EFFICACY OF A NOVEL ORAL AMYLIN ANALOG AND THE DEVELOPMENT OF AN ORAL AMYLIN/GLP-1 COFORMULATED TABLET TO PRODUCE HIGH IN VIVO PLASMA EXPOSURES

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Background

- Amylin and GLP-1 peptide hormones independently reduce food intake, delay gastric emptying, and decrease glucagon release[1,2]
- Amylin agonists have the potential to be effective monotherapies or supplement GLP-1 receptor agonists (RA) in combination therapy for improved efficacy[1]
- VRB-103, a novel oral amylin analog, is being developed for the treatment of obesity and was designed as a dual amylin and calcitonin receptor agonist (DACRA)
- VRB-103 was designed leveraging rational peptide engineering to improve potency and half-life, in addition to proprietary oral delivery technology (T2026) to provide a once-weekly oral VRB-103 formulation
- VRB-103 in development with VRB-101, a GLP-1 analog, is explored in this poster as a once-weekly oral combination therapy (fixed dose oral combination)

Methods

PK study

- An oral coformulated tablet of VRB-103, VRB-101, and T2026 was dosed daily in cynomolgus monkeys for 7 days and PK samples were collected and analyzed

***In vitro* potency study**

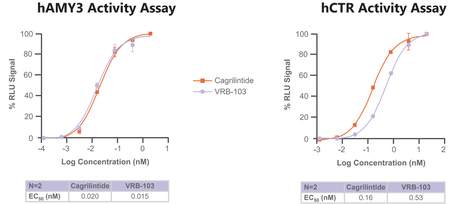
- CHO-K1 CRE reporter cells overexpressing either the rat, cynomolgus monkey, or human amylin receptor complex (calcitonin receptor and Ramp3) (hAMY3), or calcitonin receptor alone (hCTR) were treated with VRB-103 or a comparator (cagrilintide, an amylin analog); receptor activation was measured by luciferase expression

Efficacy in a DIO rat model

- DIO rats (n=5 animals per group; 17 weeks on a high-fat diet [research diets, D12492]) received QD subcutaneous injections for 3 weeks of either vehicle, VRB-103, VRB-101, or VRB-103 in combination with VRB-101

Results #1

FIGURE 1. VRB-103 WAS DESIGNED FOR POTENT hAMY3 AND hCTR ACTIVITY[3]



N=2	Cagrilintide	VRB-103
EC_{50} (nM)	0.020	0.015

N=2	Cagrilintide	VRB-103
EC_{50} (nM)	0.16	0.53

- VRB-103 activated hAMY3 and hCTR with similar potency to cagrilintide

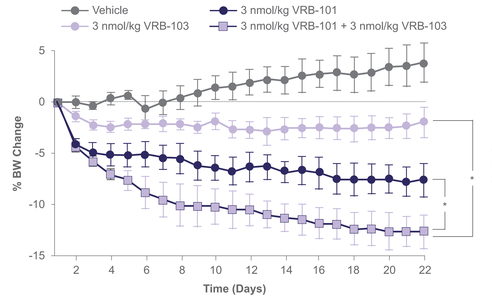
Results #2

TABLE 1. CROSS SPECIES *IN VITRO* POTENCY OF VRB-103 AND CAGRILINTIDE IN CHO-K1 CRE REPORTER CELLS EXPRESSING HUMAN, MONKEY, OR RAT AMY3[3]

Sample ID	Average EC_{50} (nM) ± SD		
	Human	Monkey	Rat
Cagrilintide	0.701 ± 0.130	0.731 ± 0.075	23.095 ± 3.195
VRB-103	1.122 ± 0.553	2.012 ± 0.156	292.2 ± 59.3

- Oral amylin peptide VRB-103 has high potency against the human AMY3 receptor
- VRB-103 has reduced potency on rodent AMY3 receptors, making rodent obesity models less predictive for clinical performance

FIGURE 2. DESPITE LOWER POTENCY IN STIMULATING RODENT AMY3, VRB-103 INDUCES SIGNIFICANT WEIGHT REDUCTION IN MONOTHERAPY AND IN COMBINATION WITH VRB-101[3]



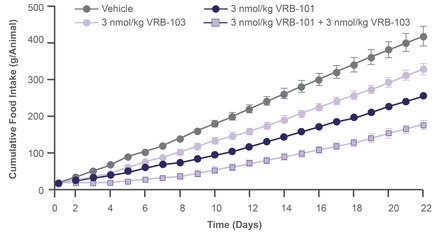
Analyzed by One-Way ANOVA.

