Efficacy and safety of HSG4112, a novel anti-obesity oral agent in diet-induced obesity (DIO) mice
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Background and aims: Obesity is defined by excess adipose mass and adipose tissue expansion, which occurs through adipocyte hypertrophy and hyperlasia. Hypertrophic adipocytes (sick fat) secrete pro-inflammatory cytokines, such as, TNF-α, IL-6, resistin and MCP1 etc., which lead to chronic inflammation that causes problems with triglyceride metabolism. The currently existing drugs for obesity are altering either appetite or absorption of calories. Yet, there are no approved drugs to solve the fundamental problem of triglyceride metabolism. The purpose of this study was to evaluate HSG4112 as a new drug candidate to resolve the fundamental energy metabolism in obesity.

Materials and methods: HSG4112 is a novel small molecule anti-obesity oral agent discovered and developed by Glaceum Inc. and its efficacy was tested in DIO mice. HSG4112 was given orally once daily for 7 days for 6 consecutive weeks (qd×7×6). The test consisted of a normal control group (normal diet), a vehicle control group (high fat diet), a test group (HSG4112 100mg/kg) and a pair-fed group.

Results: After 6 weeks, the total mean weight loss was 10.2g (-26.0%) in the test group. The contribution made by reduced food intake was 38.0% and the energy expenditure effect was 62.0%. Increase of O₂ consuming and CO₂ generating rates and decrease of 5’ Adenosine Monophosphate-activated Protein Kinase (AMPK) activity in hypothalamus after oral administration of HSG4112 to DIO mice were observed. Furthermore, enhanced browning effect with the characteristics of high mitochondria content was observed in scapular brown adipose tissue. As a result, lean and fit body shape was achieved in the test group. Single oral dose toxicity study of HSG4112 was performed with rat and dog. The Maximum Tolerated Dose (MTD) 2,000mg/kg was observed from both rat and dog.

Conclusion: In nonclinical studies, HSG4112 demonstrated its weight reduction efficacy mainly by increased energy consumption with excellent safety profiles. These results suggest HSG4112 as a promising new drug candidate to resolve the fundamental energy metabolism in the treatment of obesity.

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