RV-8451, a Pre-Clinical, Muscle-Preserving GLP-1R NPA, Outperforms Orforglipron in Obesity Models

Sol Collado[1], Melissa Luse[1], Harry R. Chobanian[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

Abstract # 079

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 rebound 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.

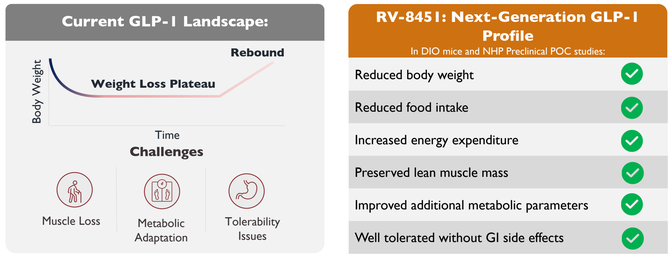
The Unmet Clinical Need

- Obesity is a chronic disease that needs chronic treatment options. 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 potential best-in-class, oral, small-molecule GLP-1R non-peptide agonist (NPA) designed to overcome the clinical limitations of current incretin therapies.
- Study Objective: To compare RV-8451 to other GLP-1R NPAs for weight loss quality and efficacy in non-human primate (NHP) and mouse models of obesity.

RV-8451: Next-Gen Oral Small Molecule GLP-1 That Preserves Muscle for Durable, Quality Weight Loss

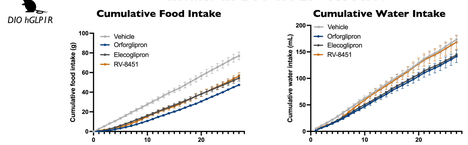


Methods

- Preclinical evaluations were conducted using diet-induced obese (DIO) humanized GLP-1R (hGLP-1R) mice and DIO non-human primates (NHPs).
- Male DIO hGLP-1R mice were fed high-fat diet for at least 10 weeks and treated with RV-8451, orforglipron, elecoglipron or vehicle for 28 days. Food and water intake was measured daily. Weight loss (WL) efficacy was evaluated daily throughout the 28-day study, with body composition quantified by EchoMRI at day 0 and 28.
- After a 3-day baseline, male DIO hGLP-1R mice were treated with RV-8451, orforglipron, elecoglipron or vehicle for 14 consecutive days under thermoneutrality. Energy expenditure and fat and glucose oxidation were assessed by indirect calorimetry using the Promethion (Comprehensive, High-resolution Behavioral Analysis Systems, Sable Systems Int.).
- 28-day efficacy studies in DIO NHPs compared RV-8451 with orforglipron assessing daily food intake, weight loss, and body composition by DEXA.

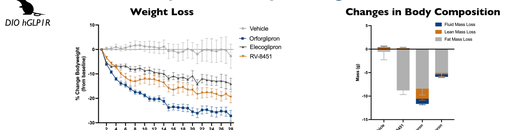
Results

1 RV-8451 Reduces Food Intake While Preserving Water Intake in DIO hGLP-1R Mice



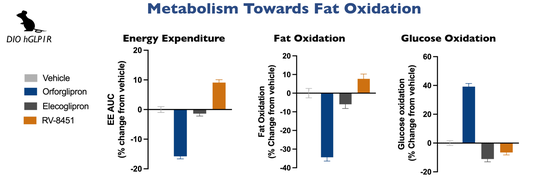
- In DIO hGLP-1R mice at the doses investigated, RV-8451 and elecoglipron had similar effects on cumulative food intake reduction (RV-8451: -27% vs elecoglipron: -29%).
- Compared to orforglipron, RV-8451 elicited a more moderate, but competitive, reduction in cumulative food intake (RV-8451: -27% vs orforglipron: -38%)
- Reduction in water intake typically associated with GLP-1R agonists was seen for orforglipron (-18%) and elecoglipron (-17%) while the RV-8451 treated group had no significant reduction in water intake (-3%) compared to vehicle.

