The Simplici-T1 trial: Glucokinase activator (GKA) TTP399 improves glycemic control in patients with type 1 diabetes (T1D)

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Disclosures – John Buse

- JBB's contracted consulting fees and travel support for contracted activities are paid to the University of North Carolina by Adocia, AstraZeneca, Dance Biopharm, Eli Lilly, MannKind, NovaTarg, Novo Nordisk, Sanofi, Senseonics, vTv Therapeutics, and Zafgen
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- Consultant to Cirius Therapeutics Inc, CSL Behring, Mellitus Health, Neurimmune AG, Pendulum Therapeutics, and Stability Health
- Stock/options in Mellitus Health, Pendulum Therapeutics, PhaseBio, and Stability Health

TTP399-203 (Simplici-T1): Adaptive Phase 1b/2 Study Trial Design

	1 site	4 sites	13 sites
Study design	**Phase 1** (Sentinels) ▪ Open-label ▪ **7 day** dose escalation up to 1200mg QD ▪ **5 adult subjects** with T1D on CSII and CGM(1)	**Phase 2-Part 1** (Learning Phase) ▪ Double-blind Placebo control ▪ **12 weeks** dosing 800mg QD ▪ **19 adult subjects** with T1D on CSII and CGM(1) ▪ **Primary Endpoint**: Δ in HbA1c ▪ Baseline HbA1c optimized prior to commencement of the study (baseline HbA1c 7.3%)	**Phase 2-Part 2** (Confirming Phase) ▪ Double-blind Placebo control ▪ **12 weeks** dosing 800mg QD ▪ **85 adult subjects** with T1D (all comers) ▪ **Primary Endpoint**: Δ in HbA1c ▪ Baseline HbA1c optimized prior to commencement of the study (baseline HbA1c of 7.6%)

Clinical results	**March 2018**
	▪ **No** incidents of **severe hypoglycemia or DKA**
	▪ Indications of **improved glycemic control, while reducing insulin dose**
	  ▪ Increase % time in range
	  ▪ Reduce % time in hyperglycemia
		June 2019(2)
		▪ Placebo-subtracted **reduction in HbA1c of 0.7%**
		▪ **Decreased insulin usage** was observed in the group treated with TTP399
		▪ **No report of diabetic ketoacidosis or severe hypoglycemia**
		▪ **Improved time in range**
			February 2020(2)
			▪ Placebo-subtracted **reduction in HbA1c of 0.32%**
			▪ **Reduced total daily mealtime bolus insulin dose by 11%** relative to baseline
			▪ **No report of diabetic ketoacidosis, fewer symptomatic hypoglycemic episodes** in TTP399 vs. placebo
			▪ **2-hour increase in time in range** relative to placebo

Note: ClinicalTrials.gov Identifier: NCT03335371.

(1) Subjects with Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM).

