Metabolic Adaptation of Liver With Treatment of HM15275, A Long-acting GLP-1/GIP/Glucagon Triple Agonist, Supporting Lean Mass Preservation

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Poster 755-P

Introduction

Introduction and Objective:

Weight-loss quality (WLQ) has emerged as a challenge in developing GLP-1-based therapies. Previous nonclinical studies demonstrated that HM15275, a novel long-acting GLP-1/GIP/Glucagon (GCG) triple agonist, exhibited a well-balanced body composition profile with potent weight loss. This study aimed to elucidate the underlying mechanism by which HM15275 regulates metabolic pathways to achieve better WLQ.

Methods:

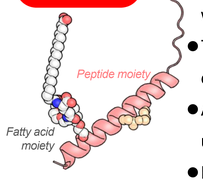
To extract mechanistic insight of different WLQ from altered metabolic pathways influenced by either treatment, RNA sequencing was conducted on liver and white adipose tissue (WAT) from diet-induced obese (DIO) mice treated withHM15275 or TZP for 11 days. Biological processes affected by the treatment were identified using normalized RNA expression data. Gene Set Variation Analysis (GSVA) was performed with pathways from the Molecular Signature Database (MSigDB), including Hallmark, KEGG, Reactome, WikiPathways, and Gene Ontology. GSVA scores were calculated using the GSVA R package (version 1.50.5) and visualized in GraphPad Prism V10 (GraphPad Software, USA). Statistical significance was assessed via paired t-tests with FDR-adjusted p-values.

Results:

Transcriptomic analysis revealed that HM15275 sustained fat metabolic pathways, while down-regulated in TZP, contributing to greater fat mass loss under fasting-related metabolic challenges. HM15275 suppressed amino acid catabolic pathways relative to TZP, supporting lean mass preservation. HM15275 activated pathways related with glucose generation greater than TZP revealed by enrichment of gluconeogenesis and lactate recycling pathway, however, fasting blood glucose remained lower than vehicle treated implying limited effect on glucose intolerance. Furthermore, HM15275 downregulated ketone body synthesis compared to TZP, priming production of glucose rather than ketone body.

Background

HM15275 is a novel long-acting GLP-1/GIP/Glucagon triple agonist conjugated with fatty acid moiety, optimally designed for treatment of obesity and relative complications.

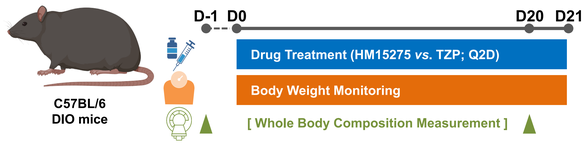


- Designed and optimized to maximize body weight reduction (activity balance)
- The extended half-life is sufficient for weekly dosing
- Additional CVRM benefits expected by proper utilization of glucagon
- P1 study in United States completed

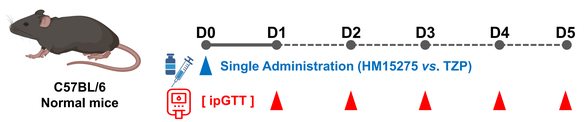
GLP-1	GIP	Glucagon
Weight loss by appetite regulation		Weight loss by energy expenditure
Indirect effects from BW loss and BG control and CVRM benefits		Direct tissue effect for CVRM benefits

Methods

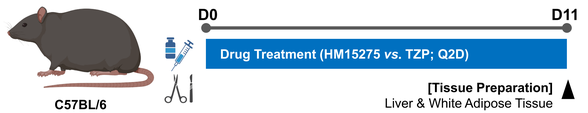
A. Body weight efficacy study design



B. Glycemic control – ipGTT study design



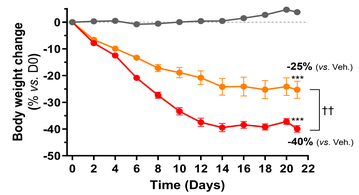
C. Liver and adipose tissue RNA sequencing study design



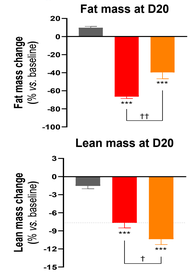
Weight Loss Effect & Glycemic Control

Figure 1. Comparison of weight loss effect & glycemic control

A. BW change over time



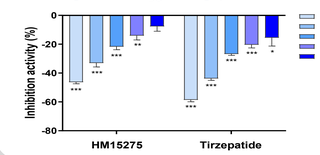
B. Changes in body composition



*** p<0.001, vs. Vehicle, by One-way ANOVA test.
†~†† p<0.05~0.01, vs. HM15275 20 nmol/kg by an unpaired t-test..

- In DIO mice, HM15275 significantly reduced body weight and favorably regulated fat-to-lean composition , yielding enhanced therapeutic benefits than TZP

