Discovery of RV-8451, a Novel, Oral, Muscle-Preserving Small Molecule GLP-1 Receptor Agonist

Sol Collado[1], Harry Chobanian[1], Melissa Luse[1], Brianna Dalesandro[1], Tom Richardson[2], Anchi Scott[2], Christin Hamilton[1], Steve Eaton[1], Aaron Cole[1], Omer Khan[1], Jameel Dennis[1], Ariele Viacava Follis[1], Shaharyar Khan[1]

[1]Rivus Pharmaceuticals, Charlottesville, VA, USA; [2]PharmaDirections, Cary, NC, USA

2574-P

Background

Current Landscape & Limitations

- GLP-1RAs are highly effective obesity treatments but are restricted by tolerability issues and significant loss of lean muscle mass.

The Role of Muscle Preservation

- Losing lean mass is strongly associated with weight loss plateau and weight regain following treatment discontinuation.
- While resistance exercise can attenuate this loss, there is a critical need for pharmacological solutions that support durable, long-term weight loss.

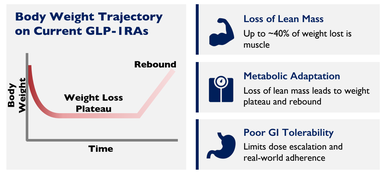
The Unmet Clinical Need

- Next-generation GLP-1RAs must drive significant weight loss while simultaneously preserving muscle to optimize overall metabolic health.

Our Research: RV-8451

- RV-8451 is a novel, oral, non-peptide GLP-1RA currently in preclinical development, designed to be muscle-preserving.
- Objective: To characterize the discovery, *in vitro* and *in vivo* pharmacology, and muscle-preserving efficacy of RV-8451.

Current GLP-1RAs Have Persistent Limitations



Loss of Lean Mass
Up to ~40% of weight lost is muscle

Metabolic Adaptation
Loss of lean mass leads to weight plateau and rebound

Poor GI Tolerability
Limits dose escalation and real-world adherence

Methods

In Vitro Studies:

Binding Assay: GLP-1 receptor binding was quantified using a time-resolved fluorescence (TRF) assay measuring the competitive displacement of fluorescent Red-Exendin.

cAMP Assay: cAMP levels were quantified using the HitHunter cAMP Assay. Danuglipron served as a reference.

β-arrestin Assay: β-arrestin recruitment was quantified using Eurofins hGLP1R β-arrestin CHO-K1 cells and detection reagents. Exendin served as a reference.

In Vivo Studies:

Male diet-induced obese (DIO) humanized GLP-1R (hGLP-1R) mice were fed high-fat diet for at least 10 weeks and treated with a low dose of RV-8451 (QD) for 2 days and a high dose of RV-8451 for the following 12 days. Treatment ceased at day 14, with a 14-day follow-up. Food and water intake was measured daily for the first 14 days. Weight loss (WL) efficacy was evaluated daily throughout the 28-day study, with body composition quantified by EchoMRI at day 8, 15, 21, and 28.

After a 3-day baseline, male DIO hGLP-1R mice were treated with a high dose of RV-8451 for 4 consecutive days. Respiratory Exchange Ratio (RER) was assessed using the Promethion (Comprehensive, High-resolution Behavioral Analysis Systems, Sable Systems International).

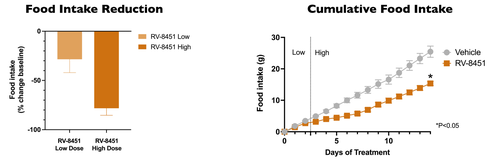
Results

1 RV-8451 is a Potent Biased GLP-1R Non-peptide Agonist

	RV-8451	Orforglipron	Danuglipron
In Vitro Potency			
hGLP-1R cAMP, EC_{50}, nM	< 50	2	0.2
MkGLP-1R cAMP, EC_{50}, nM	< 2	< 1	< 1
hGLP-1R binding, K_i, nM	< 500	20	200
Biased Signaling			
hGLP-1R β-arrestin2, EC_{50}, nM / E_{max}, %	>30,000 / <10	>30,000 / <10	>800/ <60
Cross Species Activity			
Human, NHP, rat, mouse, dog	+, +, -, -, -	+, +, -, -, -	+, +, -, -, -