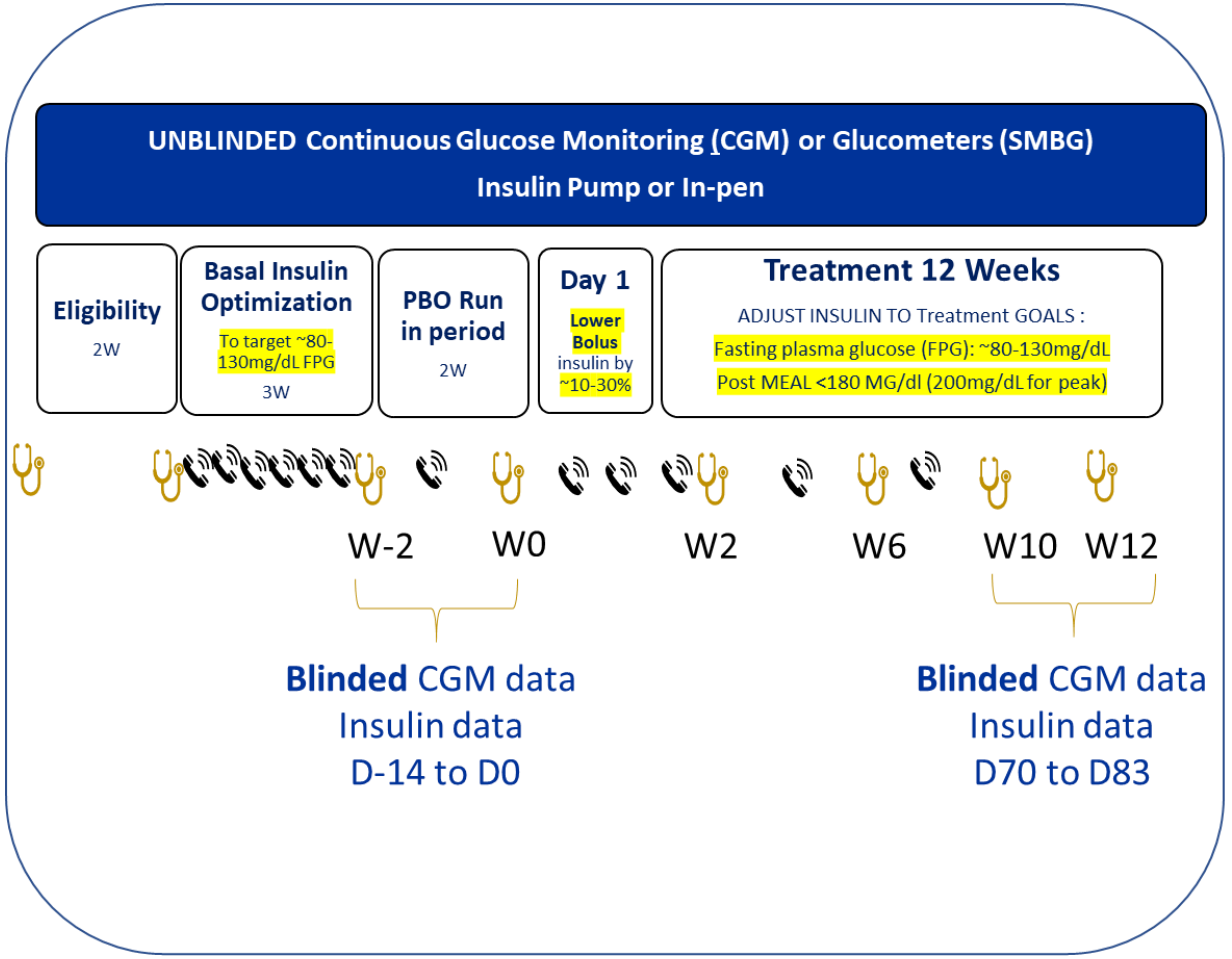
(2) Top line results.

JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

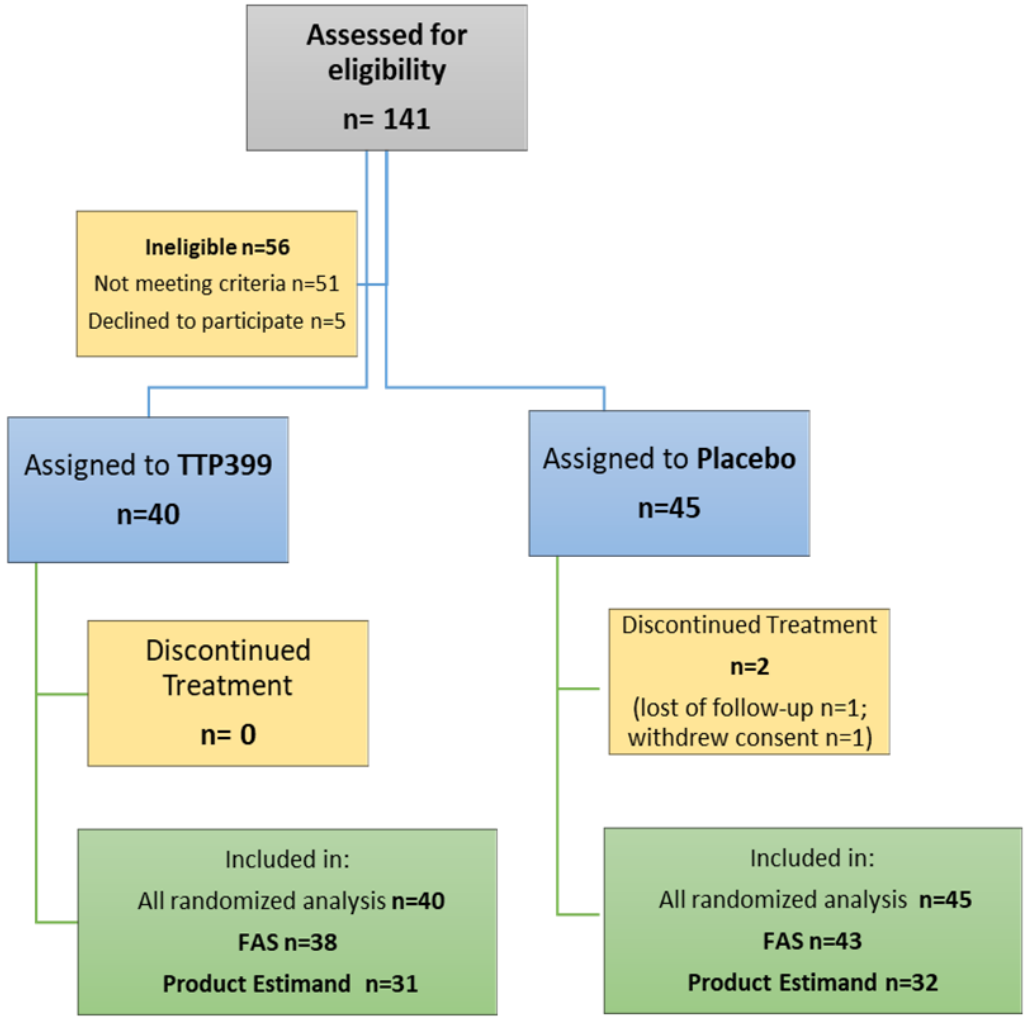
simplici-T1

Phase 2 - Part 2 (Confirming Phase)

