The MetAP2 Inhibitor ZGN-1061 Improves Glycemia in High-Fat Diet-Induced Obese Mice
Bryan F. Burke1, James E. Vath1, Margaret Wyman1, Steven Vickers2, Sharon Cheetham1, Keith Dickinson1, Gareth Birmingham1, Thomas E. Hughes1
1Zafgen, Inc., Boston, MA, 2Renalis Ltd, Nottingham, UK

ABSTRACT
Results

1) ZGN-1061 reduced body weight and body fat in DIO mice
- Weight loss with ZGN 0.03 mg/kg in DIO mice was dose dependent and lasted for the 26-week treatment (Figure 1, Table 1).
- For the 0.1 mg/kg and 0.3 mg/kg ZGN treatment groups, weight loss was maintained until the end of the study (Week 26).

2) ZGN-1061 improved glucose tolerance and lowered insulin levels in DIO mice
- For 26 weeks of treatment, ZGN-1061 produced a dose-dependent reduction in plasma glucose levels (Figure 2).
- The 0.1 mg/kg and 0.3 mg/kg ZGN produced a significant improvement in an oral glucose challenge (Figure 3).

3) ZGN-1061 improved lipid and cardiometabolic biomarkers in DIO mice
- In long-term treatment, ZGN-1061 decreased plasma triglycerides and NEFA concentrations (Figure 4).
- Cholesterol levels were reduced with ZGN-1061, with the lowest dose improving LDL and total cholesterol (Figure 6).

CONCLUSION
- In insulin resistant obese mice, ZGN-1061 produced similar weight loss, loss of fat mass, and improved glucose tolerance in an established MetAP2 inhibitor, beloranib.
- The improvement in glucose tolerance with ZGN-1061 can be dissociated, at least in part, from a weight loss effect or food intake effect.
- Improvements in glucose tolerance were observed with the lowest dose of ZGN-1061 (0.03 mg/kg) and occurred in the absence of a change in body weight, body composition, or food intake.
- The improvement in glucose tolerance were similar in the middle (0.1 mg/kg) and high (0.3 mg/kg) ZGN-1061 dose groups, despite greater weight loss with the higher dose.
- Changes in the cardiometabolic biomarkers, including NEFA, β-hydroxybutyrate, and leptin, are consistent with loss of fat mass as well as increased fat mobilization and oxidation.

The novel MetAP2 inhibitor, ZGN-1061, represents a novel treatment for type 2 diabetes and obesity.

METHODS

1) ZGN-1061 reduced body weight and body fat in DIO mice
- Weight loss with ZGN (0.03 mg/kg) in DIO mice was dose dependent and lasted for the 26-week treatment (Figure 1, Table 1).
- The 0.1 mg/kg and 0.3 mg/kg ZGN treatment groups had no effect on fat mass after one month of dosing.
- ZGN-1061, where the lowest dose improved HOMA-IR by 40.3% and the highest dose by 81.2%.
- Oral glucose tolerance was improved with treatment as shown by 12.0%, 27.2% and 33.2% reductions of the glucose AUC 0-120 and insulin after an oral glucose challenge.
- The low (0.03 mg/kg) dose of ZGN-1061 normalized glucose to that of lean mice.

2) ZGN-1061 improved glucose tolerance and lowered insulin levels in DIO mice
- For 26 weeks of treatment, ZGN-1061 produced a dose-dependent reduction in plasma glucose levels (Figure 2).
- For 26 weeks of treatment, ZGN-1061 produced a dose-dependent reduction in plasma glucose levels (Figure 2).
- The 0.1 mg/kg and 0.3 mg/kg ZGN produced a significant improvement in an oral glucose challenge (Figure 3).

3) ZGN-1061 improved lipid and cardiometabolic biomarkers in DIO mice
- In long-term treatment, ZGN-1061 decreased plasma triglycerides and NEFA concentrations (Figure 4).
- Cholesterol levels were reduced with ZGN-1061, with the lowest dose improving LDL and total cholesterol (Figure 6).

CONCLUSION
- In insulin resistant obese mice, ZGN-1061 produced similar weight loss, loss of fat mass, and improved glucose tolerance in an established MetAP2 inhibitor, beloranib.
- The improvement in glucose tolerance with ZGN-1061 can be dissociated, at least in part, from a weight loss effect or food intake effect.
- Improvements in glucose tolerance were observed with the lowest dose of ZGN-1061 (0.03 mg/kg) and occurred in the absence of a change in body weight, body composition, or food intake.
- The improvement in glucose tolerance were similar in the middle (0.1 mg/kg) and high (0.3 mg/kg) ZGN-1061 dose groups, despite greater weight loss with the higher dose.
- Changes in the cardiometabolic biomarkers, including NEFA, β-hydroxybutyrate, and leptin, are consistent with loss of fat mass as well as increased fat mobilization and oxidation.

The novel MetAP2 inhibitor, ZGN-1061, represents a novel treatment for type 2 diabetes and obesity.

REFERENCES
- Zafgen, Inc., Boston, MA, 2Renalis Ltd, Nottingham, UK
- This research was funded by Zafgen, Inc. For more information, contact info@zafgen.com.