2 RV-8451 Shows Competitive Weight Loss Efficacy with Superior Quality of Weight Loss



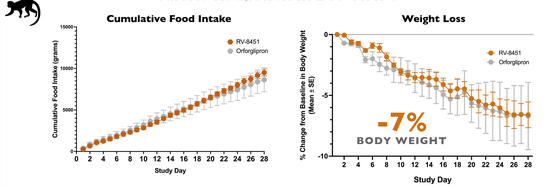
- RV-8451 outperformed elecoglipron in weight loss (-20% vs. -14%) and fat loss (-61% vs. -35%) with comparable reductions in cumulative food.
- Compared to orforglipron, RV-8451 induced greater fat loss (-61% vs. -57%), despite a more moderate reduction in food intake and weight loss (-20% vs. -27%).
- RV-8451 uniquely preserved lean mass (+1%), in contrast to the reductions seen with orforglipron (-10%) when compared to baseline values.
- For orforglipron, 70% of the weight loss was fat mass and 18% lean muscle mass. Conversely, 100% of RV-8451 weight loss was fat specific.
- Fluid mass loss was seen for orforglipron (-34%) and elecoglipron (-18%) while the RV-8451 treated group had no fluid loss (+2%) compared to baseline measurements.

3 RV-8451 Increases Energy Expenditure and Shifts Metabolism Towards Fat Oxidation



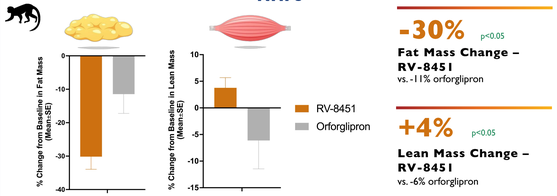
- RV-8451 increases energy expenditure along with lean mass preservation and shifts metabolism towards fat oxidation in DIO hGLP1R mice.
- In a 14-day IC study, RV-8451 maintained a modest increase in EE (+9% vs. vehicle), directly contrasting the metabolic adaptation (decreased EE) seen with orforglipron (-16%) and the neutral effect of elecoglipron (-1%).
- Furthermore, RV-8451 significantly enhanced fat oxidation (+8% vs. vehicle) compared to orforglipron (-34%) and elecoglipron (-6%).

4 RV-8451 Matches Orforglipron's Weight Loss at Equal Caloric Reduction in DIO NHPs



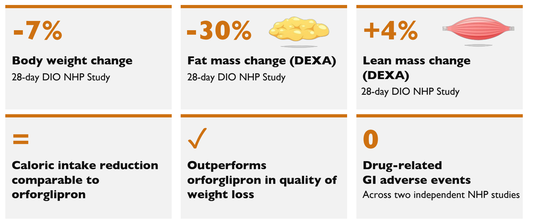
- RV-8451 was dose-matched to Orforglipron to achieve similar reduction in caloric intake
- Pharmacological equivalent doses of RV-8451 and orforglipron yielded similar food intake and weight loss (-7%).

5 RV-8451 Delivers Next-Generation Weight Loss Quality in DIO NHPs



- RV-8451 provided superior effect on body composition, achieving greater fat loss (-30% vs. -11%, RV-8451 vs. orforglipron) and preserving lean mass (+4% vs. -6%).

6 Summary of Results in H2H NHP Study



Conclusions

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

High-Quality Weight Loss:
In 28 day studies, RV-8451 results in selective fat loss with full preservation of lean mass, in both DIO NHPs and hGLP-1R mice, demonstrating superior weight loss quality to other GLP-1s.

Superior Metabolic Efficiency:
By concurrently reducing energy intake and increasing energy expenditure and fat oxidation, RV-8451 achieves fat specific weight loss that exceeds the results of caloric restriction alone.

Overcoming Metabolic Adaptation:
The muscle preservation may counteract the compensatory metabolic slowdown typically seen in caloric restriction.

Potentially Improved Tolerability Profile:
Increasing energy expenditure while reducing caloric intake may allow for a reduced GLP-1 effect and associated AEs for the same weight loss. No drug-related GI adverse events observed. Hydration status preserved.

Potential for Chronic Clinical Use:
With its fat-specific, muscle-preserving phenotype, RV-8451 establishes itself as a highly differentiated oral GLP-1 for potential treatment of obesity, a chronic cardiometabolic disease. RV-8451 is advancing in IND-enabling studies to support a planned Phase 1 clinical trial in obesity.

Acknowledgements

We would like to thank Dr. Nathan Qi, Dr. Zhe Wu and the team at University of Michigan Animal Phenotyping Core for conducting the indirect calorimetry studies. The core is supported by grant 1U2CDK135066 (MMPC-Live).