Exploring the therapeutic potential of glucagon/GLP-1 receptor dual agonist ZP2929 in a mouse model of diet induced and biopsy-confirmed non-alcoholic steatohepatitis

J. SKARBAJLENE1, A.N. MADSEN2, U. MOURITZEN1, H.H. BAK1 and R. JUST1
1Zealand Pharma A/S, Smedeland 36, 2600 Glostrup, Denmark
2Gubra ApS, Hørsholm, Denmark

INTRODUCTION
Non-alcoholic fatty liver disease and its more severe form non-alcoholic steatohepatitis (NASH) are considered the hepatic manifestation of the metabolic syndrome and are strongly associated with obesity, diabetes and insulin resistance. ZP2929 is a glucagon/GLP-1 receptor dual agonist invented at Zealand Pharma A/S, which has been shown to decrease body weight or body weight gain in diet-induced obese (DIO) mice. This effect has been demonstrated to be more pronounced than seen for the GLP-1 receptor agonist liraglutide at equimolar doses.

AIM
Here we investigated the effects of dual acting glucagon/GLP-1 receptor agonist ZP2929 on metabolic parameters and development of liver disease in a diet-induced obese (DIO)-NASH mouse model.

METHOD
Male C57Bl/6 mice were kept on a diet high in trans-fat (40%), sucrose (20%) and cholesterol (2%) for 29 weeks before study start and maintained on the diet throughout the treatment period. The mice (n=12/group) were treated, 5x bid for 4 weeks with ZP2929 (0.025 and 0.05 mg/kg, with up-titration to final doses of 0.05 and 0.075 mg/kg, respectively after 3 weeks of treatment). Reference compound liraglutide was up-titrated by 0.05 mg/kg daily for the initial 4 days of dosing until reaching target dose of 0.2 mg/kg. A group of mice was food restricted to elicit a similar degree of calorie intake as that observed in ZP2929 high dose group (Pair-fed to ZP2929 High dose). Metabolic endpoints were assessed: body weight (BW), food intake (FI), plasma levels of alanine/aspartate aminotransferase (ALT/AST), plasma and liver lipid content (triglyceride (TG) and total cholesterol (TC), and body composition (EchomRI). A liver biopsy was obtained for histological assessment of the clinically derived NAFLD Activity Score (NAS) (steatosis, inflammation, ballooning degeneration) and fibrosis stage.

RESULTS
ZP2929 reduced body weight throughout the 8 week study period

Figure 3. Effects of ZP2929 and liraglutide on body weight, fat mass and food intake. Data are presented as mean ±SEM, two-way ANOVA with Bonferroni’s post hoc tests (body weight change, food intake) and one-way ANOVA with Dunnett’s Multiple Comparison tests (fat mass). Lines below indicate significant differences *p < 0.05 vs. NASH vehicle control, n=12.

ZP2929 improved liver function, lipid profiles and hepatic steatosis

Figure 4. Effects of ZP2929 and liraglutide on NAS4L activity score. Data are presented as mean ±SEM, one-way ANOVA with Dunnett’s Multiple Comparison tests, *p < 0.05, **p < 0.01, ***p < 0.001 vs. NASH vehicle control, n=12.

CONCLUSION
Treatment with ZP2929 caused:
• Potent and sustained body weight reduction
• Improvement in liver function and lipid profiles
• Improvement in steatosis, inflammation and ballooning degeneration, which are the key hallmarks of hepatocellular injury in NASH.

We conclude that dual agonism of glucagon/GLP-1 receptors may offer an attractive treatment option for patients with NAFLD/NASH.

CONTACT INFORMATION
info@zealandpharma.com, +45 50 50 30 42