*P<0.0001.

- Despite the reduced potency on rodent amylin receptors, VRB-103 induces significant weight reduction and reduced food intake in rodents
- Combination dosing with GLP-1 (VRB-101) significantly increased BW reduction relative to VRB-101 or VRB-103 alone

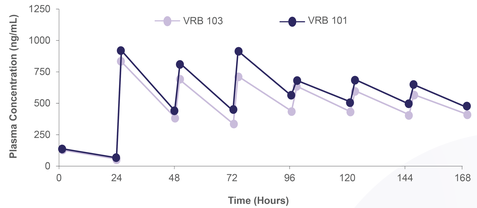
Results #3

FIGURE 3. VRB-103 ALONE OR IN COMBINATION WITH VRB-101 RESULTS IN SUSTAINED REDUCED FOOD INTAKE



- In DIO rats, the combination of VRB-103 and VRB-101 resulted in significantly greater weight reduction and less food intake than either alone

FIGURE 4. VRB-103 AND VRB-101 DELIVER THERAPEUTIC PLASMA EXPOSURES WHEN DOSED ORALLY IN A COFORMULATED TABLET IN CYNOMOLGUS MONKEYS[3]



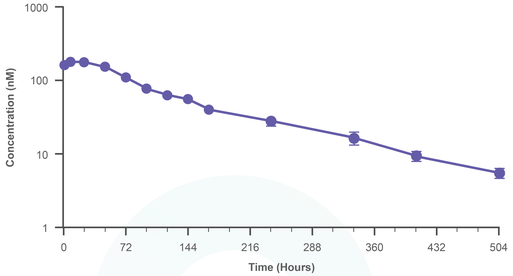
Cyno PK confirms high exposure with a single fixed-dose coformulated tablet (7 mg/7 mg per animal, QD)

Candidate	MoA	PO $AUC_{0\text{-}168h}$ (h*ng/mL)
VRB-101	GLP-1RA	93,249
VRB-103	Amylin-RA	79,352

ANOVA=analysis of variance. $AUC_{0\text{-}t}$=area under the plasma concentration-time curve from time zero to time t. $AUC_{0\text{-}inf\_obs}$=observed area under the plasma concentration-time curve from time zero to infinity. BW=body weight. cAMP=cyclic adenosine monophosphate. C_{max}=maximum concentration. CHO-K1=chinese hamster ovary cell line K1. CRE=cAMP response element. h=hour. DIO=diet-induced obesity. EC_{50}=half maximal effective concentration. FI=food intake. GLP-1=glucagon-like peptide-1. MOA=mechanism of action. $MRT_{0\text{-}inf\_obs}$=observed mean residence time from time zero to infinity. PO=per os (by mouth). PK=pharmacokinetic. QD=once-daily. RLU=relative light unit. SD=standard deviation. SC=subcutaneous. $t_{1/2}$=half-life. T_{max}=time to maximum concentration.

Results #4

FIGURE 5. PK OF SINGLE-DOSE VRB-103 (0.1 mg/kg SC) IN CYNOMOLGUS MONKEYS[3]



Parameter	Unit	21051815	21052405	22030109	Average
$t_{1/2}$	h	121.5	104.6	117.0	114.4
T_{max}	h	24.0	8.0	24.0	18.7
C_{max}	nmol/L	198.1	193.4	182.9	191.4
$AUC_{0\text{-}t}$	nmol/L*h	25546.7	20457.6	27442.5	24482.3
$AUC_{0\text{-}inf\_obs}$	nmol/L*h	26718.1	21054.7	28534.9	25435.9
$MRT_{0\text{-}inf\_obs}$	h	140.6	127.0	149.7	139.1

Conclusions

- In a preclinical model, the combination of the amylin analog VRB-103 and GLP-1 analog VRB-101 demonstrated an additive effect on body weight reduction
- Both VRB-103 and VRB-101 achieved high plasma exposures in cynomolgus monkeys when dosed daily from a single coformulated oral tablet containing VRB-103, VRB-101, and the oral absorption enhancer T2026
- This work supports continued development of the once-weekly oral VRB-103 as a potential monotherapy and combination therapy with VRB-101 (GLP-1 analog), as well as the optionality for a fixed dose combination of VRB-101 and VRB-103 for the treatment of obesity and cardiometabolic diseases

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1. Dehestani B, et al. *J Obes Metab Syndr.* 2021;30(4):320-325. 2. Collins L and Costello RA. StatPearls [Internet]. 2024. 3. Data on File. Verdiva Bio.