Simplici-T1: First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes

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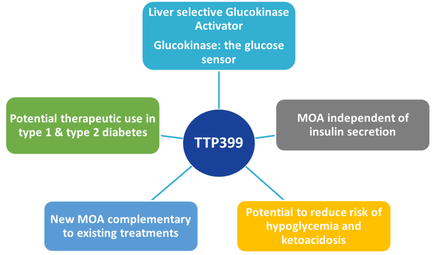
Introduction

Glucokinase (GK) plays an essential role in blood glucose homeostasis. In the liver, GK determines the rates of glucose uptake and glycogen synthesis. GK is also thought to be essential for the regulation of various glucose-responsive genes.

TTP399 is **a liver-selective** GK activator that has shown normalization of glycemic control in animal models and in subjects with type 2 diabetes (T2DM) on stable doses of metformin. These results occurred without inducing hypoglycemia or dyslipidemia. Data from preclinical studies also showed that no abnormal accumulations of glycogen or triglycerides occurred in the liver after treatment with TTP399, even at doses up to 100-fold the therapeutic dose in humans for 9-months.



TTP399 has been well tolerated in eleven clinical trials conducted to date, with no demonstrated safety concerns.

In the Phase 2 studies evaluating TTP399 in T2DM subjects, TTP399 has shown significant reductions in postprandial glucose, increasing % time in range and decreasing % time in hypo or hyperglycemia. In the AGATA study, a 6-month Phase 2b clinical trial in subjects with T2DM, TTP399 significantly reduced HbA1c (placebo-subtracted change = -0.9%; p<0.01) and the effect was sustained for the duration of the study without significant hypoglycemia, dyslipidemia or ketoacidosis

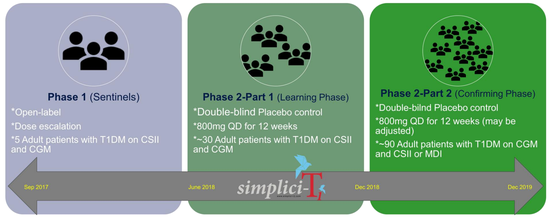
Data from insulin-deficient animals shows that a selective increase in hepatic GK is the only requirement for the normalization of the metabolic profile, suggesting that selective activation of liver GK could provide a mechanism to reduce blood glucose in subjects with type 1 diabetes (T1DM).

Aim

The aim of the study was to examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 in subjects with T1DM on insulin-pump (CSII) and continuous glucose monitoring (CGM).

Simplici-T1 Study Design

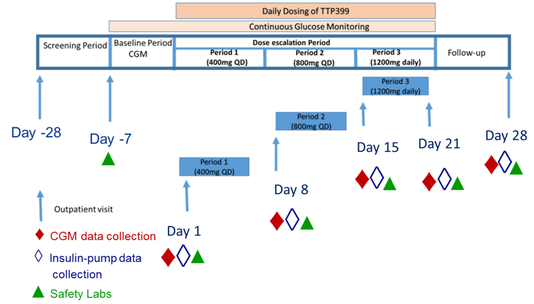
This Adaptive Proof of Concept study evaluating TTP399 as a potential adjunctive treatment for T1DM will occur in three parts (sentinels, learning phase (Part 1) and confirming phase (Part 2)) **(NCT03335371)**.



The adaptive design allows for the exploration of the appropriate dose and appropriate endpoints to evaluate TTP399 in T1DM.

Sentinel Phase Design

The Sentinel phase was an open-label, weekly dose escalation study with up to 3 dose escalations. Five adult subjects with T1DM who were using CGM and CSII were dosed with a once daily dose of 400, 800 or 1200mg of TTP399 for seven days at each dose level.



Demographics and Baseline Characteristics

Sex	Age (years)	Race	HbA1c (%)	Weight (kg)
Male (n=2); Female (n=3)	22-42 years	White (n=5)	Mean 6.9 (6.3-8.4)	Mean 75 (75-79.5)

Well-tolerated in the 5 subjects

Dose of TTP399	400 mg QD (n=5)	800 mg QD (n=5)	1200mg QD (n=5)	Off-drug# (n=5)
SAEs or Deaths	**0**	**0**	**0**	**0**
Related to TTP399 and Insulin	1 (symptomatic hypoglycemia)	**0**	**0**	**0**
Related to TTP399	1 (headache)	1 (hypocalcemia)	1 (right eye discomfort)	2 (lower back pain, nausea)
Not related*	1	1	4	3

