AN OPTIMIZED NOVEL GLP-1-GIP RECEPTOR DUAL AGONIST WITH POTENT EFFECTS ON BODY WEIGHT AND GLUCOSE CONTROL IN MICE HAS THE POTENTIAL FOR ONCE-WEEKLY ADMINISTRATION IN HUMANS

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Abstract

Analog of the incretin hormone glucagon-like peptide 1 (GLP-1) are being used for the management of T2D and are often accompanied by modest weight loss. Approaches to enhance the absorption and efficacy profile are particularly needed. Furthermore, the efficacy of GLP-1 agonists includes its co-administration with other antihyperglycemic agents like metformin. The present report focuses on the potential pharmacodynamic parameters (e.g. enhances the weight loss induced by GLP-1)...

Here we report the characterization of a novel balanced GLP-1-GIP receptor dual agonist (ZP-DI) agonist. ZP-DI-70, with selectively >100-fold over the glucagon receptor (GLP-R) in the GIP-R in vitro functional assay, with a very narrow therapeutic window (26.5±5.5 ng/mL) and a long-lasting effect in vivo (with an elimination half-life of 4.8h). This was also observed in a 9 week GLP-1 administration to mice. ZP-DI-70 administered SC once every third day, dose-dependently reduced body weight in diet-induced obese (DIO) mice. Changing with body weight led to a relative weight loss of 13 % over 3 weeks of treatment. When given SC 2 h prior to a glucose challenge, ZP-DI-70 (3 nmol/kg) significantly reduced blood glucose levels 15-18 min after an IP bolus of glucose in diabetic diet mice.

These results suggest ZP-DI-70 as a promising candidate for the treatment of T2D with superior body weight lowering effect compared to existing therapies. This in vivo profile of the compound further suggest that ZP-DI-70 could be used as a convenient once-weekly treatment.

Potential & Selective GLP-1/GIP-1 dual incetin agonist

The dual incetin agonist, ZP-DI-70, was tested for efficacy on the human GFP (GLP-1) and GIP-R receptors using the QMMP pathways (B). For comparison, the data from the experiments with ZP-DI-70 was screened for inhibition or activation of 105 other human GPCRs using the B-Scan pathway. No other agonist activation of ZP-DI-70 was found (data not shown).

Highly effective on body weight and blood glucose

The pharmacological parameters obtained from mice and monkeys (Table 2) were used to predict the human pharmacological profile. Assuming a 1 component model with 1% decline/increase in body weight, the predicted weight loss in human (Figure 4C) was calculated as the mean of mice and monkeys and the dosimetry in the predicted profile set to 100%. The exercise demonstrates that ZP-DI-70 has a pharmacological profile that could support the development of a GLP-1-GIP receptor dual agonist for a convenient once-weekly dosing schedule in humans (Figure 4C).

Conclusions

We have developed a novel selective and potent GLP-1/GIP receptor dual agonist, ZP-DI-70, which demonstrates promising effects on glucose control and body weight reduction in mouse models of diabetes. Pharmacokinetic evaluation in mice and monkeys indicate the potential for convenient once-weekly dosing in humans for improved treatment compliance.

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References: