**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 high-stimulation of the β-cells (as could be predicted from the phenotype of patients with GK-activating mutations) and/or the accumulation of lipids in the liver (consistent with the disruption of GK and GKRP interaction by these activators). 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 on stable doses of Metformin.

**Aim**

The aim of this pilot study was to examine the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of TTP399 in subjects with T2DM that were naïve to drug treatment.

**Study Design**

Randomized, Double-blind, Placebo-Controlled, Multiple-ascending-dose Multicenter Trial

- Subjects in the clinic
- Day 0
- Last dose Day 10
- Cohort 1 (50 mg q.d., N=4, Day 10)
- Cohort 2 (200 mg q.d., N=6, Day 10)
- Cohort 3 (400 mg q.d., N=6, Day 10)

**Pharmacokinetics**

Dose-dependent improvement on postprandial glucose without increasing plasma Lactate

**Conclusions**

- TTP399 improved glycemic control and insulin resistance without inducing hypoglycemia or having detrimental effects in plasma lipids.
- The results confirm the safety and usefulness of liver-specific GK activators for the treatment of Type 2 Diabetes.
- The safety and the beneficial effects seen in this very mild drug-naïve diabetic population (mean A1c≤7%) suggest that TTP399 could also be used early in the disease, in prediabetes or as intensive therapy without risk of hypoglycemia.