TTP399, a Novel, Liver Selective Glucokinase Activator: Results from a 10 Day Pilot Study in Patients with Type 2 Diabetes Mellitus (T2DM) Naïve to Drug

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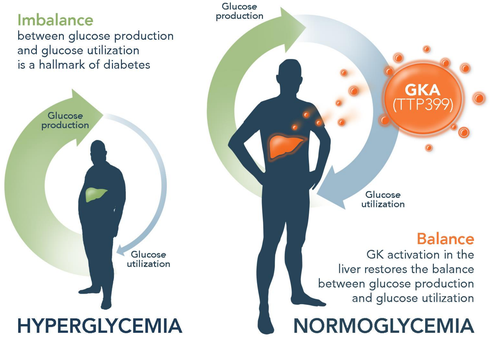
Introduction

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 ß-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 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. These results came about without inducing hypoglycemia or dyslipidemia and without increasing glycogen or TG in the liver.

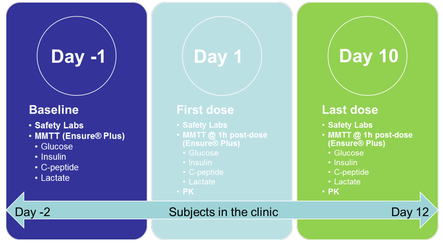


Aim

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



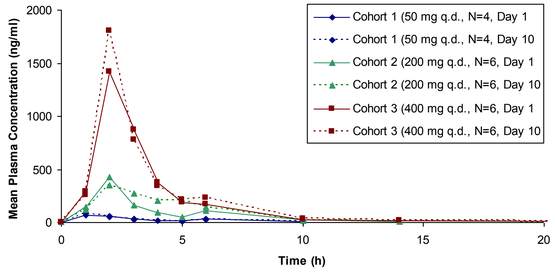
Mild Drug-naïve Type2 Diabetics with average A1c ≤ 7%

Characteristic	Statistic	Placebo (n=6)	TTP399-50 mg (n=4)	TTP399-200 mg (n=6)	TTP399-400 mg (n=6)
Sex (#)	Male	4	2	2	3
	Female	2	2	4	3
Race (#)	White/Black/Other	3/3/0	4/0/0	3/2/1	3/3/0
Age (yr)	Mean (SD)	60 (10.4)	52 (17.9)	55 (6.4)	59 (6.4)
BMI (kg/m^2)	Mean (SD)	31 (3.6)	32 (3.7)	30 (4.6)	32 (4.6)
HbA_{1c} @ screening (%)	Mean (SD)	**6.7 (1.2)**	**6.9 (1.2)**	**6.7 (0.7)**	**7.0 (1.0)**
Completers (#)	Completer (Dropout)	6 (0)	4 (0)	6 (0)	6 (0)

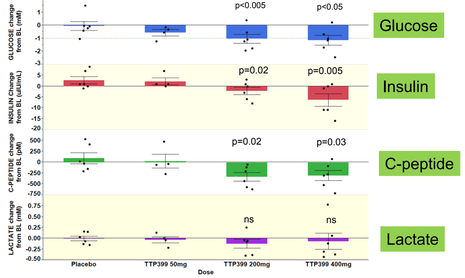
Safe and Well-tolerated. No Hypoglycemia

	Placebo (n=6)	TTP399-50 mg (n=4)	TTP399-200 mg (n=6)	TTP399-400 mg (n=6)
Number of Subjects Reporting Treatment Emergent Aes	6 (100%)	3 (75%)	4 (67%)	5 (83%)
Serious Adverse Events	0	0	0	0
AEs of Especial Interest				
Hypoglycemia	**0**	**0**	**0**	**0**
Gastrointestinal Disorders	1 (17%)	1 (25%)	2 (33%)	0 (0%)
Constipation	1 (17%)	0 (0%)	2 (33%)	0 (0%)
Flatulence	0 (0%)	1 (25%)	0 (0%)	0 (0%)
LFT elevations	0 (0%)	0 (0%)	0 (0%)	0 (0%)

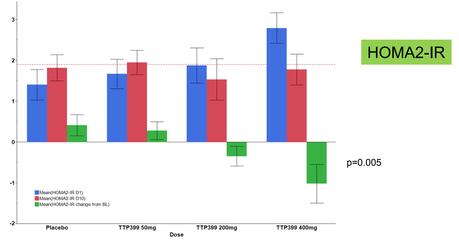
Pharmacokinetics



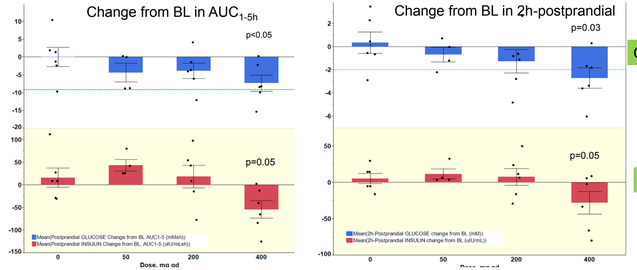
Dose dependent reduction in Fasting: Glucose, Insulin and C-peptide. No changes in lactate



Dose-dependent improvement of Insulin Resistance

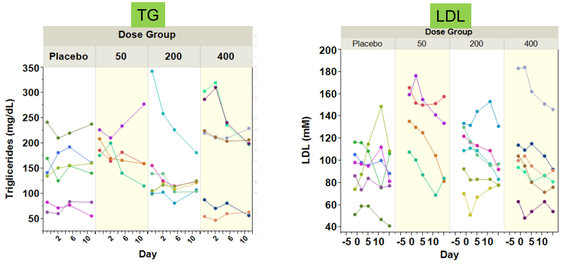


Dose-dependent improvement on postprandial glucose without increasing plasma Lactate



Postprandial C-peptide changes mimic those of insulin. No changes in postprandial lactate from BL at any dose.

No detrimental effects on plasma lipids



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.