TTP399, A Liver Selective Glucokinase Activator Increases Efficacy of Currently Marketed Therapies for Type 2 Diabetes

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Abstract

Glucokinase (GK) is an enzyme localized primarily in the liver and pancreatic β-cells and acts as a glucose sensor to elicit glucose specific responses from the respective cell types. In the liver, GK is a major regulator of glucose metabolism. TTP399 is an oral, liver-selective GK activator (GKA) in clinical development for the treatment of type 2 diabetes mellitus (T2DM). At anticipated therapeutic concentrations, TTP399 stimulates the liver to metabolize glucose while inducing little or no insulin secretion, thus providing an attractive safety profile by greatly reducing the risk of hypoglycemia.

To determine if TTP399 can provide added benefit to currently marketed therapies, suboptimal doses of TTP399 and current therapies were combined in subchronic *in vivo* models of diabetes. Results from these studies demonstrate that combining TTP399 with metformin, sitagliptin, or exenatide shows additive and/or synergistic effects on reducing postprandial glucose, increasing insulin sensitivity and/or reducing body weight without causing hypoglycemia. All combinations studies were safe and well tolerated indicating that TTP399 is ideal for combination with currently-marketed therapies for type 2 diabetes.

Introduction

Despite current available pharmaceuticals, many type 2 diabetes mellitus (T2DM) patients are unable to maintain glycemic control, putting them at risk of developing life-threatening vascular complications. Glucokinase (GK), also called Hexokinase IV or D, plays an essential role in blood glucose homeostasis by catalyzing glucose phosphorylation, the rate-limiting reaction for glycolysis. GK as a therapeutic target in T2DM is supported by studies in humans that have identified activating mutations in the gene encoding GK. Mutations that inactivate GK are associated with maturity-onset diabetes of the young type-2 (MODY2). Additional support from GK knockout and diabetic transgenic animal studies suggest that **selective** activation of liver glucokinase can provide a safe mechanism for reduction of blood glucose.

Numerous animal models of diabetes have shown that treatment with the liver specific GKA, TTP399 is efficacious with respect to improved glycemic control, improved insulin resistance and plasma and liver triglyceride lowering, without increasing lactate or liver glycogen levels as summarized in the table below and available in more detail at Poster 1168.

	TTP399
Activation of GK in ß-cells	No
Activation of GK in liver	Yes
Affect GK / GKRP interaction	No
Stimulation of insulin secretion independent of glucose	No
Hypoglycemia	No
Increase lipids	No
Liver toxicity	No

Combining two or more therapies is a recommended clinical strategy for normalizing blood glucose when a single agent does not result in appropriate glycemic control. To date, no clinically marked therapies have been tested in combination with a liver specific GKA *in vivo*. Therapies that are expected to complement the mechanism of action of TTP399 include the biguanidine metformin, the dipeptidyl peptidase (DPP-IV) inhibitor sitagliptin, and the GLP-1 receptor agonist exenatide.

1. Combination of TTP399 with Metformin in ob/ob Mice

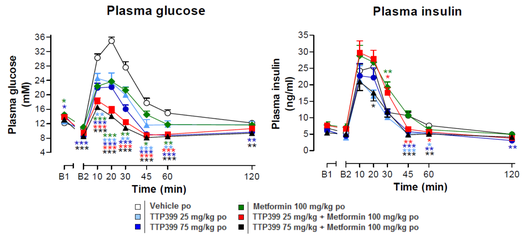

Figure 1: Effects of 14-day administration of TTP399 and metformin, alone and in combination on glucose tolerance in male *ob/ob* mice. Mice were dosed for 13 days, fasted overnight and were dosed again with vehicle or test compound and then 60 min later with a glucose challenge (2 g/kg po). Baseline blood samples were taken immediately before dosing (B1; -60 min) and immediately before the glucose challenge (B2; 0 min) and at additional indicated times. Samples were analyzed for plasma glucose and insulin content and the means (n=8-9) and SEM are shown. Significances are denoted by *p<0.05, **p<0.01 and ***p<0.001.

