The Importance of Tissue Selectivity and Preservation of the Physiological Regulation when Targeting Key Metabolic Regulators as Glucokinase

Introduction

Previously identified GKAs evaluated in the clinic for the treatment of Type 2 diabetes demonstrate improved glucose control; however, these GKAs also show increased incidence of hypoglycemia and hyperlipidemia and an apparent lack of durability. These liabilities have been correlated to hyper-stimulation of the β-cells (as could be predicted by the phenotype of patients with GK-activating mutations) and/or the accumulation of lipids in the liver (consistent with the phenotype of patients with GK loss and gain of function). These results came about without inducing hypoglycemia or dyslipidemia and without increasing glycogen or TG in the liver.

Rational

**Hypothesis**

Liver selective GKAs that do not activate GK in β-cells or affect the GK-GKRP interaction are expected to demonstrate a superior profile.

Results

TTP399 is a liver-selective GKA that does not disrupt the interaction between GK and GKRP and has shown normalization of glycemic control in animal models and in Type 2 diabetic subjects. These results came about without inducing hypoglycemia or dyslipidemia and without increasing glycogen or TG in the liver.

1. **TTP399 Liver Selectivity Protects Against the Severe and Prolonged Hypoglycemia seen with Dual Acting GKAs**

   **Differential Uptake into Rat Hepatocytes Compared to a Rat β-cell Line**

   **Does not Affect Insulin Secretion in contrast with dual acting GKAs**

   **No hypoglycemia, compare to dual acting GKAs**

   **No hypoglycemia in the clinic after 6wks of treatment. (T2 Diabetes on metformin)**

   Data from the continuous glucose monitoring confirmed that the frequency of hypoglycemic events was not different between placebo and the treated groups.

2. **TTP399 Does not Interfere with the Interaction between GK and GKRP and does not Increase Plasma or Hepatic Lipids**

   **Normal regulation of GK by GKRP**

   **NO increase in Hepatic or Plasma TGs**

   **NO Liver Toxicity in animals***

   **No increase in plasma lipids or LFTs in the clinic after 6wks of treatment (T2 Diabetes on metformin)**

3. **TTP399 Significantly Improved Glycemic Control in ob/ob mice and Humans after only 6 weeks of treatment**

   **Conclusion**

   These results indicate that TTP399 has a superior profile compared to other GKAs and demonstrate the importance of tissue selectivity and preservation of the physiological regulation when targeting key metabolic regulators such as GK.