VRB-103 IS A POTENT, ORALLY BIOAVAILABLE AMYLIN ANALOG WITH A STRONG SELECTIVITY TOWARDS HUMAN AMYLIN RECEPTORS VS. CALCITONIN RECEPTOR

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Background

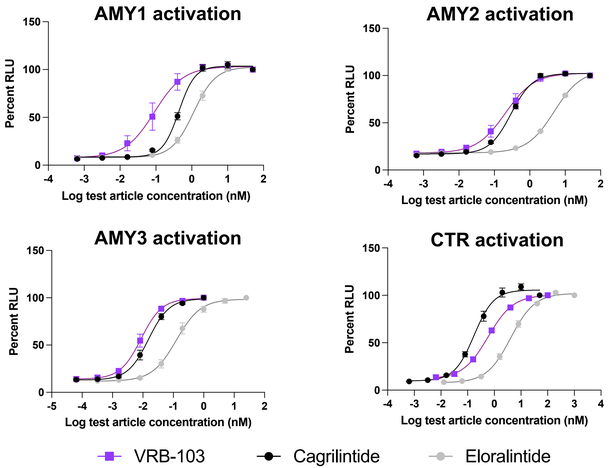
- Amylin is a peptide gut hormone secreted from pancreatic β-cells that reduces appetite, delays gastric emptying, and decreases glucagon release
- Amylin activates human amylin receptors (AMY1, AMY2 and AMY3), which consist of the calcitonin receptor (CTR) with receptor activity modifying proteins (RAMP1-3)
- Subcutaneously-administered amylin analogs in clinical development, such as cagrilintide and eloralintide, demonstrate distinct profiles for tolerability and body weight reduction
- Amylin analogs also vary in their selectivity for AMY1-3 relative to CTR, which may have implications for clinical efficacy and tolerability[1, 2]
- VRB-103 is a novel amylin analog optimized for oral administration. Here we evaluated the in vitro potency of VRB-103 for activation of AMY1-3 and CTR, and its relative selectivity.

Methods

- VRB-103 and comparators, cagrilintide and eloralintide, were tested for receptor activation potency in Chinese hamster ovary (CHO) reporter cells stably overexpressing human CTR and RAMP1, 2, or 3 (AMY1, 2, or 3) or CTR alone.
- Cells were treated with compounds for 5 or 6 hours at 37°C in medium containing 10% fetal bovine serum (FBS).
- Receptor agonism was measured by luciferase expression.

Results

FIGURE 1. RECEPTOR ACTIVATION



Mean of three independent experiments and SEM are plotted, with the exceptions of five independent experiments for cagrilintide (AMY1-3) and two independent experiments for eloralintide (CTR).

TABLE 1. RECEPTOR ACTIVATION

	EC_{50} (nM) (mean ± SEM)			
	AMY1	**AMY2**	**AMY3**	**CTR**
VRB-103	0.091 ± 0.025	0.205 ± 0.036	0.009 ± 0.001	0.585 ± 0.060
Cagrilintide	0.435 ± 0.024	0.297 ± 0.017	0.015 ± 0.002	0.204 ± 0.019
Eloralintide	1.129 ± 0.102	4.891 ± 0.190	0.126 ± 0.017	3.387 ± 0.428

Mean of at least three independent experiments and SEM.

TABLE 2. RELATIVE RECEPTOR ACTIVATION

	AMY1 vs CTR	**AMY2 vs CTR**	**AMY3 vs CTR**	**AMY1 vs AMY3**
VRB-103	6.43	2.85	65.00	0.10
Cagrilintide	0.47	0.69	13.60	0.03
Eloralintide	3.00	0.69	26.88	0.11

AMY vs CTR calculated as EC_{50} of CTR/ EC_{50} of AMY1, 2, or 3. Higher number indicates more selectivity for AMY.

AMY1 vs AMY3 calculated as EC_{50} of AMY3/ EC_{50} of AMY1. Higher number indicates more selectivity for AMY1.

TABLE 3. RELATIVE RECEPTOR ACTIVATION COMPARED TO CAGRILINTIDE

	AMY1 vs CTR	**AMY2 vs CTR**	**AMY3 vs CTR**	**AMY1 vs AMY3**
VRB-103	13.7	4.2	4.8	2.9
Cagrilintide	1.0	1.0	1.0	1.0
Eloralintide	6.4	1.0	2.0	3.2

Calculated from Table 2 values as EC_{50} ratio of each test article/ EC_{50} ratio of cagrilintide.

Higher number indicates more selectivity than cagrilintide for AMY (vs CTR) or AMY1 (vs AMY3).

Conclusions

- VRB-103 is an orally bioavailable selective amylin analog
- VRB-103 showed potent activation of human amylin receptors in vitro
- VRB-103 was more potent than cagrilintide and eloralintide for AMY1-3 activation in cell culture
- VRB-103 showed strong selectivity towards human amylin receptors relative to calcitonin receptor, with approximately 3 to 65-fold lower potency for CTR activation compared to AMY1-3 activation
- The relative amylin receptor selectivity of VRB-103 was more pronounced than that of the comparators
- VRB-103 is currently in development as a potential once weekly oral tablet for weight reduction and long-term maintenance of weight reduction in adults with obesity or overweight , both as a monotherapy and in combination

References

1. Briere et al. *Mol Metab*. 2025; 102:102271.
2. Kruse et al. *J. Med. Chem.* 2021; 64(15): 11183.

Abbreviations: AMY, amylin receptor; CHO, Chinese hamster ovary cell line; CTR, calcitonin receptor; EC_{50}, half maximal effective concentration; FBS, fetal bovine serum; SEM, standard error of the mean; RAMP, receptor activity modifying protein; RLU, relative light units

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