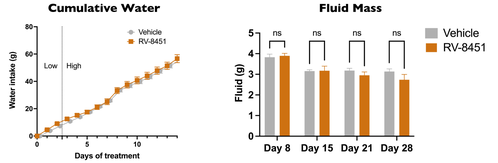
- RV-8451 specifically binds to hGLP-1R *in vitro* and produces robust activation of the Gαs–cAMP pathway without measurable β-arrestin2 recruitment, consistent with a fully G-protein biased agonist profile.
- Like other GLP-1R non-peptide agonists, RV-8451 only activates human and monkey, but not rodent or dog GLP-1R.

2 RV-8451 Reduced Food Intake



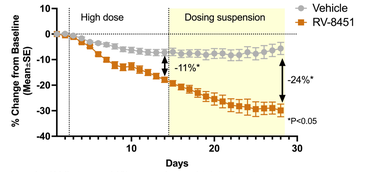
- RV-8451 results in a significant, dose-dependent reduction of food intake in DIO hGLP-1R mice:
  - 28% reduction at lower doses
  - 78% (maximum) reduction at high doses

3 RV-8451 Did Not Alter Water Intake or Cause Dehydration



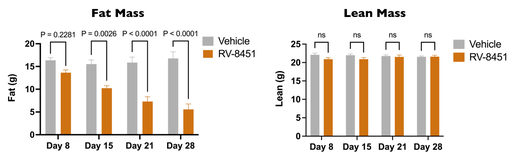
- RV-8451 did not cause a reduction in water intake or fluid mass loss
- In contrast, current GLP-1s reduce water intake and show fluid mass loss
- Preventing dehydration may reduce the risk of kidney injury

4 RV-8451 Drove Significant and Sustained Weight Loss



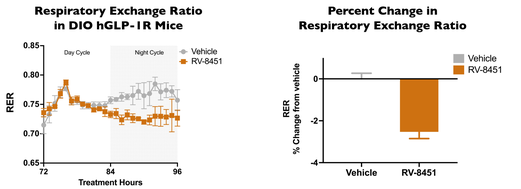
- RV-8451 produced marked WL (up to 11% more than vehicle) after 14 days
- WL continued for 7 days post treatment, then was sustained for 7 additional days, resulting in a cumulative 24% reduction in body weight (vs vehicle) after 28 days.

5 RV-8451 Induced Fat Loss while Preserving Lean Mass



- RV-8451 drove significant fat mass reduction (up to 34%) after 14 days of treatment, with no change in lean mass.
- Fat mass continues to decline during washout period. At day 28, a 67% reduction in fat mass was observed, without loss of lean mass.

6 RV-8451 Reduced RER, Shift Toward Greater Fat Oxidation



- RV-8451 lowered RER (-2.5%) on the last day of treatment (day 4), suggesting a shift toward greater fat oxidation.

Conclusions

Differentiation:
RV-8451 is an oral non-peptide GLP-1RA with a unique pharmacological profile designed to address the lean-mass loss limitations of current incretin therapies.

High-Quality Weight Loss:
RV-8451 delivered significant weight and fat mass loss while successfully preserving lean muscle mass and hydration status.

Superior Metabolic Effect:
RV-8451 achieves fat loss that exceeds the results of caloric restriction alone by concurrently reducing caloric intake and increasing fat oxidation.

Overcoming Metabolic Adaptation:
The muscle preservation may counteract the compensatory metabolic slowdown that typically causes weight-loss plateaus in current GLP-1RAs like orforglipron.

Clinical Potential:
With its fat-specific, muscle-preserving phenotype, RV-8451 is a highly-differentiated oral GLP-1 for the potential treatment of obesity, a chronic cardiometabolic disease.

Acknowledgements

We would like to thank Dr. Louise Lantier and the team at Vanderbilt Mouse Metabolic Phenotyping Center for conducting the indirect calorimetry studies.

We would like to thank Beau Merhige and Amy Figueroa for their support.