucagon levels

4-weeks treatment with ZP8396

- Lowered both Hb1Ac and blood glucose
- Improved glucose tolerance (as measured by IPGTT)

Key finding:

- When compared to pair-fed animals (with equivalent energy consumption), treatment with ZP8396 improved glycemic control to a greater extent than with pair-feeding alone
- Supports specific drug-mediated treatment effects on glycemic control

Conclusions:
Effects of a novel amylin analogue (ZP8396) in ZDF rats

ZP8396 is a long-acting amylin analogue with unique physical-chemical characteristics suitable for formulation at physiologic pH (please see our poster # 1406-P)

ZP8396 has been shown to reduce body weight and is currently in clinical development for the treatment of overweight and obesity

ZP8396 significantly improves glycemic control in ZDF rats which supports the potential for this novel long-acting amylin analogue for the management of diabetes

Thank you!

For your attention