

Introduction

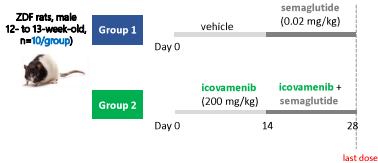
- GLP-1-based therapies have reported lean mass reductions of up to 25–30% of total weight loss in people with overweight or obesity¹.
- Menin is a scaffold protein with a key role in the negative regulation of beta cell proliferation and function, as previously demonstrated through increased beta-cell mass generation in *Men1* knockout mice².
- Menin also modulates signaling pathways critical for muscle health.
- Menin-depleted mice display increased intercostal muscle mass and enhanced myogenesis³.
- Icovamenib is an oral covalent menin inhibitor previously shown to enhance response to GLP-1 therapies and beta cell proliferation in human islets and in a T2D rat model⁴⁻⁶.
- Here, the direct impact of icovamenib on myotube recovery and lean mass preservation was investigated.

Methods

- Ex-vivo iPSC-derived 3D-engineered healthy human myotubes were cultured with icovamenib (150 nM or 300 nM) or vehicle from days 12–28, or beginning one day prior to atrophy induction with Activin A or dexamethasone. Myotube morphology was assessed in healthy conditions or in the presence of atrophy inducers.



- Additionally, Zucker diabetic fatty (ZDF) rats treated with icovamenib orally once daily (200 mg/kg) or vehicle for 14 days followed by 14 days with low dose semaglutide (0.02 mg/kg) were examined for body composition parameters.



Icovamenib augments healthy human myotube length and width

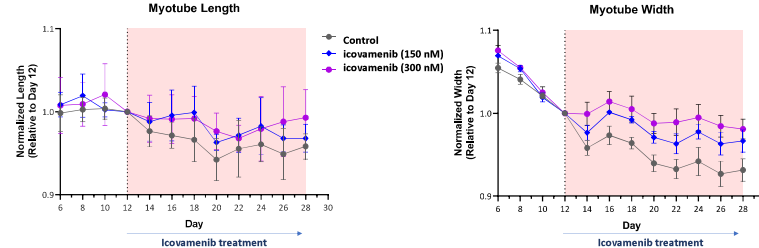


Figure 1. Icovamenib promotes healthy myotube length and width. Human myotube cultures (n=3 per condition) treated with icovamenib from Days 12 to 28 were assessed for morphological changes. Icovamenib treatment induced a dose-dependent increase in myotube length and width compared to vehicle control throughout the entire treatment period until tissues were harvested on Day 28.

Icovamenib diminishes drug-induced human myotube atrophy

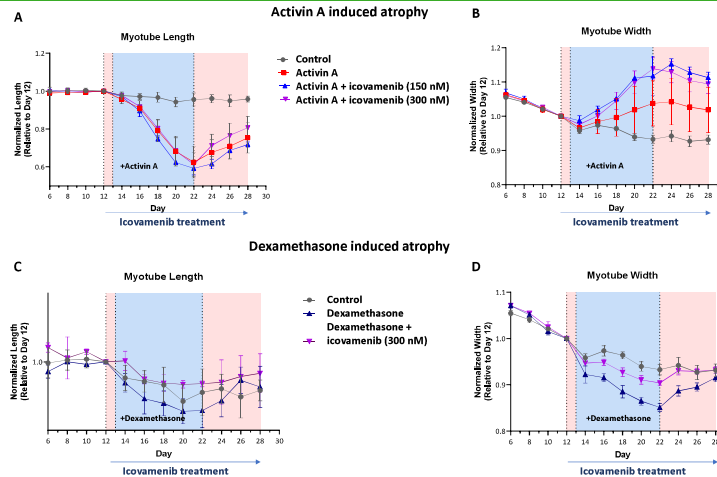


Figure 2. Icovamenib diminishes myotube atrophy induced by Activin A and dexamethasone. Human myotubes were treated with icovamenib starting on Day 12 and atrophy was induced with Activin A (n=3) or dexamethasone (n=2) from Days 13 to 22. Icovamenib treatment was continued until Day 28. Icovamenib protected against Activin A-induced myotube atrophy, displaying a pronounced increase in myotube width (A and B). Dexamethasone decreased myotube length and width, which were also rescued by icovamenib (C and D).

Combination of icovamenib and low dose semaglutide selectively promotes fat loss with complete lean mass preservation in ZDF rats

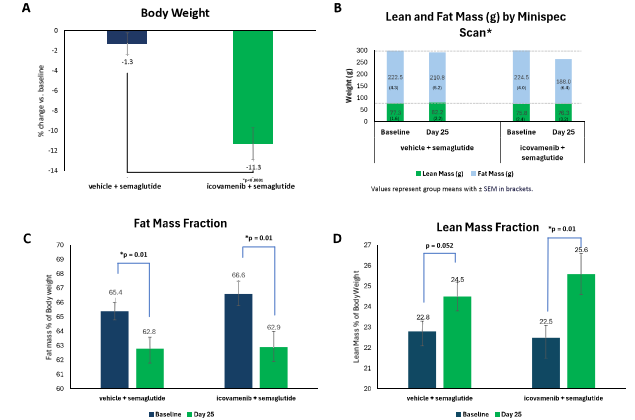


Figure 3. Icovamenib significantly reduces body weight with complete preservation of lean mass in combination with low dose semaglutide in ZDF rats. Combination treated ZDF rats were examined for body weight by manual weighing (A) and fat mass and lean mass composition by Minispec analysis on Day 25 of treatment (B-D). Combination treated rats displayed enhanced body weight reduction by weighing (A) and increased fat mass loss with complete preservation of lean mass (B). Importantly, fat mass loss was enhanced in the combination treated group with complete preservation of lean mass (+12% change vs. baseline in lean mass fraction in combination treated rats vs. +7% change vs. baseline in semaglutide-alone-treated rats (C and D). Values represent group means (± SEM).

Conclusions

- Icovamenib enhanced healthy myotube morphology and diminished drug-induced atrophy by Activin A or dexamethasone *ex vivo*.
- In ZDF rats, combination of icovamenib and low dose semaglutide induced greater body weight reduction driven by fat mass loss with complete preservation of lean mass.
- Collectively, these results support combination of icovamenib with GLP-1RA-based therapies as a promising strategy to enhance body weight reduction with preservation of muscle homeostasis.

References

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