Rescuing Lean Mass:
GLP-1R NPA RV-8451 Reverses Orforglipron-Induced Muscle Loss in DIO Mouse Model

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Abstract # 327

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

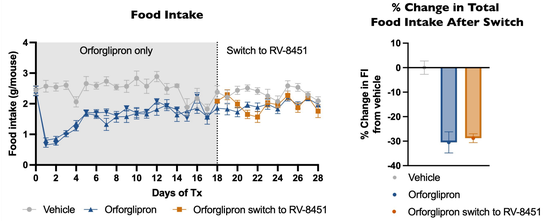
Poor GI Tolerability
Limits dose escalation and real-world adherence

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 orforglipron for 17 days. On day-18 a cohort of mice were switched from receiving orforglipron to RV-8451 while the remainder of the mice stayed on orforglipron treatment.
- Body weight, and both food and water intake were measured daily. Body composition measurements via EchoMRI were taken throughout the study
- Group breakdown:
  - Vehicle group: 28-day vehicle only
  - Orforglipron only group: 28-day orforglipron only
  - Crossover group: 17-days orforglipron switch to RV-8451 on day 18-28

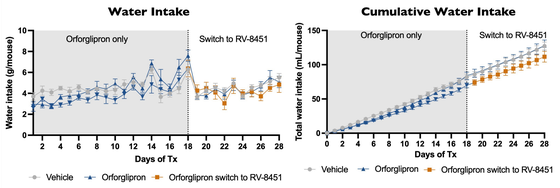
Results

1 RV-8451 and Orforglipron Induced Similar Food Intake Reduction



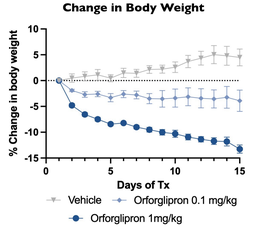
- Daily food consumption was tracked across a 28-day study period. During Days 0–18, both treatment cohorts received orforglipron monotherapy, exhibiting initial hypophagia followed by steady daily intake. On Day 18 (dotted line), one cohort was switched to RV-8451 treatment, maintaining stable daily food suppression equivalent to continuous orforglipron through Day 28.
- Importantly, switching to RV-8451 did not compromise metabolic efficacy; food intake remained significantly lower on day 28 than vehicle controls (-12% for RV-8451 vs. -4% orforglipron).
- Percent change in total food intake after switch was calculated by quantifying the cumulative food consumed by each mouse from each group from days 18-28.

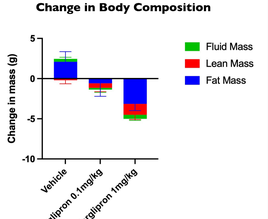
2 Water Consumption is Unaffected by Switch to RV-8451 from Orforglipron



- Although water intake was moderately impacted in one of the orforglipron cohorts, no impact on water intake was seen after switch to RV-8451

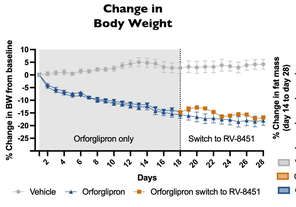
3 Orforglipron as a Monotherapy Leads to Lean Mass Loss Even at Low Doses

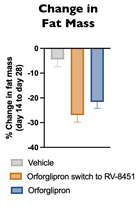


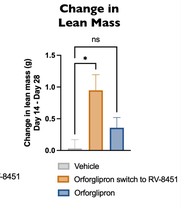


- Orforglipron induces dose-dependent body weight loss, with 0.1 mg/kg producing a modest reduction (3.8% loss) and 1 mg/kg driving rapid, robust weight reduction (13.3% loss) compared to weight gain in vehicle controls (+4.5%).
- Vehicle-treated animals gained predominantly fat mass (~+2.0 g). orforglipron at 0.1 mg/kg resulted in a total mass reduction of ~1.3 g, composed of ~0.6 g fat mass loss, ~0.6 g lean mass loss (~46% of total loss), and ~0.1 g fluid mass loss. orforglipron at 1 mg/kg produced a total mass reduction of ~5.0 g. composed of ~3.1 g fat mass loss, ~1.4 g lean mass loss (~28% of total loss), and ~0.5 g fluid mass loss.

4 Rescue with RV-8451 Improves Lean Mass After Orforglipron Treatment







- Initial treatment with orforglipron drove significant total weight loss (-15%), including lean mass reduction (-7%).
- Upon switching to the RV-8451 intervention, mice began to exhibit lean mass recovery within just 10 days. By the end of the study, the RV-8451 crossover group demonstrated a robust 82% recovery in lean mass equaling vehicle lean mass levels.
- In contrast, muscle mass remained relatively stagnant in the cohort that continued with orforglipron.
- Furthermore, the RV-8451 rescue cohort achieved modestly greater fat loss than the continuous orforglipron group (-27% vs. -22%), yielding a highly comparable overall weight loss at Day 28 (-17% for RV-8451 vs. -18% for orforglipron).

Conclusions

GLP-1R Agonist Monotherapy Causes Substantial Lean Mass Loss:
Orforglipron monotherapy drives robust, dose-dependent weight reduction (up to ~13.3% at 1 mg/kg), but 28% to 46% of the total mass lost comes from functional lean muscle tissue.

Seamless Anorectic Efficacy Upon Transitioning:
Switching from orforglipron to RV-8451 on Day 18 seamlessly maintains food intake suppression (~28% reduction vs. vehicle), demonstrating equivalent appetite control to continuous Orforglipron (~30% reduction) without rebound hyperphagia.

Reversal of Lean Mass Loss:
Transitioning to RV-8451 on Day 18 stimulates a significant increase in lean body mass (+0.95 g gain, $p < 0.05$ vs. vehicle), actively recovering muscle mass lost during initial GLP-1R agonist monotherapy.

Clinical Potential:
RV-8451 successfully reverses the muscle loss induced by current incretin therapies like orforglipron in obese mice. By rescuing lean mass while simultaneously driving superior fat loss and maintaining suppressed food intake, RV-8451 demonstrates a highly differentiated, muscle-restorative pharmacological profile. These preclinical studies demonstrate that RV-8451 has promise as a muscle-preserving, fat-specific weight-loss therapy, as well as a potential rescue intervention for patients experiencing lean muscle loss on current incretins.

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