Novel Dual Incretin Receptor Agonists Reduce Body Weight and Improve Metabolic Profile in DIO Mice

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Background

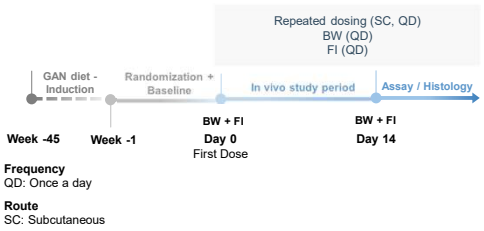
The beneficial effects of glucagon-like peptide-1 (GLP-1) receptor activation may be impaired in obese subjects, even those with normal glucose tolerance. Concomitant activation of glucose-dependent insulinotropic polypeptide (GIP) receptors may potentiate the satiety and insulin-sensitizing effects of GLP-1 receptor activation, leading to enhanced clinical benefits. We developed a series of novel agonists to assess the effect of dual GLP-1/GIP receptor activation on body weight (BW) and other metabolic parameters. We report herein the results from an evaluation of these compounds in a rodent model of obesity.

Methods

Male C57Bl/6J mice were fed the GAN diet (40% fat (primarily palm oil), 40% carbohydrate (22% fructose) and 2% cholesterol) for 45 weeks prior to randomization. These DIO-NASH mice received daily subcutaneous injections of vehicle (n=9) or tirzepatide (GLP-1/GIP receptor agonist; 10 nmol/kg, n=9) or each compound from a series of novel dual GLP-1/GIP receptor agonists VK2735 and VK2742-VK2747 (each 10 nmol/kg, n=9) for 2 weeks. Daily body weight and food intake were assessed. At termination, plasma glucose, insulin, total cholesterol and triglycerides, and hepatic steatosis were measured.

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

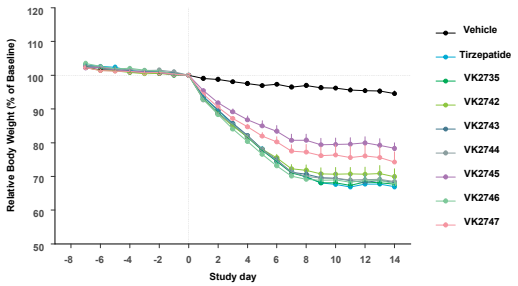
Study Design



Results

Treatment with novel dual GLP-1/GIP receptor agonists resulted in reductions to BW (up to 28%, p<0.0001), plasma glucose, plasma triglycerides, and plasma cholesterol (up to 26%, 37%, and 39%, respectively, p<0.005 for each), and liver triglycerides (up to 49%, p<0.05) compared to vehicle treatment. Weight loss effects in cohorts treated with VK peptides were comparable to those observed in tirzepatide-treated animals, while liver lipid reductions were numerically greater among animals treated with the VK series of compounds.

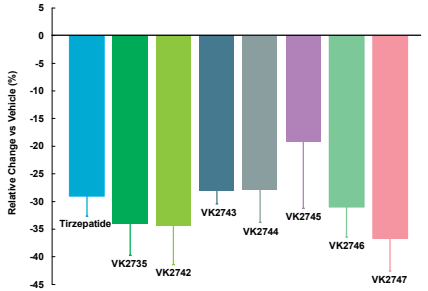
Relative Weight Change



Treatment	Relative Change in Body Weight vs. Vehicle	p-value vs. Vehicle
Tirzepatide	-29.22%	<0.0001
VK2735	-28.42%	<0.0001
VK2742	-26.03%	<0.0001
VK2743	-27.92%	<0.0001
VK2744	-27.62%	<0.0001
VK2745	-17.18%	<0.0001
VK2746	-28.26%	<0.0001
VK2747	-21.45%	0.0001

Figure 1 and Table 1. Relative body weight loss in DIO-NASH mice treated for 14 days with VK2735, VK2742-VK2747 or tirzepatide. VK2735, VK2742-VK2747 and tirzepatide each reduced body weight compared to vehicle. Values expressed as mean of n = 8-9 + SEM (Standard Error of Mean).

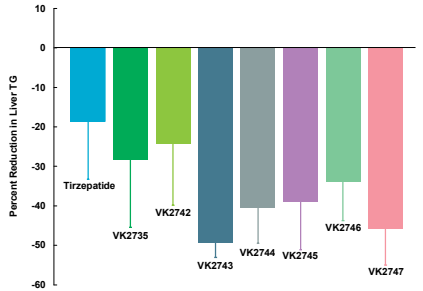
Change in Plasma Triglycerides (TG) vs. Vehicle



Treatment	Relative Change in Plasma TG vs. Vehicle	p-value vs. Vehicle	Relative Reduction in Plasma TG vs. Tirzepatide
Tirzepatide	-29.05%	0.0124	-
VK2735	-34.09%	0.0053	-17.36%
VK2742	-34.37%	0.0081	-18.34%
VK2743	-28.12%	0.0138	3.18%
VK2744	-27.84%	0.0196	4.16%
VK2745	-19.32%	0.2121	33.50%
VK2746	-30.97%	0.0092	-6.60%
VK2747	-36.65%	0.0035	-26.16%

Figure 3 and Table 3. Relative change in plasma triglycerides following 14 days of treatment with VK2735, VK2742-VK2747 or tirzepatide compared with vehicle. All cohorts demonstrated reductions in plasma triglycerides at Day 14 compared to vehicle. Values expressed as mean of n = 7-9 + SEM.

