

Supplementary Materials

The SimpliciT1 study: A randomized, double-blind placebo-controlled, Phase 1b/2 adaptive study of TTP399, a hepatoselective glucokinase activator, for adjunctive treatment of type 1 diabetes mellitus

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References

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Sentinel Phase Protocol and Results

TTP399 has been studied in 11 clinical trials up to six months in duration and has been administered to over 500 healthy volunteers and volunteers with type 2 diabetes. However, prior to the current study, TTP399 had not been evaluated in the type 1 diabetes patient population nor dosed in conjunction with insulin. To allow for close monitoring of patients, the Sentinel phase was conducted as an open-label, 3-week dose escalation study evaluating the safety and efficacy of once daily dosing of 400 mg, 800 mg, and 1200 mg TTP399 (dosed for seven days at each dose level) at a single diabetes center (University of North Carolina Diabetes Care Center, Chapel Hill, NC USA).

The sentinel phase evaluated safety and efficacy in five adult subjects with type 1 diabetes (2 male and 3 female) who were using unblinded continuous glucose monitors (CGM) and continuous subcutaneous insulin infusion (CSII). Key entry criteria included: 18-60 years of age, diagnosed with type 1 diabetes prior to 40 years of age and a minimum of 1 year prior to screening, and use of a Dexcom CGM and CSII for at least three months. To be enrolled, patients had to demonstrate awareness of hypoglycemia and manage their diabetes with insulin and no adjunctive drug therapy. Patients also had to be of generally stable health with a BMI \leq 32 kg/m², TG \leq 600 mg/dL and an HbA1c value of $<9\%$ at screening.

TTP399 was well tolerated with no incidents of severe hypoglycemia or DKA and no detrimental effects on liver function or plasma lipids during the three weeks of dosing. Similar to the experience in dosing TTP399 in volunteers with type 2 diabetes, there were no significant safety signals observed during the sentinel phase. No serious AEs, deaths, or discontinuations of drug occurred during the sentinel phase. Treatment emergent AEs were reported for four of the five patients. All AEs were mild in severity with no severe AEs. All related AEs resolved without sequelae. Efficacy results from the sentinel phase showed trends towards improved glycemic control while reducing insulin dose and were presented at the ADA in Orlando.¹ Results from the sentinel phase provided adequate safety and efficacy information to justify expanding to a larger number of sites and patients in Part 1. Based on the data (see Table S1 and S2 below), a dose of 800mg was selected for the rest of the study.

Expanded Statistical Analysis

Power calculations:

Sample sizes were done for Part 2 of the study. A standard deviation (SD) of 1% was assumed; 34 patients per group provided 80% power to detect a difference between the group treated with TTP399 and the group treated with placebo of 0.7% in HbA1c using $\alpha = 0.049$.

Randomization of 68 patients (34 patients randomized to each arm) was determined in the protocol to provide adequate power for this study to meet its objectives related to HbA1c changes.

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (1998), the following population of analysis were planned and used for all statistical analysis

- The full analysis set (FAS) included all randomized patients who receive any study medication and had a baseline assessment.
- The per-protocol set (PPS) included all patients in the FAS excluding patients who have major protocol violations. (This was also called the second estimand in Part 2.)
- The safety set (SAF) included all patients who receive any study medication.

The FAS was planned and used for all hypothesis tests of efficacy. The PPS (specified as the second estimand) was used for supportive analyses and provided more realistic estimates of treatment benefit that more closely represented the free-living population of subjects with type 1 diabetes.

SAS version 9.4 or later was used for statistical analysis of Part 1 and Part 2.

Efficacy analysis for Part 1 included planned hypothesis testing as follows: The primary objective was to show superiority (using a 2-sided test) of TTP399 to placebo at 12 weeks in patients treated with insulin on a dichotomous variable to delineate patients treated with insulin plus placebo from patients treated with modified insulin with TTP399 added followed by a non-inferiority evaluation of change in HbA1c followed by a superiority evaluation of change in HbA1c.

The hypotheses tested in Part 1 were as follows:

- H_{01} : The proportion of responders at Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H_{11} : The proportion of responders at Week 12 for the group treated with 800 mg TTP399 was not equal (was superior) to that of the placebo group.

Conditional on statistical significance, statistical evaluation continued.

The second conditional evaluation was that TTP399 added to treatment with insulin in a modified manner was non-inferior to placebo added to insulin alone following usual standard of care.

- The 95% confidence interval was constructed for the difference between the two treatment groups in mean change in HbA1c to Week 12 using the ANCOVA model as described in the statistical methodology section.
- If the 95% confidence interval was entirely bounded by 0.25% (where a difference of 0.25% reflected the placebo mean is 0.25% better than the mean of the patients treated with TTP399), then the statistical conclusion followed that treatment with 800 mg TTP399 combined with a modified regimen of insulin was non-inferior to placebo added to insulin following the usual standard of care.

