CHARACTERIZATION AND PRECLINICAL EFFICACY OF A NOVEL UNIMOLECULAR AMYLIN AND GLP-1 RECEPTOR DUAL AGONIST, VRB-104

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Background

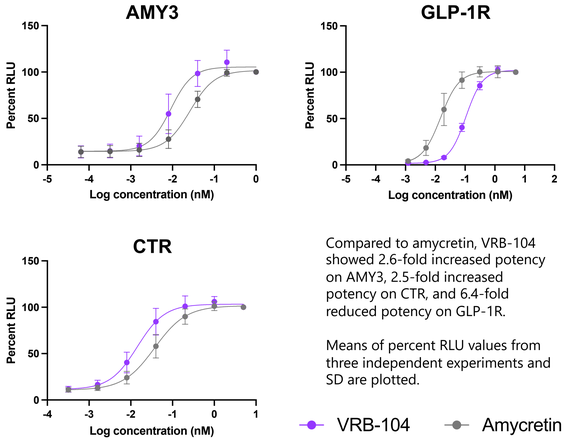
- GLP-1 and amylin are peptide hormones that independently reduce appetite, slow gastric emptying, and decrease glucagon release.
- Combination of GLP-1 and amylin receptor agonists has demonstrated greater weight loss and glycemic control than either agent alone.
- Here we assessed the in vitro potency, in vivo efficacy, and pharmacokinetics (PK) of VRB-104, a novel unimolecular amylin and GLP-1 receptor dual agonist.

Methods

- VRB-104 was tested in reporter cell lines overexpressing human GLP-1 receptor (GLP-1R), calcitonin receptor (CTR), or amylin receptor (AMY3); amycretin was used as a comparator.
- VRB-104, amycretin, or vehicle were administered via daily subcutaneous injection at 10 nmol/kg in a diet-induced obese (DIO) rat model (n = 5 per group) for 14 days, with body weight and food intake recorded daily.
- Single dose subcutaneous PK studies with VRB-104 and amycretin were performed in rats (0.1 mg/kg), mini pigs (0.1 mg/kg), and cynomolgus monkeys (0.1 mg/kg).

Results

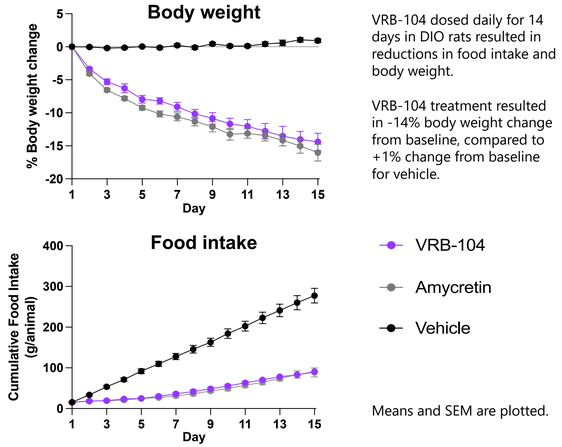
FIGURE 1. IN VITRO RECEPTOR ACTIVATION



Compared to amycretin, VRB-104 showed 2.6-fold increased potency on AMY3, 2.5-fold increased potency on CTR, and 6.4-fold reduced potency on GLP-1R.

Means of percent RLU values from three independent experiments and SD are plotted.

FIGURE 2. EFFICACY IN DIO RAT



VRB-104 dosed daily for 14 days in DIO rats resulted in reductions in food intake and body weight.

VRB-104 treatment resulted in -14% body weight change from baseline, compared to +1% change from baseline for vehicle.

Means and SEM are plotted.

TABLE 1. IN VITRO RECEPTOR ACTIVATION

	EC_{50} (nM) (mean ± SD)		
	AMY3	**CTR**	**GLP-1R**
VRB-104	0.010 ± 0.004	0.016 ± 0.008	0.108 ± 0.013
Amycretin	0.026 ± 0.007	0.040 ± 0.019	0.017 ± 0.009

Means of EC_{50} values from three independent experiments and SD.

TABLE 2. PK PARAMETERS

		$T_{1/2}$ (h)	T_{max} (h)	C_{max} (nM)	AUC_{0-t} (h*nM)
Rat	VRB-104	12.3	6	20.1	596.7
	Amycretin	13.9	6	19.1	530.7
Pig	VRB-104	67.9	8	55.8	5406.9
	Amycretin	55.8	8	71.6	6022.2
Cyno	VRB-104	33.7	8	56.9	3274.1
	Amycretin	33.3	8	88.9	4614.4

AUC_{0-t} = AUC from time 0 to 48 h (rat), 216 h (mini pig), and 168 h (cynomolgus monkey)

Conclusions

- VRB-104 is a novel unimolecular amylin and GLP-1 receptor dual agonist, with selectivity for AMY3 over GLP-1R
- Reduced GLP-1R potency and increased AMY3 potency was incorporated into the design of VRB-104 with the goal of maintaining clinical efficacy while reducing GLP-1 associated adverse events
- In vitro, VRB-104 showed ~3-fold increased potency on AMY3 compared to amycretin, while showing ~6-fold reduced potency on GLP-1R compared to amycretin
- In the DIO rat model, VRB-104 dosed daily for 14 days induced a 14% body weight loss from baseline compared to 1% weight gain for vehicle
- Single subcutaneous dose PK studies showed a half-life for VRB-104 of 12.3 h in rats, 67.9 h in mini pigs, and 33.7 h in cynomolgus monkeys
- These data support the development of VRB-104 for the potential treatment of obesity and long term weight maintenance

Abbreviations: AMY3, amylin receptor 3; AUC_{0-t}, area under the plasma concentration-time curve from time zero to time t; C_{max}, maximum concentration; CTR, calcitonin receptor; DIO, diet-induced obese rat; EC_{50}, half maximal effective concentration; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; h, hours; PK, pharmacokinetics; SD, standard deviation; SEM, standard error of the mean; $t_{1/2}$, half-life; T_{max}, time to maximum concentration

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