Design



Disposition

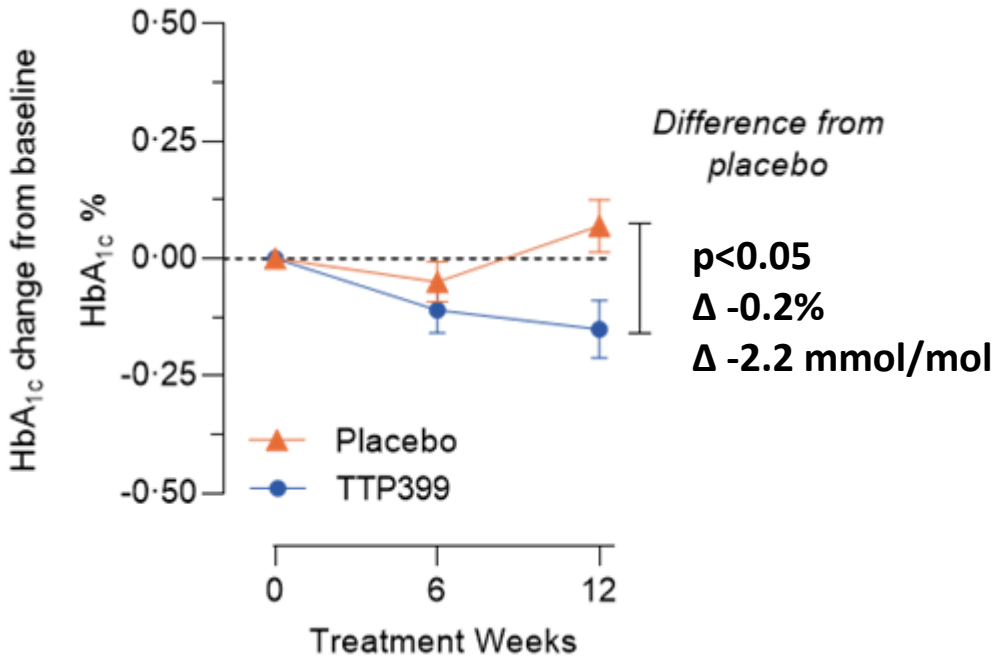


Demographics

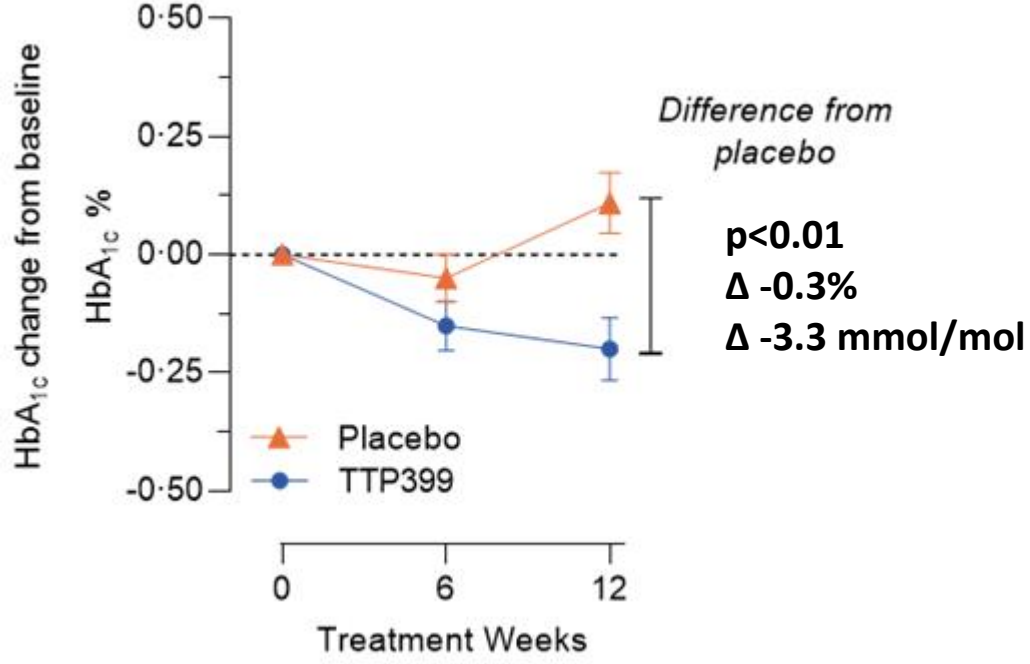
Trait	Statistic	Placebo (N=45)	TTP399 800 mg (N=40)
Age (Years)	Mean [Median] (min, max)	42.4 [38.0] (24, 70)	43.4 [43.5] (20, 69)
Gender	Female (%)	25 (55.6%)	15 (37.5%)
Ethnicity	Not Hispanic or Latino (%)	43 (95.6%)	39 (97.5%)
Race	White (%)	43 (95.6%)	38 (95.0%)
Weight (kg)	Mean [Median] (min, max)	83.5 [83.0] (54, 117)	83.4 [80.8] (47, 123)
BMI (kg/m^2)	Mean [Median] (min, max)	28.2 [28.3] (21, 38)	27.9 [27.4] (20, 37)
HbA1c at Randomization	Mean [Median] (min, max)	7.52 [7.30] (6.5, 8.8)	7.66 [7.60] (6.7, 8.9)
C-peptide at Baseline	Mean [Median] (min, max)	0.14 [0.00] (0.0, 2.6)	0.05 [0.00] (0.0, 0.4)
Undetectable C-peptide (<0.004ng/mL)	%	53%	57%
CGM Use	CGM User (%)	56%	60.%
Insulin Device	Pump (%)	62%	55%
Age at Diagnosis (yrs)	Mean [Median] (min, max)	16.09 [14.00] (1.0, 37.0)	16.35 [14.00] (4.0, 35.0)
Time Since Diagnosis (yrs)	Mean [Median] (min, max)	26.30 [22.10] (5.5, 59.2)	26.92 [24.55] (3.1, 58.3)
Baseline Average Total Insulin (u/kg/day)	Mean [Median] (min, max)	0.64 [0.60] (0.3, 1.1)	0.68 [0.62] (0.3, 1.4)
Baseline Average Bolus Insulin (u/kg/day)	Mean [Median] (min, max)	0.30 [0.28] (0.1, 0.6)	0.31 [0.27] (0.1, 0.9)
Baseline Average Basal Insulin (u/kg/day)	Mean [Median] (min, max)	0.34 [0.33] (0.1, 0.6)	0.37 [0.32] (0.2, 0.8)

Primary Endpoint:
Statistically significant reduction in HbA1c

Primary endpoint (FAS)



Treatment estimand*



All Randomized: Δ= -0.2%, 95%CI -0.38, -0.02, p<0.05

*Treatment estimand analysis evaluated the effect on HbA1c for patients without evidence of noncompliance with prescribed treatment who did not administer increases of bolus insulin of three or more units per day. This second estimand analysis was pre-specified in the SAP and conducted consistent with current regulatory guidance. Data are LSmean +/- SE.