Conditional on the statistical conclusion of non-inferiority of TTP399 relative to placebo, statistical evaluation continued.

- H_{03} : The mean change from baseline to Week 12 in HbA1c for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H_{13} : The mean change from baseline to Week 12 in HbA1c for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

Planned hypothesis tests for Part 2 included planned evaluations as follows:

First Compound Statistical Evaluation (full alpha):

The first evaluation was non-inferiority of treatment with TTP399 800 mg daily plus a modified regimen of insulin and treatment with optimized insulin as determined by the insulin-optimization period of the study, if needed, per protocol:

- *Evaluation 1:*

Noninferiority was considered to have been established if the 95% confidence interval was completely bounded by the non-inferiority margin of 0.3%, which is specified in the draft guidance: *Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutics Biologics for Treatment and Prevention* (CDER; February 2008), Section V.G.1, “Typically we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials.”

- The 95% confidence interval was constructed for the difference between the two treatment groups in mean change in HbA1c to Week 12 using the ANCOVA model as described in the statistical methodology section.
- If the 95% confidence interval was entirely bounded by 0.3% (where a difference of 0.3% reflected the placebo mean is 0.3% better than the mean of the patients treated with TTP399), then the statistical conclusion followed that treatment with 800 mg TTP399 combined with a modified regimen of insulin is non-inferior to placebo added to insulin following the usual standard of care.

Conditional on the statistical conclusion of non-inferiority of TTP399 relative to placebo, statistical evaluation continued.

It was noted that noninferiority relative to change from baseline in insulin was planned using the confidence interval approach to demonstrate that the maintenance of control of HbA1c achieved during the insulin-optimization period was not driven by an increase in insulin among subjects treated with TTP399. Formal evaluation of this aspect of non-inferiority was not planned, so the statistical evaluation was considered to be nominal rather than rigorous.

The Hochberg method was used for alpha control for Evaluation 2 and Evaluation 3.

- *Evaluation 2:*

Superiority on HbA1c was evaluated:

- H_{01} : The change from baseline in HbA1c at Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H_{11} : The change from baseline in HbA1c at Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

- *Evaluation 3:*

It was noted that strict application of the Hochberg methodology implied that rigorous p-values may not be applicable in the event of failure to reject either hypothesis in Evaluation 2. The intersection hypothesis was, however, applicable, and it was the intention of this analysis plan to continue testing under the intersection hypothesis and interpret p-values as rigorous as opposed to nominal.

Superiority on treatment response was evaluated:

- H_{02} : The proportion of treatment responders at Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H_{12} : The proportion of treatment responders at Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

The study was declared to have met its primary endpoint if Evaluation 1 concluded TTP399 plus the modified regimen of insulin was noninferior to optimized insulin

AND

Using the Hochberg method, either Evaluation 2 found TTP399 to be superior on HbA1c or Evaluation 3 found TTP399 to be superior on the proportion of treatment responders.

Conditional on achievement of endpoints, statistical evaluation continued.

Conditional Second Statistical Evaluation:

- *Evaluation 4:*

Superiority on daytime time in range was evaluated:

- H_{03} : The mean change in daytime time in range from baseline to Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.

- H₁₃: The mean change in daytime time in range from baseline to Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

Conditional Third Statistical Evaluation:

- *Evaluation 5:*

Superiority on time in hypoglycemia using 70 mg/dl as the threshold was evaluated:

- H₀₄: The mean change in time in hypoglycemia using 70 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H₁₄: The mean change in time in hypoglycemia using 70 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

Conditional Fourth Statistical Evaluation:

- *Evaluation 6:*

Superiority on time in hypoglycemia using 54 mg/dl as the threshold was evaluated:

- H₀₅: The mean change in time in hypoglycemia using 54 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H₁₅: The mean change in time in hypoglycemia using 54 mg/dl as the threshold from baseline to Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

Conditional Fourth Statistical Evaluation:

- *Evaluation 7:*

Superiority on Quality of life Likert scale score was evaluated:

- H₀₆: The mean score for the single-item Likert scale for overall improvement in quality of life at Week 12 for the group treated with 800 mg TTP399 was equal to that of the placebo group.
- H₁₆: The mean score for the single-item Likert scale for overall improvement in quality of life at Week 12 for the group treated with 800 mg TTP399 was not equal to that of the placebo group.

The statistical model for Part 1 for HbA_{1c} was a main-effects ANCOVA model with baseline HbA_{1c} as a covariate where multiple imputation (MI) with 100 invocations based on Monte Carlo methods was planned and used. Part 2 used a main-effects ANCOVA model with baseline HbA_{1c}, baseline insulin use, and randomization stratum as covariates where MI with 100 invocations based on Monte Carlo methods was planned and used.