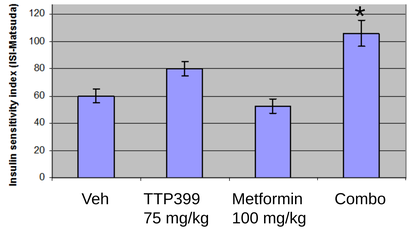

Figure 2: Insulin sensitivity index for *ob/ob* mice treated with TTP399 and or Metformin: The Insulin Sensitivity Index-Matsuda (ISI-M) for the ob/ob mice was calculated according to the following formula: ISI-M=10,000/sqrt(1h WMG*1hWMI*FPG*FPI). * p=0.0006

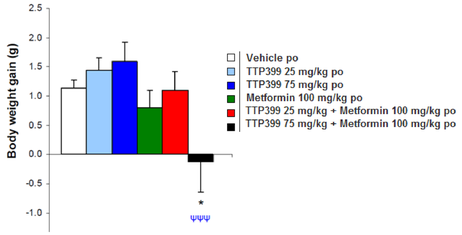

Figure 3: Effects of TTP399 and Metformin, alone and in combination on body weight gain in male ob/ob mice. Mice were treated as described and the means (n = 8 - 9) SEMs are shown. Significant differences vs vehicle: * p <0.05. Significant differences vs the same dose of TTP399 is denoted by ψψψ p<0.001.

2. Combination of TTP399 with Exenatide in *ob/ob* mice

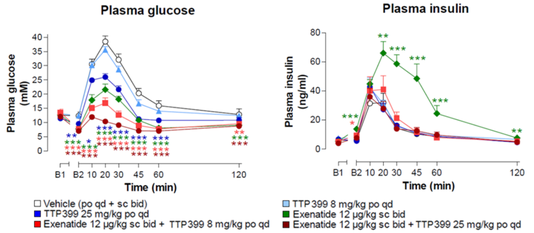

Figure 4: Effects of 14 days dosing on glucose tolerance in male ob/ob mice. Mice were dosed for 13 days, fasted overnight and were dosed again with vehicle or test compound and then 60 min later with a glucose challenge (2 g/kg po). Baseline blood samples were taken immediately before dosing (B1; -60 min) and immediately before the glucose challenge (B2; 0 min) and at additional indicated timepoints. Samples were analyzed for plasma glucose and insulin content and means (n=7-8) and SEM are shown. Significances are denoted by *p<0.05, **p<0.01 and ***p<0.001.

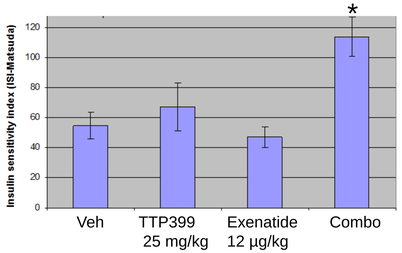

Figure 5: Insulin sensitivity index for *ob/ob* mice treated with TTP399 and or exenatide: The Insulin Sensitivity Index-Matsuda (ISI-M) for the ob/ob mice was calculated according to the following formula in Figure 2. p=0.002

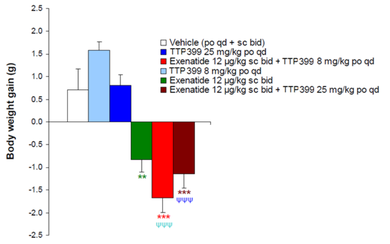

Figure 6: Effect of 14 days of administration of TTP399 and exenatide, alone and in combination, on body weight gain in male *ob/ob* mice. Data are adjusted means (n = 7 - 8) and SEMs. Significant differences vs vehicle: **p <0.01, ***p<0.001. Significance of the combination treatments compared to exenatide alone and to the same dose of TTP399 are denoted by ψψψ p<0.001.

3. Combination of TTP399 with Sitagliptin in DIO Rats

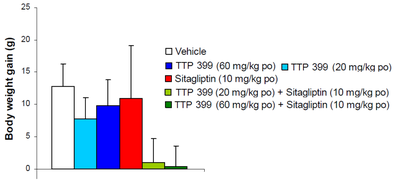

Figure 7: Female Wistar rats were fed a high fat diet to induce obesity. Animals were dosed for 14 days. Data are mean and SEM for body weight gain from Day 1 to Day 14 (n = 9-10).

Summary of Results

Combination	Animal model	Main results
TTP399 + Metformin	*ob/ob* Mice	• Additive in reducing postprandial glucose • Synergistic in increasing insulin sensitivity • Synergistic in reducing body weight
TTP399 + Sitagliptin	DIO Rats	• Synergistic effect in reducing body weight
TTP399 + Exenatide	*ob/ob* Mice	• Additive in reducing glucose • Synergistic in increasing insulin sensitivity • Additive in reducing body weight

Conclusions

TTP399 combinations with currently marketed therapies are safe and well tolerated in animal models of diabetes

Combination of TTP399 and currently marketed therapies metformin, sitagliptin and exenatide showed additive or synergistic benefits over each of the drug alone in *ob/ob* mice and DIO rat models

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For more information on current clinical trials with TTP399 visit: www.MyAgata.com or www.clinicaltrials.gov