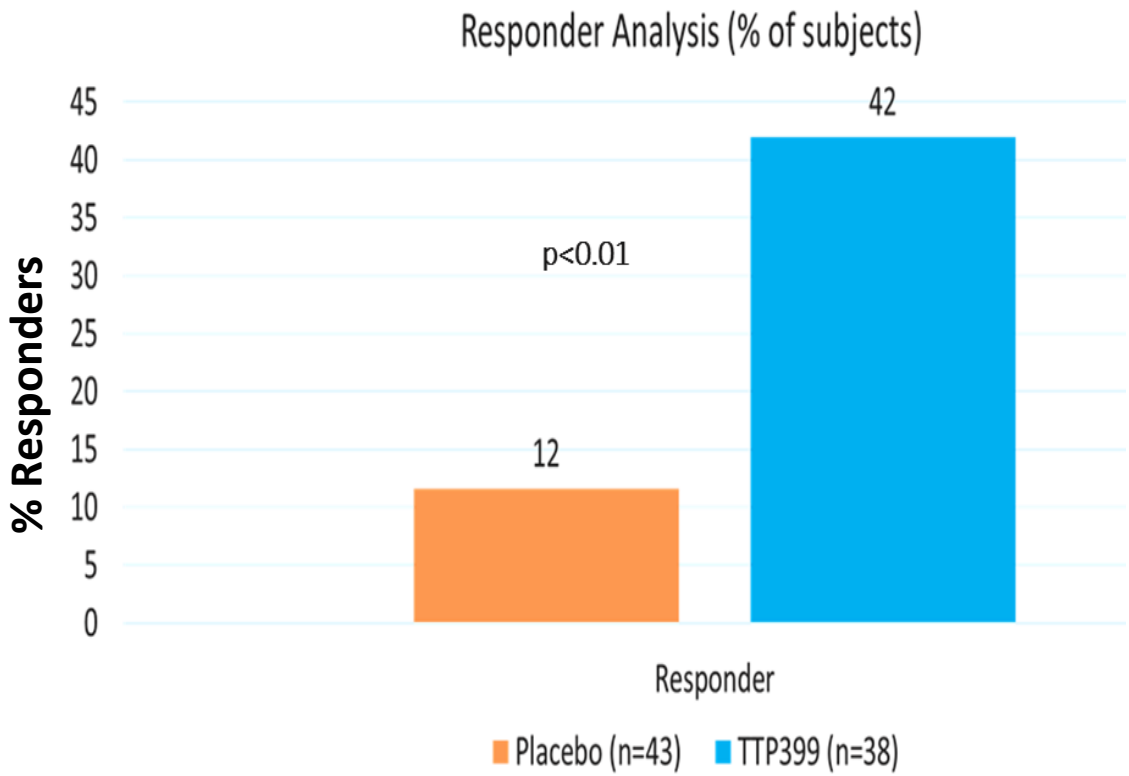
Primary Endpoint: % of Responders

Statistically significant greater % of responders

Responder Definition:

Proportions of subjects with improvement in HbA1c without:

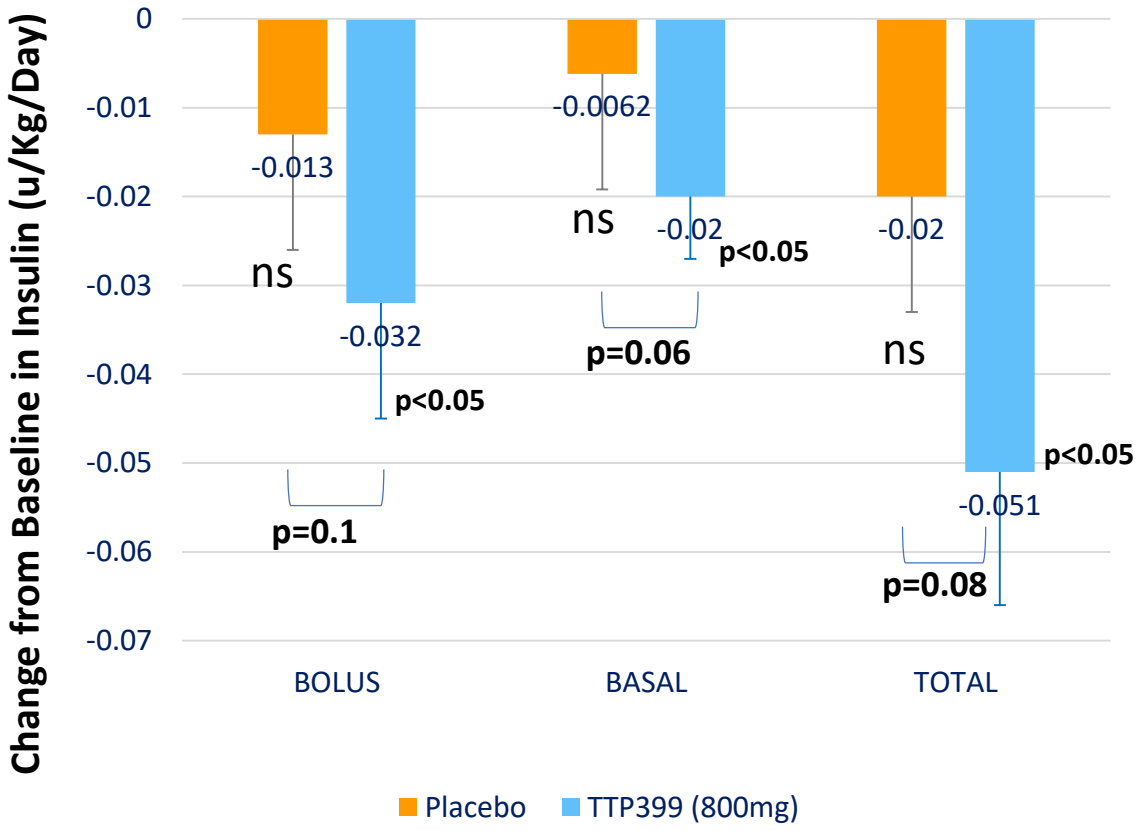
- abnormal ketones in plasma,
- abnormal lactate in blood,
- no increase in insulin bolus ≥3 units/day
- symptomatic or severe hypoglycemia