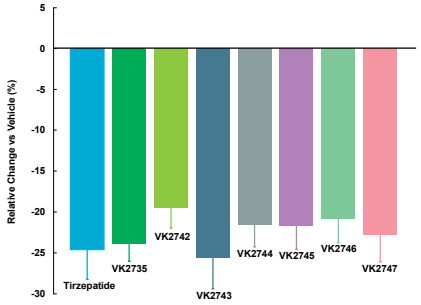
Change in Liver Triglycerides (TG) vs. Vehicle



Treatment	Relative Change in Liver TG vs. Vehicle	p-value vs. Vehicle	Relative Reduction in Liver TG vs. Tirzepatide
Tirzepatide	-18.63%	0.3924	-
VK2735	-28.39%	0.2300	-52.41%
VK2742	-24.39%	0.2756	-30.93%
VK2743	-49.36%	0.0115	-164.95%
VK2744	-40.36%	0.0362	-116.66%
VK2745	-38.89%	0.0628	-108.75%
VK2746	-33.83%	0.0796	-81.60%
VK2747	-45.70%	0.0204	-145.35%

Figure 5 and Table 5. Relative reduction in liver triglycerides in DIO-NASH mice treated for 14 days with VK2735, VK2742-VK2747 or tirzepatide, compared with vehicle. All cohorts demonstrated reductions in liver triglycerides at Day 14 compared to vehicle. Values expressed as mean of n = 8-9 + SEM.

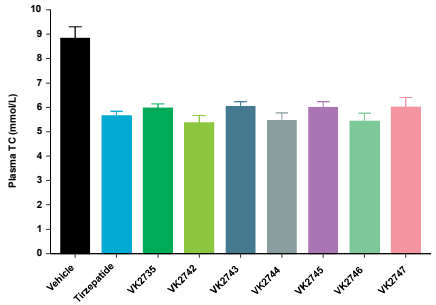
Change in Blood Glucose vs. Vehicle



Treatment	Relative Change in Blood Glucose vs. Vehicle	p-value vs. Vehicle
Tirzepatide	-24.63%	<0.0001
VK2735	-23.87%	<0.0001
VK2742	-19.45%	<0.0001
VK2743	-25.58%	<0.0001
VK2744	-21.61%	<0.0001
VK2745	-21.75%	<0.0001
VK2746	-20.86%	<0.0001
VK2747	-22.83%	<0.0001

Figure 2 and Table 2. Relative change in blood glucose in DIO-NASH mice treated for 14 days with VK2735, VK2742-VK2747 or tirzepatide. VK2735, VK2742-VK2747 and tirzepatide each significantly reduced blood glucose compared to vehicle. Values expressed as mean of n = 8-9 + SEM.

Change in Plasma Total Cholesterol (TC)



Treatment	Relative Reduction in Plasma TC vs. Vehicle	p-value vs. Vehicle
Tirzepatide	-35.99%	<0.0001
VK2735	-32.51%	<0.0001
VK2742	-39.30%	<0.0001
VK2743	-31.63%	0.0002
VK2744	-38.19%	<0.0001
VK2745	-32.16%	<0.0001
VK2746	-38.47%	<0.0001
VK2747	-31.96%	0.0003

Figure 4 and Table 4. Change in plasma total cholesterol following 14 days of treatment with VK2735, VK2742-VK2747 or tirzepatide compared with vehicle. All cohorts demonstrated reductions in plasma cholesterol at Day 14 compared to vehicle. Values expressed as mean of n = 8-9 + SEM.

Conclusion

- A novel series of dual agonists of the GLP-1 and GIP receptors produced significant reductions in BW, plasma lipids, and liver lipids compared with vehicle in a 14-day study in DIO-NASH mice.
- Novel dual agonists produced significant reductions in blood glucose and insulin (not shown), suggesting improved glucose control and insulin sensitivity relative to vehicle.
- Effect sizes observed in plasma and tissues were generally comparable to those observed in the tirzepatide positive control group.
- Dual incretin receptor activation may lead to improvements in measures of body weight, glucose, and lipid control relative to GLP-1 receptor activation alone (see accompanying Poster 206).
- Dual agonism of GLP-1 and GIP receptors represents a promising therapeutic approach to metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic steatohepatitis.
- Further evaluation of these compounds is ongoing.