Novel Co-agonists of GLP-1 and GIP Receptors Produce Robust Weight Loss in a Rodent Model of Obesity

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Introduction

Worldwide obesity has nearly tripled since 1975. In 2016, 39% of adults aged 18 years and over were overweight. In 2019, an estimated 38.2 million children under the age of 5 years were overweight or obese.[1] GLP-1 (glucagon-like peptide-1) receptor agonists are a promising drug class originally developed for the treatment of type 2 diabetes, but recently shown to be effective for weight loss in non-diabetic patients with obesity or overweight BMI when given as adjunctive therapy to diet and exercise.[2]

GLP-1 has been shown to decrease glucose, reduce appetite, lower body weight, and improve insulin sensitivity.[3] Endogenous GIP (glucose-dependent insulinotropic polypeptide) also stimulates glucose-dependent insulin secretion and is responsible for a greater proportion of the incretin effect than GLP-1. One difference between GIP and GLP-1 is the effect on glucagon secretion. Unlike GLP-1, GIP has dual functions: a glucagonotropic property in the normoglycemic and hypoglycemic state, and glucagonostatic activity in the hyperglycemic state.[4] Unimolecular dual receptor agonists targeting both the GLP-1 and the GIP receptors may lead to enhanced therapeutic benefits when compared to corresponding mono-agonists of the individual receptors.

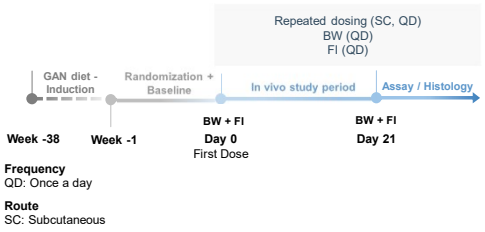
We generated a series of novel multi-receptor agonists to assess the effect of dual GLP-1/GIP receptor activation compared with conventional therapy with the GLP-1 receptor mono-agonist semaglutide. We report herein the results from an evaluation of these compounds in a rodent model of obesity and fatty liver disease.

Methods

Male C57Bl/6J mice were fed the GAN diet (40% fat (primarily palm oil), 40% carbohydrate (22% fructose) and 2% cholesterol) for 38 weeks prior to randomization. These DIO-NASH mice received daily subcutaneous injections of vehicle (n=12) or semaglutide (GLP-1 receptor agonist; 30 nmol/kg, n=12) or novel dual GLP-1/GIP receptor agonists VK2735, VK2736, or VK2737 (each 30 nmol/kg, n=12) for 3 weeks. Daily body weight and food intake were assessed. At termination, plasma glucose, insulin, total cholesterol and triglycerides, and total hepatic triglycerides and steatosis were measured.

Statistical analysis: A t-test was used for between group comparisons. Relative change vs. vehicle and vs. semaglutide was computed for each animal in the treatment group. Error bars represent standard error of mean (SEM).

Study Design



Results

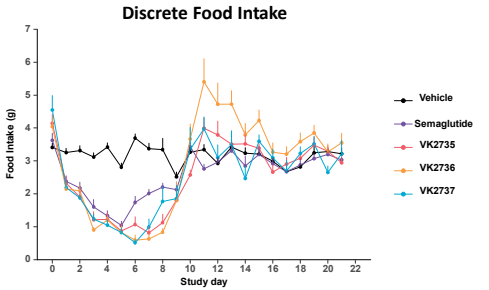
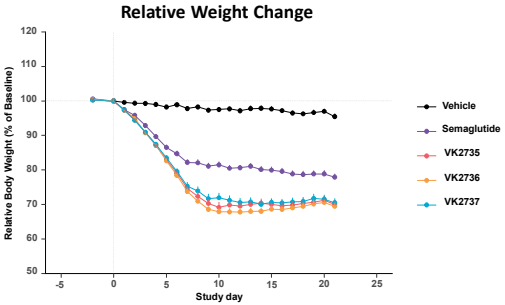
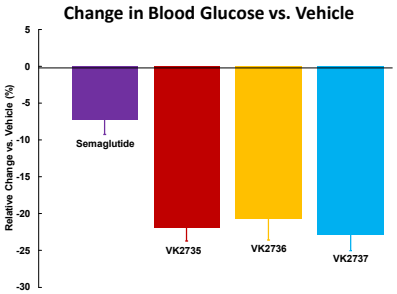


Figure 1. Treatment with VK2735, VK2736, VK2737, and semaglutide led to a transient reduction in food intake when compared to vehicle treatment. Food intake resumed to normal after approximately 10 days. Values expressed as mean of n = 8-12 + Standard Error of Mean (SEM).



