OK acts as a glucose sensor to elicit glucose specific responses, primarily from hepatocytes and pancreatic β-cells. Previously identified GKAs evaluated in the clinic for the treatment of Type 2 diabetes demonstrate improved glucose control; however these GKAs show increased incidence of hypoglycemia and hyperlactemia and an apparent lack of durability. These liabilities have been correlated to hyper-stimulation of the β-cells and/or the accumulation of lipids in the liver, consistent with the disruption of GK and GKRP interaction. Thus, liver selective GKAs that do not activate GK in β-cells or affect the GK-GKRP interaction are expected to demonstrate a superior profile. TTP399 is a novel liver selective KGA that has shown normalization of glycemic control in animal models and Type 2 diabetic subjects without inducing hypoglycemia or dyslipidemia.

The purpose of the studies described herein was to evaluate TTP399 effects on GK, and GKRP interaction in vivo and to examine in vivo evidence of hypoglycemia, dyslipidemia or changes in hepatic glycogen/fatty content. Experiments were conducted in vivo to evaluate the effects of TTP399 on the nuclear localization of GK at various glucose concentrations in hepatocytes to measure the GK-GKRP interaction, in vivo changes in plasma glucose, liver glycogen and triglycerides (TG) were evaluated after chronic treatment with TTP399 in ob/ob mice and minipigs. Our results demonstrate that TTP399 is a liver selective KGA that does not disrupt the interaction between GK and GKRP. Further in vivo evidence confirms that at anticipated therapeutic concentrations, TTP399 stimulates the liver to metabolize glucose while inducing little or no insulin secretion, no dyslipidemia and no increase in glycogen or TG in the liver. These results indicate that TTP399 has a superior profile compared to previous GKAs by greatly reducing the risk of hypoglycemia and dyslipidemia while maintaining durability.

**Conclusions**

- **In vivo GK translocation:** TTP399 does not disrupt the interaction between GK and GKRP.
- **Chronic treatment of TTP399 in ob/ob mice results in:**
  - Increased GK activity without increase in protein levels
  - Lowering of plasma glucose and HbA1c
  - Dose dependent lowering of liver triglycerides (TG) and glycogen
  - No observable signs of hypoglycemia
- **Following chronic dosing of TTP399 in normal minipigs, there is:**
  - No significant increase in liver glycogen, TG or free glycerol content
  - No changes in plasma lactate or TG
  - No changes in liver function
  - All of the above at plasma concentration of TTP399 over 100-fold higher than those at therapeutic doses in humans
- **TTP399 stimulates the liver to metabolize glucose**
  - While inducing little or no insulin secretion
  - Without causing hypoglycemia
  - Without causing dyslipidemia or increasing hepatic glycogen or hepatic TG
- **Results in animal models confirmed in the clinic** (results presented at ADA in 2014 122-OR):
  - Following 4 weeks of daily oral dosing of vehicle or TTP399 to C57BL/6J male and female (n=14/group) for 4 weeks, cytosolic liver GK activity was assayed in the presence of 25mM glucose and GK protein from the liver was quantified using western blotting. In addition, HbA1c levels were measured in plasma and triglyceride and glycogen levels from liver samples were also analyzed using standard methods. The mean and SEM are reported. Significance is indicated by *p<0.05, **p<0.01, ***p<0.001 as compared to vehicle.

**References**


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