The responder analysis was done in Part 1 with Fisher's exact test. Logistic regression was planned and used for the responder analysis for Part 2.

Expanded Second Estimand Specification

In accordance with the ICH E9 Addendum, the specification of the second estimand was included in the statistical analysis plan with the 4 attributes detailed in ICH E9 Addendum, Section A.3.1:

- A. The Population, that is, the patients targeted by the scientific question:

For this study, the population consisted of subjects with type 1 diabetes who met eligibility requirements for the study, qualified through the basal insulin-optimization period (if needed) and the placebo run-in period, received double-blind medication, and had at least one valid post-baseline measurement of HbA1c.

- B. The variable (or endpoint) to be obtained for each patient, that is required to address the scientific question:

For this study, the primary endpoint was HbA1c with co-primary importance on treatment responsiveness (whether or not the subjects were treatment responders).

- C. The specification of how to account for intercurrent events to reflect the scientific question of interest:

For this study, intercurrent events such as blood transfusion or medical treatment with prednisone or major modification in insulin regimen/doses or requiring rescue therapy that would render subsequent values as not protocol-meaningful were set to missing. Primary statistical methodologies of multiple imputation were used to predict what the values were likely to be had the intercurrent events not happened.

- D. The population-level summary for the variable that provides, as required, a basis for comparison between treatment conditions:

For this study, the population-level summary for the variable was the least-squares mean of the treatment in the mean change from baseline in HbA1c.

Analysis of HbA1c and insulin by insulin subgroups

A data-driven approach for analysis of change in insulin (average change in bolus insulin and average change in total insulin, separately) was prespecified in the statistical analysis plan:

1. The pooled group median of each insulin variable (change in average bolus and change in average basal) was used to create a 2x2 display of subjects treated with TTP399 and subjects treated with placebo.
 - a. Within each category (each of the 4 cells of the 2x2 display), the number of subjects in each treatment group was counted and the proportions calculated (median test).
 - b. Subgroups were created based on insulin changes: taking more insulin use (change above the median) and taking less insulin (change below the median).
 - c. The mean change in HbA1c was calculated for each treatment group within each subgroup for descriptive analysis. The mean (median) change in HbA1c was compared between treatment groups among subjects with changes more than the median insulin and also among subjects with changes less than the median amount of insulin.
2. The median change in insulin usage (basal and bolus) for each treatment group was determined. The subjects treated with TTP399 taking more than the TTP399 median were compared with the placebo-treated subjects taking more than the placebo median. Comparisons were made for insulin and also HbA1c changes.

Table S1: Safety Data during the Sentinel Phase with 400mg, 800mg, and 1200mg of TTP399

	400 mg QD (n=5)	800 mg QD (n=5)	1200 mg QD (n=5)	Off-drug (n=5)
Number of AEs	3	2	5	5
Number of subjects reporting AEs	2	2	2	3
SAEs or death	0	0	0	0
AEs Related to TTP399	2 (headache hypoglycemia)	1 (hypocalcemia)	1 (right eye discomfort)	2 (lower back pain, nausea)
DKA	0	0	0	0
Hypoglycemia				
Severe hypoglycemia	0	0	0	0
Hypoglycemia (documented symptomatic)	1	0	0	0
Liver Function				
ALT (U/L)	16.0 (7.0)	15.6 (7.2)	15.6 (7.6)	17 (8.2)
AST (U/L)	19.0 (6.4)	17.8 (5.6)	18.6 (7.2)	22.8 (15.9)
Total Bilirubin (μmol/L)	9.0 (3.4)	7.6 (2.4)	6.2 (1.8)	6.6 (1.7)
Fasting Lipids				
Cholesterol (mmol/L)	4.5 (0.7)	4.5 (0.8)	4.4 (0.6)	4.4 (0.7)
HDL (mmol/L)	2.0 (0.6)	1.9 (0.5)	1.8 (0.4)	1.9 (0.5)
LDL (mmol/L)	2.2 (0.3)	2.3 (0.6)	2.2 (0.5)	2.3 (0.3)
Triglycerides (mmol/L)	0.7 (0.3)	0.6 (0.1)	0.6 (0.1)	0.6 (0.1)

Data are means and (SD) for liver function and lipids.

