A NOVEL GIP RECEPTOR AGONIST ENHANCES THE BODY WEIGHT LOWERING EFFECT OF LIRAGLUTIDE IN DIET-INDUCED OBESE MICE AND HAS THE POTENTIAL FOR ONCE-WEEKLY ADMINISTRATION IN HUMANS

Pia Noerregaard, Maria A. Deryabina, Jacob U. Fog, Pernille T. Shelton, Lise Giehm, and Jens R. Daugaard. Zealand Pharma A/S, Smedeland 36, DK-2600 Glostrup, Copenhagen, Denmark

Introduction

Glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GIP) are intestinal hormones that are released in response to food intake. Both hormones stimulate glucose-dependent insulin secretion. GLP-1 agonists are commonly used in the management of Type 2 diabetes and are often accompanied by modest weight loss. One approach to enhance the body weight effect of GLP-1 receptor (GLP-1R) agonists is to develop a potent and selective GIP receptor (GIP-R) agonist, which has been demonstrated to enhance the weight loss induced by GLP-1R agonists (1-3). Thus, co-activation of GLP-1R and GIP-R receptors are considered as a promising new strategy for the treatment of Type 2 diabetes and obesity.

Here we report the characterization of a novel long-acting GIP-R agonist (I) and its effects in mice and monkeys. Pharmacokinetic properties of ZP-I-98 in mice and monkeys were characterized using a simple allometric model with monophasic disposition and two-compartment disposition for humans. The pharmacodynamic effect of ZP-I-98 was investigated in mice by measuring blood glucose and insulin levels during an oral glucose tolerance test (OGTT) following intravenous (IV) or subcutaneous (SC) bolus administration of ZP-I-98, with or without liraglutide (GLP-1R receptor agonist) co-administration, on body weight, food intake and glucose tolerance were investigated in diet-induced obese (DIO) mice. The exercise demonstrates that ZP-I-98 has a pharmacokinetic profile that could support the development of a GIP-R agonist for a convenient once-weekly dosing schedule in humans.

Pharmacokinetics of ZP-I-98 in mice and monkeys

Figure 1: The plasma concentration profiles of ZP-I-98 obtained after a single IV or SC bolus administration to C57BL/6J mice at 50 mg/kg or cynomolgus monkeys at 3 mg/kg. The plasma concentrations were estimated by LC/MS/MS and each data point represents the mean value ± SD of 2 to 3 monkeys. The pharmacokinetic parameters obtained by non-compartmental analysis of the plasma concentration profiles of ZP-I-98 in mice and monkeys. The terminal half-lives were estimated by linear regression of the least square fit in the terminal phase of the plasma concentration time-curves.

Table 2: The pharmacokinetic parameters obtained by non-compartmental analysis of the plasma concentrations profiles of ZP-I-98 in mice and monkeys. The terminal half-lives were estimated by linear regression of the least square fit in the terminal phase of the plasma concentration time-curves.

Acute effect of ZP-I-98 on glucose tolerance in mice

Figure 2: Blood glucose (BG) levels (A) and BG AUCs (B) in an OGTT in 5 tamed C57BL/6J mice following ZP-I-98 and liraglutide administration at 5 mg/kg or 20 mg/kg SC daily, on body weight, food intake and glucose tolerance were investigated in diet-induced obese (DIO) mice. The exercise demonstrates that ZP-I-98 has a pharmacokinetic profile that could support the development of a GIP-R agonist for a convenient once-weekly dosing schedule in humans.

Conclusions

We have developed a novel selective and potent GIP-R agonist, ZP-I-98. Results from DIO mice suggest that a combination treatment consisting of ZP-I-98 and a GLP-1R agonist can improve the management of Type 2 diabetes by inducing body weight loss superior to GLP-1R agonist alone. Furthermore, pharmacokinetic evaluation in mice and monkeys indicate the potential for convenient once-weekly dosing in humans.

References:

2) Zealand Pharmaceuticals Inc. EASD, September 14 - 18, 2015, Stockholm