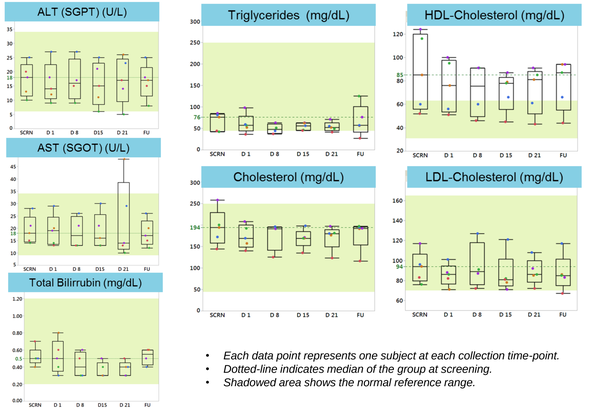
#Off-drug, either between dosing periods or during follow-up
*AEs not related to TTP399 or Insulin: following [400 mg QD dosing:; n=1 (transient paresthesias bilateral thighs)]; [800 mg QD dosing: n=1 (sore throat)]; [1200 mg QD dosing: n=1 (sore throat); n=1 (congestion); n=1(TMJ Dysfunction); n=1 (Left Eustachian Tube Dysfunction)]; Off-drug: n=1 [1(Mild LV Increased Wall Thickness); n=1 (congestion); n=1 (sore throat)]

No Severe Hypoglycemia or DKA

Level 1 Hypoglycemic events *(CGM value 70-54mg/dL for at least 15min)*	Baseline	400mg	800mg	1200mg
Total Number of events	20	9	**8**	13
Mean duration (min/event)	42	56	**40**	65
Level 2 Hypoglycemic events *(CGM value <54mg/dL for at least 15min)*	**Baseline**	**400mg**	**800mg**	**1200mg**
Total Number of events	3	7	**0**	7*
Mean duration (min/event)	23	26	**0**	36
Level 3 Severe Hypoglycemia	**Baseline**	**400mg**	**800mg**	**1200mg**
Total Number of events	0	0	**0**	0
DKA	**Baseline**	**400mg**	**800mg**	**1200mg**
Total Number of events	0	0	**0**	0

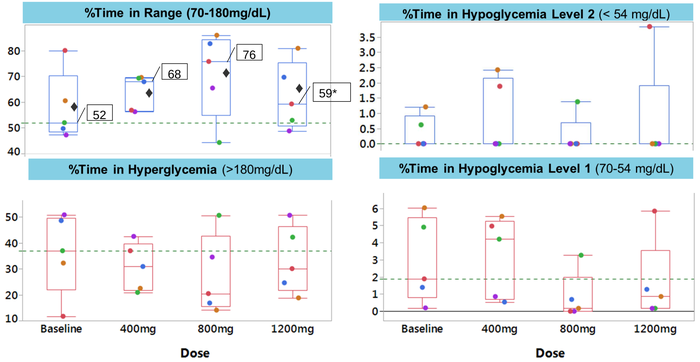
*All seven events occurred in the same patient.

No Detrimental Effects on LFTs or Plasma Lipids



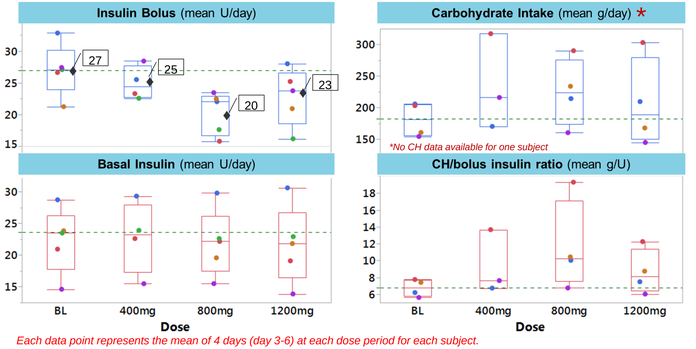
- *Each data point represents one subject at each collection time-point.*
- *Dotted-line indicates median of the group at screening.*
- *Shadowed area shows the normal reference range.*

Trend Towards Improvement of Glycemic Control …



Each data point represents the median of 4 days (day 3-6) at each dose period for each subject. Dotted-line indicates median of the group for the baseline period.
**PK data indicate that in the 1200mg group TTP399 concentrations were lower in 3 out of the 5 subjects when compare to the 800mg group*

…while Reducing Insulin Bolus



Each data point represents the mean of 4 days (day 3-6) at each dose period for each subject. Dotted-line indicates median of the group for the baseline period.

Conclusions

- TTP399 was well tolerated in the Sentinel Phase, with no incidents of severe hypoglycemia or DKA and no detrimental effect on liver function or plasma lipids.
- Trends towards improved glycemic control, while reducing insulin dose.
- The results support continuing to the randomized, placebo-controlled phase 2 of the study, but should be interpreted cautiously due to the intrinsic limitations of an open-label study with small number of subjects.