Table S2: CGM Data and Insulin Pump Data during the Sentinel Phase with 400mg, 800mg, and 1200mg of TTP399

	Baseline (n=5)	400 mg QD (n=4)	800 mg QD (n=5)	1200 mg QD (n=5)
CGM data				
% Time in Range (70-180 mg/dL)	56 (44-81)	67 (55-79)	74 (44-82)8	57 (47-77)
% Time in Hypoglycemia Level 2*	1 (0-3)	2 (0-2)	0 (0-1)	0 (0-6)
Level 2 hypoglycemia Number of events	3	7	0	7
% Time in Hypoglycemia Level 1**	3 (2-10)	6 (1-8)	1 (0-4)	3 (1-13)
Level 1 hypoglycemia Number of events	20	9	8	13
% Time in Hyperglycemia Level 1***	40 (14-54)	31 (23-44)	24 (17-52)	30 (22-53)
CGM Mean Glucose (mmol/L)	9.5 (7.3-10.2)	8.6 (7.8-10)	8.7 (7.4-10.3)	8.4 (7.9-10.3)
CGM Mean Glucose (mg/dL)	171 (132-183)	155 (140-181)	156 (134-186)	151 (142-185)
Insulin pump data				
Total Insulin (U/day)	48 (10)	48 (6)	43 (8)	43 (9)
Insulin bolus (U/day)	27 (7)	25 (6)	20 (6)	23 (7)
Basal Insulin (U/day)	22 (5)	23 (5)	23 (5)	22 (6)
Carbohydrate intake (g/day)	179 (60)	232 (73)	228 (82)	207 (86)
Carbs/bolus insulin ratio	6.7 (1.7)	9.2 (3.6)	12.2 (6)	8.6 (3.6)

Data are median and (ranges) for CGM data and means and (SE) for insulin pump data. *Level 2 Hypoglycemia = <54 mg/dL or 3 mmol/L. **Level 1 Hypoglycemia = 70-54 mg/dL or 3.9-3 mmol/L. ***Level 1 Hyperglycemia = >180mg/dL or 10 mmol/L.

Table S3: Incidence of Hypoglycemia AEs in Insulin Change Subgroups in Part 2

Insulin Use	Treatment	Hypoglycemia AEs			
		Day 1 to end of study		Week 2 to end of study	
		Severe	Symptomatic	Severe	Symptomatic
Insulin Reduced	Placebo (n=12)	1 (8%); 1	4 (33%); 7	1 (8%); 6	3 (33%); 6
	TTP399 (n=15)	0	2 (13%); 2	0	0
Stable Insulin	Placebo (n=13)	0	4 (31%); 19	0	4 (31%); 13
	TTP399 (n=13)	0	2 (15%); 6	0	1 (7%); 5
Insulin Increased	Placebo (n=11)	0	1 (9%); 1	0	1 (9%); 1
	TTP399 (n=4)*	0	1 (25%); 4	0	1 (25%); 3**

n = number of patients in each category and treatment group. Data are number of patients (%); number of events in category. Only symptomatic or severe hypoglycemia events were considered AEs. *undetectable TTP399 levels in 2 of the patients; **occurred in one of the patients with undetectable TTP399 levels. Insulin subgroups: decreased insulin ($\Delta \leq -0.06$ U/Kg/day), stable insulin ($\Delta = -0.06 - 0.03$ U/Kg/day) and increased insulin ($\Delta \geq 0.03$ U/Kg/day).

Table S4: Abnormal Serum Ketones in Insulin Change Subgroups in Part 2

	Reduced Insulin		Stable insulin		Increased insulin	
	Placebo (n=12)	TTP399 (n=15)	Placebo (n=13)	TTP399 (n=13)	Placebo (n=11)	TTP399 (n=4)*
Improved HbA1c	2 (16%)	10 (67%)	4 (31%)	8 (62%)	4 (36%)	0
Abnormal BOHB (>0.4mM)	4 (33%)	3 (20%)	5 (38%)	2 (15%)	4 (36%)	0
Mean change in total insulin dose (% of baseline)	-16±1.7	-15±2.7	-2.9±1.2	-5.3±2	17±4	12±3

*undetectable TTP399 levels in 2 of the patients. Insulin subgroups: decreased insulin ($\Delta \leq -0.06$ U/Kg/day), stable insulin ($\Delta = -0.06 - 0.03$ U/Kg/day) and increased insulin ($\Delta \geq 0.03$ U/Kg/day).

Table S5: Most Frequently Reported AEs by System Organ Class and Preferred Term in Part 1 and Part 2

