ZGN-1061 Improves Metabolic Parameters and Hepatic Pathology in an Obese Mouse Model of Diet-Induced and Biopsy-Confirmed Nonalcoholic Steatohepatitis

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ABSTRACT

ZGN-1061, a novel MetAP2 inhibitor in clinical development for improved glycemic control in patients with type 2 diabetes, was evaluated in DIO-NASH mice. ZGN-1061 improved metabolic parameters, hepatic pathology, and nonalcoholic fatty liver disease (NAFLD) activity score (NAS; composite measure of steatosis, inflammation, and ballooning degeneration) compared to vehicle, and significantly reduced plasma liver enzymes ALT and AST and liver galectin-3. This study investigated 8 wks of treatment with ZGN-1061 (0.3 mg/kg, SC, N=11) or vehicle (N=10) on metabolic parameters, hepatic pathology, and nonalcoholic fatty liver disease (NAFLD) with progression to nonalcoholic steatohepatitis (NASH) disease (NAFLD) with progression to nonalcoholic steatohepatitis (NASH) in diet-induced obese (DIO) mice.

RESULTS

1) ZGN-1061 reduced body weight in DIO-NASH mice

- Mice treated with ZGN-1061 had reduced liver weight and lipid content (Figure 2).

2) ZGN-1061 reduced liver weight, triglycerides, and total cholesterol

- Microarray analysis with ZGN-1061 reduced liver weight and lipid content (Figure 3).

3) ZGN-1061 improved NAFLD activity score (a composite measure of steatosis, inflammation, and ballooning degeneration)

- ZGN-1061 lowered NAS in most animals whereas NAS was unchanged or higher in vehicle-treated mice (Figure 4).

4) ZGN-1061 improved markers of liver damage

- ZGN-1061 reduced plasma liver enzymes ALT and AST (Figure 5).

INTRODUCTION

The rising prevalence of diabetes is associated with increased fat accumulation in the liver, which can lead to nonalcoholic fatty liver disease (NAFLD) with progression to nonalcoholic steatohepatitis (NASH). ZGN-1061 is a MetAP2 inhibitor in clinical development for improved glycemic control in patients with type 2 diabetes.

OBJECTIVE

To determine the efficacy of ZGN-1061 on metabolic parameters, hepatic pathology, and nonalcoholic fatty liver disease score in a mouse model of diet-induced and biopsy-confirmed nonalcoholic steatohepatitis (DIO-NASH). This study investigated 8 wks of treatment with ZGN-1061 (0.3 mg/kg, SC, N=11) or vehicle (N=10) on metabolic parameters, hepatic pathology, and nonalcoholic fatty liver disease (NAFLD) with progression to nonalcoholic steatohepatitis (NASH) disease (NAFLD) with progression to nonalcoholic steatohepatitis (NASH) in diet-induced obese (DIO) mice.

METHODS

Animals (N=10-12/group) were randomized to receive once daily SC treatment with 0.06 mg/kg ZGN-1061, 0.3 mg/kg ZGN-1061, or 5% mannitol for 8 weeks. Animals were euthanized at baseline and at the end of the study. Body and liver weights were measured, and liver lipid content was assessed using imaging. Plasma and liver samples were analyzed for metabolic parameters, liver enzymes, and liver galectin-3. Histopathological scoring was performed according to modified Knodell score and NAFLD activity score.

CONCLUSION

ZGN-1061 markedly reduced body weight, liver weight, and triglyceride content. The reductions in liver weight and triglyceride content observed with ZGN-1061 were associated with improvements in liver function, steatohepatitis, and NAS composite score.

REFERENCES

6,7 This research was funded by Zafgen, Inc. For more information, contact info@zafgen.com