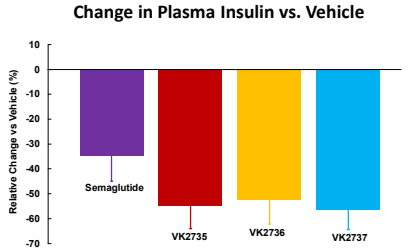
Treatment	Relative Change in BW vs. Vehicle	p-value vs. Vehicle	p-value vs. Semaglutide
Semaglutide	-18.36%	<0.0001	-
VK2735	-26.67%	<0.0001	<0.0001
VK2736	-27.18%	<0.0001	<0.0001
VK2737	-26.12%	<0.0001	<0.0001

Figure 2 and Table 1. Relative body weight loss in animals treated for 21 days with VK2735, VK2736, VK2737 or semaglutide. VK2735, VK2736 and VK2737 reduced body weight to a greater extent than semaglutide. Values expressed as mean of n = 12 + SEM.



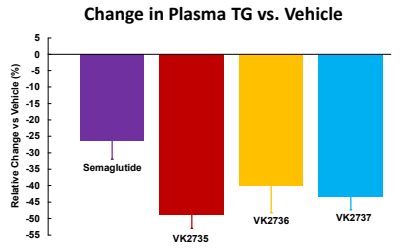
Treatment	Relative Change in Blood Glucose vs. Vehicle	p-value vs. Vehicle	p-value vs. Semaglutide
Semaglutide	-7.26%	0.0159	-
VK2735	-21.91%	<0.0001	<0.0001
VK2736	-20.67%	<0.0001	<0.005
VK2737	-22.85%	<0.0001	<0.0001

Figure 3 and Table 2. VK2735, VK2736, and VK2737 significantly reduced blood glucose at Day 21 in DIO-NASH mice when compared to vehicle and when compared to semaglutide. Values expressed as mean of n = 12 + SEM.



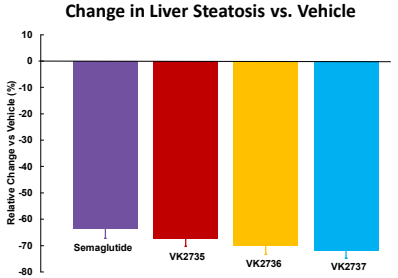
Treatment	Relative Change in Plasma Insulin vs. Vehicle	p-value vs. Vehicle	p-value vs. Semaglutide
Semaglutide	-34.76%	0.0124	-
VK2735	-55.01%	0.0001	0.1499
VK2736	-52.72%	0.0003	0.2121
VK2737	-56.75%	<0.0001	0.0998

Figure 4 and Table 3. VK2735, VK2736, VK2737, and semaglutide enhanced insulin sensitivity at Day 21 compared to vehicle in DIO-NASH mice. Values expressed as mean of n = 12 + SEM.



Treatment	Relative Change in Plasma TG vs. Vehicle	p-value vs. Vehicle	p-value vs. Semaglutide
Semaglutide	-26.38%	0.0040	-
VK2735	-48.89%	<0.0001	0.0034
VK2736	-40.15%	0.0006	0.1686
VK2737	-43.26%	<0.0001	0.0221

Figure 5 and Table 4. VK2735, VK2736, VK2737 and semaglutide reduced plasma triglycerides (TG) at Day 21 compared to vehicle. VK2735 and VK2737 were also superior to semaglutide. Values expressed as mean of n = 11-12 + SEM.



Treatment	Relative Change in Liver Steatosis vs. Vehicle	p-value vs. Vehicle	p-value vs. Semaglutide
Semaglutide	-63.38%	<0.0001	-
VK2735	-67.52%	<0.0001	0.3842
VK2736	-69.96%	<0.0001	0.2065
VK2737	-71.99%	<0.0001	0.0800

Figure 6 and Table 5. Treatment with VK2735, VK2736, VK2737 and semaglutide reduced total liver lipids at Day 21 in DIO-NASH mice. Values expressed as mean of n = 12 + SEM.

Summary

- **VK2735-VK2737 Reduced body weight.** VK dual agonist peptides reduced body weight to a greater extent than GLP-1R agonist semaglutide in DIO-NASH mice
- **VK2735-VK2737 Improved glycemic control and insulin sensitivity.** VK peptides decreased glucose and improved insulin sensitivity relative to vehicle and semaglutide
- **VK2735-VK2737 Improved lipid metabolism.** VK peptides reduced plasma triglycerides and liver lipids in DIO-NASH mice

Conclusion

- Dual activation of the GLP-1 and GIP receptors by a novel series of unimolecular agonists demonstrated significant improvement in weight loss, glucose control, and plasma lipid profile compared with the potent GLP-1 receptor mono-agonist semaglutide.
- Co-activation of the GIP receptor enhances the effect of GLP-1 receptor activation in DIO-NASH mice.
- Dual incretin receptor agonism may be an attractive approach to the treatment of obesity, type 2 diabetes, and other metabolic diseases such as non-alcoholic steatohepatitis.
- Further evaluation of these compounds is ongoing.

References

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