System Organ Class Preferred Term	Part 1		Part 2		Combined	
	Placebo (n=11)	TTP399 (n=9)	Placebo (n=45)	TTP399 (n=40)	Placebo (n=56)	TTP399 (n=49)
Infections and infestations	2 (18%)	3 (33%)	18 (40%)	14 (35%)	20 (36%)	17 (35%)
Upper respiratory tract infection	1 (9%)	1 (11%)	5 (11%)	6 (15%)	6 (11%)	7 (14%)
Nasopharyngitis	0	1 (11%)	3 (7%)	2 (5%)	3 (5%)	3 (6%)
Urinary tract infection	0	0	4 (9%)	0	4 (7%)	0
Ear infection	0	0	0	3 (8%)	0	3 (6%)
Sinusitis	0	1 (11%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Influenza	0	0	1 (2%)	2 (5%)	1 (2%)	2 (4%)
Herpes zoster	0	0	2 (4%)	0	2 (4%)	0
Metabolism and nutritional disorders	0	0	10 (22%)	7 (18%)	10 (18%)	7 (14%)
Hypoglycemia	0	0	9 (20%)	5 (13%)	9 (16%)	5 (10%)
Ketosis	0	0	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Gastrointestinal disorders	2 (18%)	2 (22%)	4 (9%)	3 (8%)	6 (11%)	5 (10%)
Nausea	2 (18%)	2 (22%)	2 (4%)	1 (2%)	4 (7%)	3 (6%)
Respiratory, thoracic, and mediastinal disorders	4 (36%)	0	2 (4%)	2 (5%)	6 (11%)	2 (4%)
Cough	2 (18%)	0	1 (2%)	2 (5%)	3 (5%)	2 (4%)
Nervous system disorders	0	0	3 (7%)	2 (5%)	3 (5%)	2 (4%)
Headache	0	0	2 (4%)	0	2 (4%)	0
Musculoskeletal and connective tissue disorders	2 (18%)	0	8 (18%)	3 (8%)	10 (18%)	3 (6%)
Joint swelling	2 (18%)	0	0	0	2 (4%)	0
Pain in extremity	1 (9%)	0	2 (4%)	2 (5%)	3 (5%)	2 (4%)

Data are for AEs reported by at least 2 patients in any group in each part of the study.

Table S6: Expanded Liver Safety Profile with TTP399 Treatment in Part 1 and Part 2

	Part 1		Part 2	
	Placebo n=11	TTP399 n=9	Placebo n=45	TTP399 n=40
ALT, AST, ALP > 1.5x ULN and/or BILI > 2x ULN	0	0	2 (4%)	1 (2%)
AST or ALT > 3x ULN and BILI > 1.5	0	0	0	0
AST, ALT > 3x ULN	0	0	0	0
AST > 3x ULN	0	0	1 (2%)	0
ALP > 1.5x ULN	0	0	1 (2%)	1 (2%)
ALT > 1.5x ULN	0	0	0	0
BILI > 2x ULN	0	0	0	0

Data is from start of treatment through follow-up and represents the number of patients with at least one episode. BILI=bilirubin. ALP =alkaline phosphatase. AST=aspartate aminotransferase. ALT= alanine aminotransferase.

Table S7: Change in Plasma Lipids with TTP399 Treatment in Part 1 and Part 2

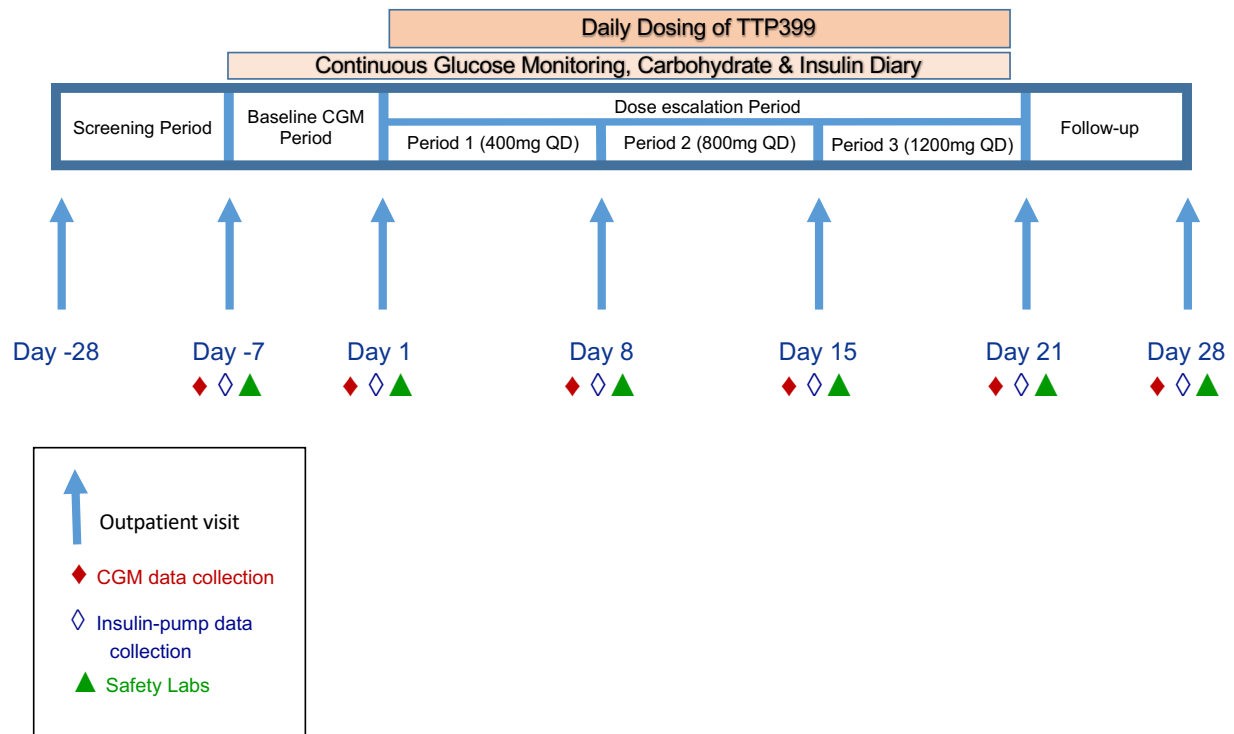
	Part 1		Part 2	
	Placebo (n= 11)	TTP399 (n=9)	Placebo (n= 45)	TTP399 (n=40)
Cholesterol (mmol/L)				
Baseline	4.4 (0.8)	4.4 (0.9)	4.6 (0.9)	4.5 (0.7)
Week 12 change from baseline	0.5 (1.1)	-0.02 (0.6)	-0.1 (0.9)	-0.01 (0.05)
HDL Cholesterol (mmol/L)				
Baseline	1.9 (0.4)	1.6 (0.6)	1.7 (0.5)	1.6 (0.5)
Week 12 change from baseline	-0.02 (0.2)	-0.1 (0.3)	-0.1 (0.2)	0.04 (0.2)
LDL Cholesterol (mmol/L)				
Baseline	2.3 (0.6)	2.4 (0.4)	2.4 (0.7)	2.4 (0.6)
Week 12 change from baseline	0.4 (1.0)	0.1 (0.4)	-0.03 (1.0)	-0.02 (0.4)
Triglycerides (mmol/L)				
Baseline	0.7 (0.2)	0.8 (0.2)	1.0 (0.5)	1.0 (1.0)
Week 12 change from baseline	0.2 (0.3)	0.05 (0.2)	-0.3 (0.4)	-0.05 (0.9)