C. Changes in AUC_{BG} during ipGTT

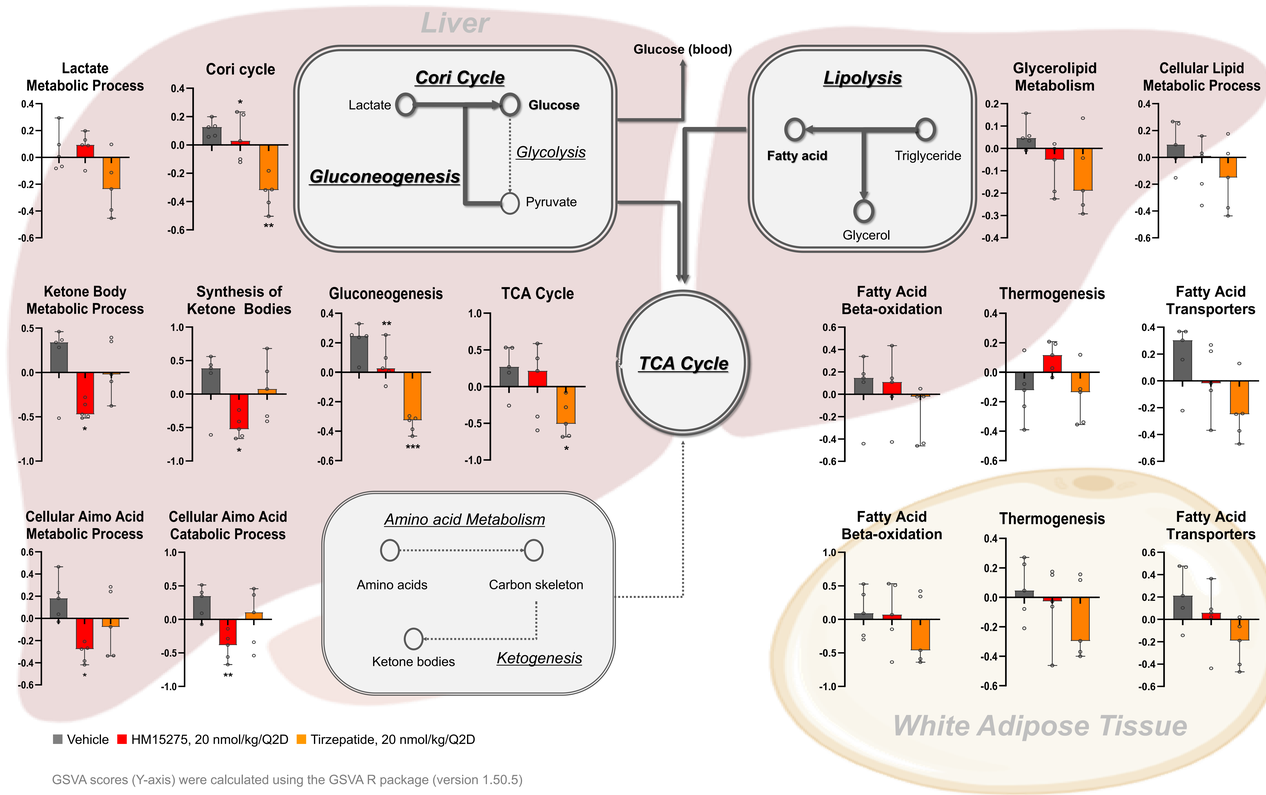


- In normal mice, HM15275 demonstrated improved glucose tolerance comparable to TZP (ipGTT).

*~*** p<0.05~0.001, vs. Normal, vehicle by One-way ANOVA test

Metabolic Adaptation in Liver & White Adipose Tissue

Figure 2. Gene Set Variation Analysis (GSVA) in liver and adipose tissue



GSVA scores (Y-axis) were calculated using the GSVA R package (version 1.50.5)

Concluding Remarks

- HM15275 induces significant metabolic adaptations, explaining improved weight-loss quality (WLQ).
- HM15275 promotes grater fat mass loss by preserving fat metabolism in liver and adipose tissue.
- HM15275 preserves lean mass by suppressing amino acid catabolism in liver.
- HM15275 supports efficient energy metabolism without causing glucose intolerance by prioritizing glucose generation over ketogenesis.
- Please note additional posters presenting preliminary results from a Ph1 study of HM15275 (Poster-1980-LB) and the robust anti-obesity effect and mechanistic insights of HM15275 (Poster-774-P)

References

1. Prado CM, Phillips SM, Gonzalez MC, Heymsfield SB. *Lancet Diabetes Endocrinol*. **2024**;12(11):785-787.
2. Neeland IJ, Linge J, Birkenfeld AL. *Diabetes Obes Metab*. **2024**;26 Suppl 4:16-27.
3. Melson E, Ashraf U, Papamargaritis D, Davies MJ. *Int J Obes (Lond)*. **2025**;49(3):433-451.
4. The graphical representations were generated with BioRender.com