Beyond Caloric Restriction:
RV-8451 GLP-1R NPA Drives Fat-Specific Weight Loss in a DIO Mouse Model

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Abstract #329

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 gain 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.

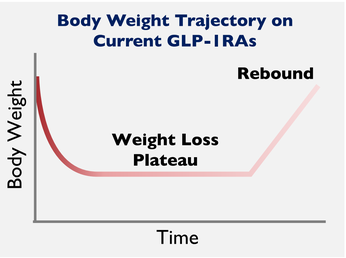
The Unmet Clinical Need

- 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 novel, oral, non-peptide GLP-1RA currently in preclinical development, designed to be muscle-preserving.
- Study 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 lean mass

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

Poor GI Tolerability
Limits dose escalation and real-world adherence

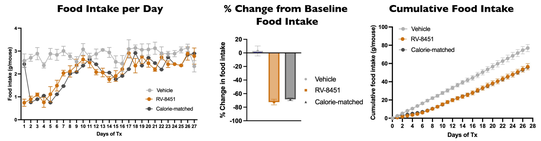
Methods

- Male diet-induced obese (DIO) humanized GLP-1R (hGLP-1R) mice were fed high-fat diet for at least 10 weeks and treated with RV-8451 (QD) or treated with vehicle (QD) and given an RV-8451 calorie-matched diet 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 for 14 consecutive days. Energy expenditure and fat oxidation were assessed under thermoneutrality by indirect calorimetry using the Promethion (Comprehensive, High-resolution Behavioral Analysis Systems, Sable Systems International).

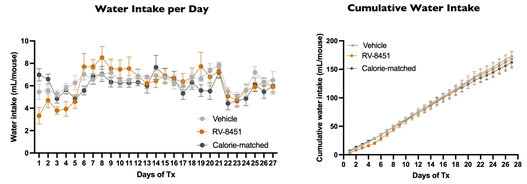
Results

1 Effect of RV-8451 and Calorie-matched Diet on Food Intake



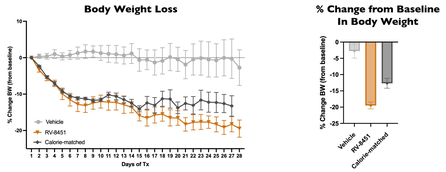
- Individual daily food consumption was tracked over the 28-day treatment period, illustrating acute anorectic response followed by gradual recovery of daily food intake in RV-8451-treated and calorie-matched groups.
- RV-8451 significantly reduced food intake (maximum food intake reduction, -72%) compared to baseline.
- Calorie-matched control followed the same pattern of food intake.

2 Effect of RV-8451 and Calorie-matched Diet on Water Intake



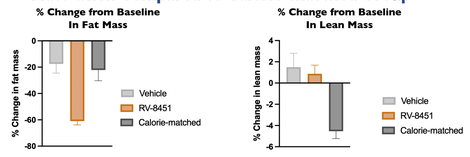
- RV-8451 and calorie-matched control had no impact on water intake.

3 RV-8451 Induced Greater Weight Loss than Calorie-matched Control



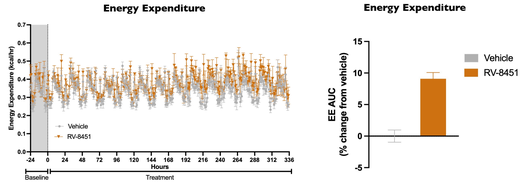
- Both RV-8451 and calorie-matched controls show initial rapid weight reduction, with RV-8451 producing greater net weight loss than calorie matching alone as treatment continues.
- RV-8451 treatment induced 20% total body weight reduction compared to 13% in calorie-matched controls and 3% in vehicle controls.

4 RV-8451 Drives Fat Specific Weight Loss while Preserving Lean Mass when Compared to Calorie-matched Group



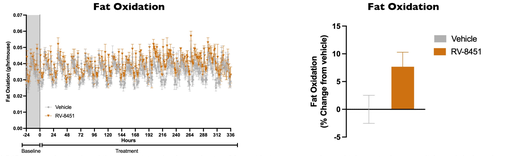
- RV-8451 treatment drives a robust reduction in total fat mass (61%), markedly surpassing the fat loss achieved by calorie-matched paired-feeding (-22%).
- RV-8451 treatment completely preserves lean body mass (0% change), whereas calorie-matched controls undergo significant lean mass catabolism (-5% loss).
- Weight loss in RV-8451–treated animals is comprised almost entirely of fat mass, sparing lean tissue, whereas weight loss in calorie-matched controls involves substantial loss of lean mass and fluid.

5 RV-8451 Increases Energy Expenditure



- RV-8451–treated animals demonstrate a sustained, moderate elevation in metabolic rate compared to vehicle controls across diurnal light/dark cycles.
- RV-8451 treatment induces a modest, sustained 9% increase in total energy expenditure.

6 RV-8451 Drives Fat Specific Weight Loss Through Increased Fat Oxidation



- RV-8451–treated animals exhibit a consistently elevated rate of fat oxidation compared to vehicle controls across light and dark cycles.
- RV-8451 treatment induces a sustained 8% increase in whole-body fat oxidation compared to vehicle.
- Indirect calorimetry revealed that this "metabolic gap" is driven by a modest increase in energy expenditure and enhanced fat oxidation when compared to vehicle. Thus, RV-8451 does not lead to compensatory metabolic adaptation (decreased EE) typically seen with conventional GLP-1RAs.

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:
Unlike caloric restriction alone, RV-8451 demonstrates a unique ability to deliver significant weight and fat mass loss while successfully preserving lean muscle mass and hydration status in pre-clinical models of obesity.

Superior Metabolic Efficiency:
By concurrently reducing energy intake and increasing 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.

Clinical Potential:
With its fat-specific, muscle-preserving phenotype in vivo in preclinical models, RV-8451 demonstrates a differentiated profile for the potential treatment of obesity, a chronic cardiometabolic disease.

Acknowledgements

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