Data are means and (SD).

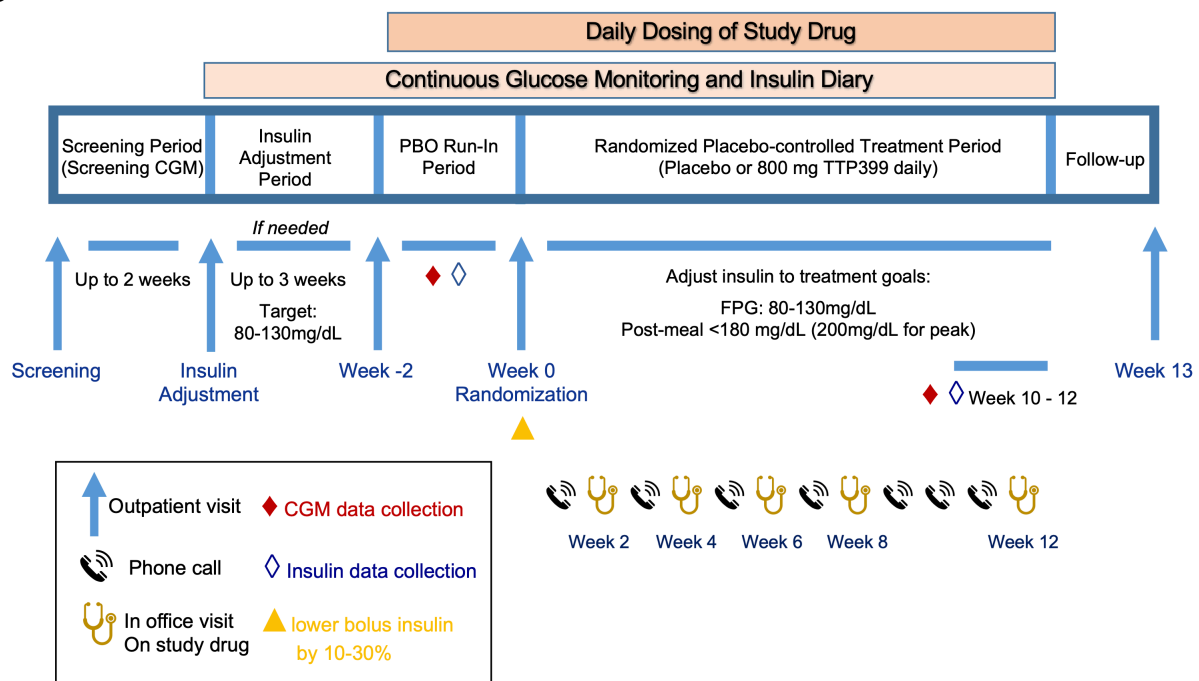
Figure S1: Study design for the Sentinel Phase, Part 1, and Part 2.

The schema for the Sentinel (A), Part 1 (B), and Part 2 (C) of the SimpliciT1 study are outlined below.

A



B



C

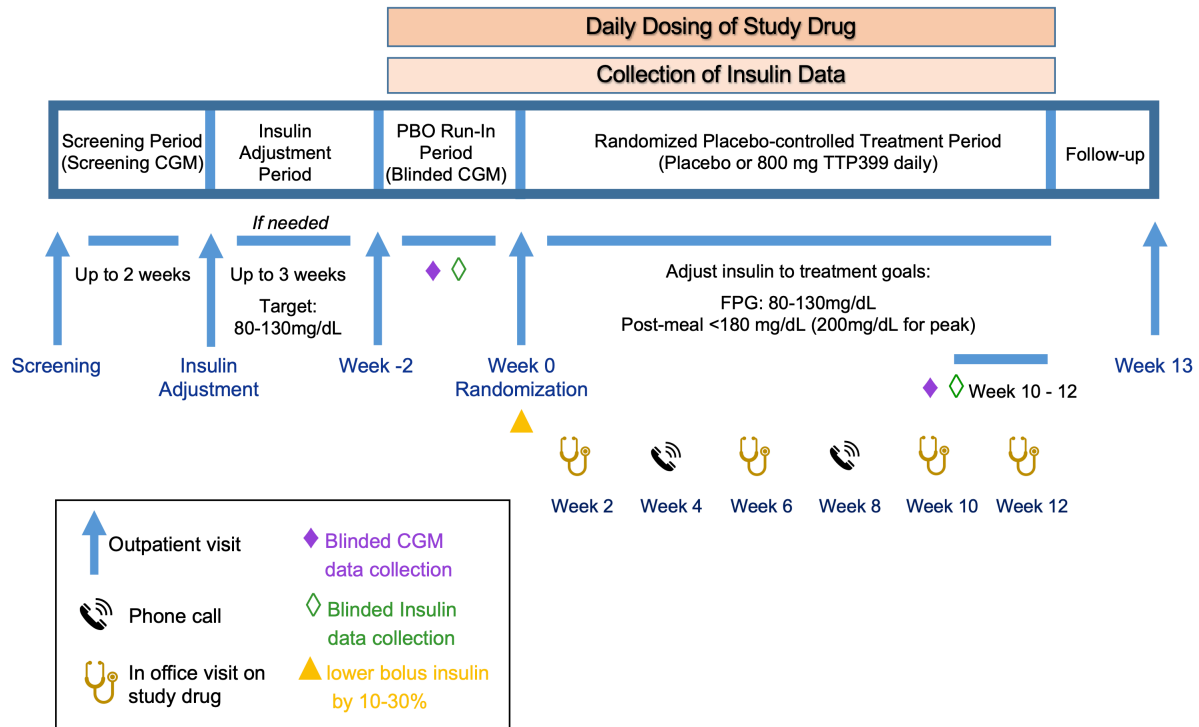
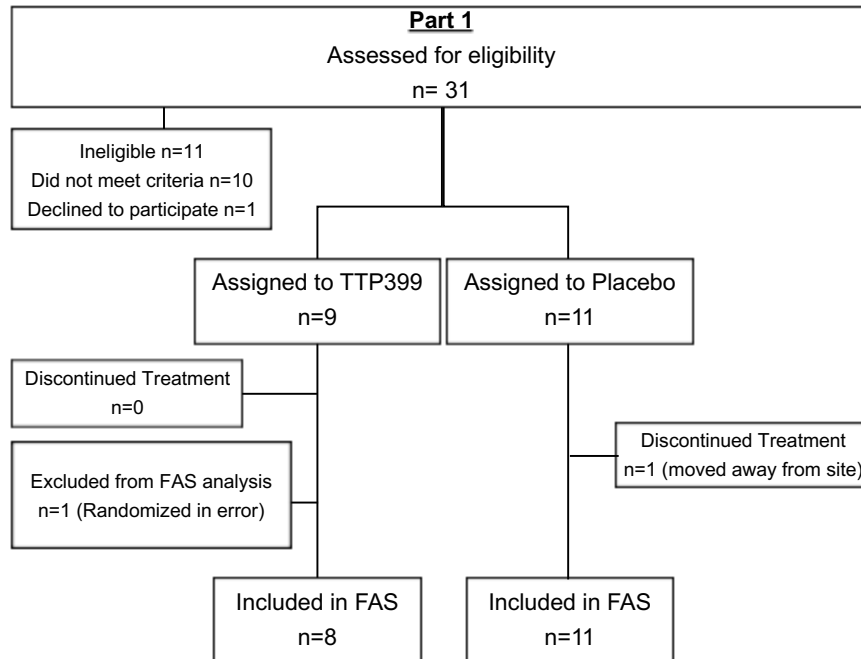


Figure S2: Trial Profile

Consort diagrams are presented for (A) Part 1 and (B) Part 2 of the SimpliciT1 study. FAS = full analysis set.

A



B

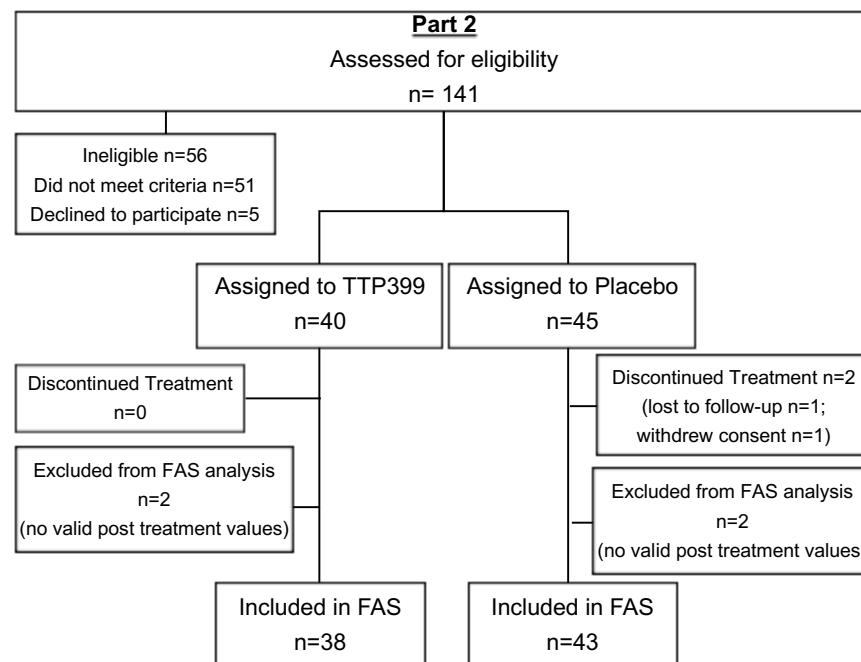
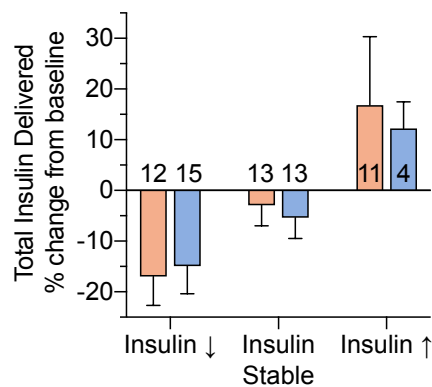


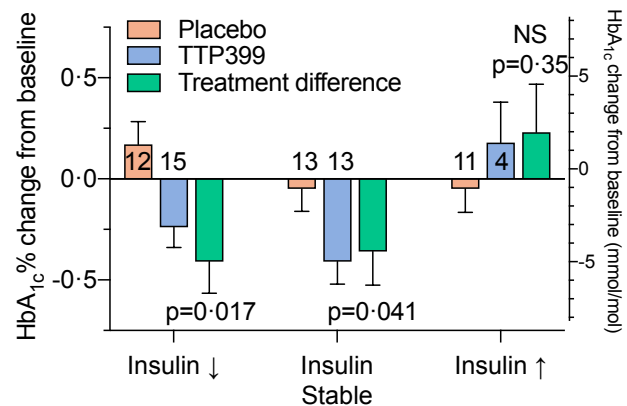
Figure S3: Change in Insulin Dosing and HbA1c by Subgroup Analysis in Part 2

A pre-specified subgroup analysis based on changes in total insulin dose during the dosing period in Part 2 identified three subgroups of patients: decreased insulin, stable insulin, and increased insulin. Panel (A) demonstrates the mean percent change in baseline total insulin dose for participants in each subgroup. Decreased insulin was defined by $\Delta \leq -0.6\text{U/kg/day}$, stable $\Delta = -0.6 - 0.03\text{U/kg/day}$, and increased $\Delta \geq 0.6\text{U/kg/day}$. Panel (B) demonstrates the percent change in HbA1c from baseline for participants by subgroup. The population analyzed in both A and B are all participants with insulin and HbA1c data at baseline and week 12.

A



B



References

1. Buse, JB, Valcarce, C, Freeman JLR, et al. Simplici-T1: First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes. *Poster presentation at: Annual Scientific Meeting of the American Diabetes Association; 2018 June 22-26; Orlando Fl.* <(https://vtvtherapeutics.com/wp-content/uploads/pdf/ada_gka_poster_lb_june2018.pdf).>