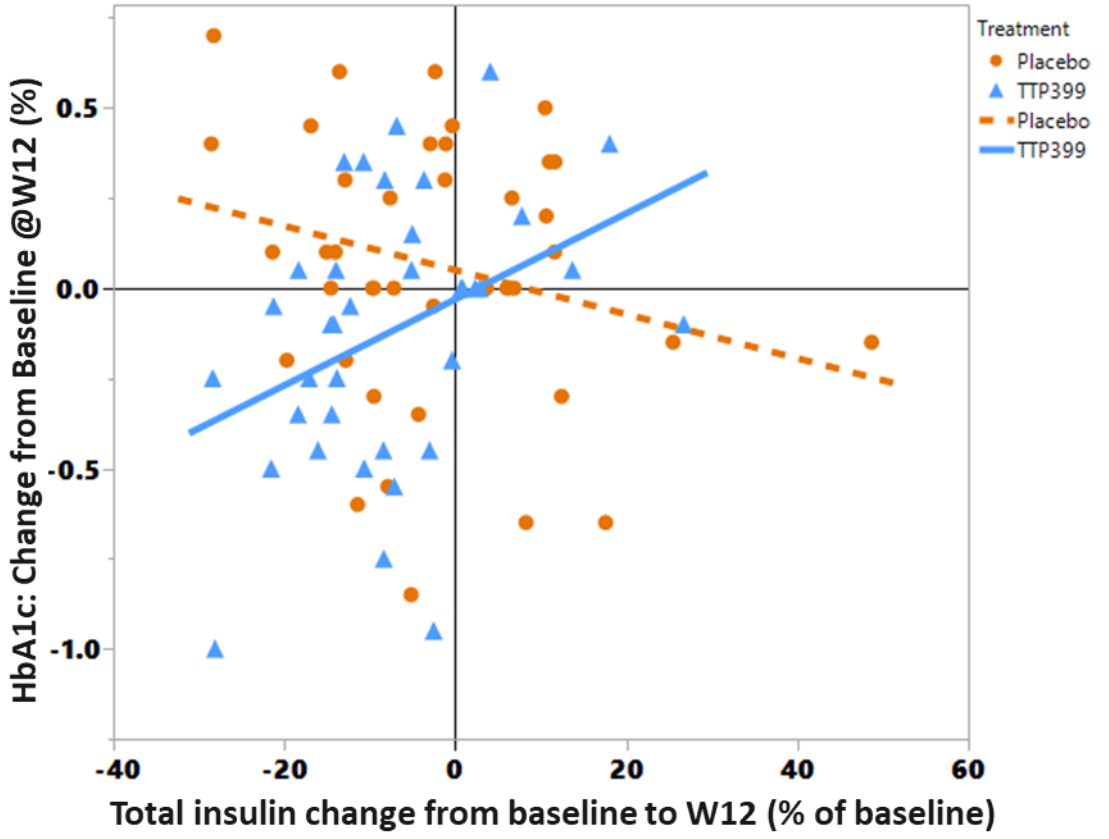
Changes in Insulin Dose

Bolus insulin dose reductions with TTP399 treatment

Insulin Change from Baseline



ΔA1c *vs* ΔTotal Insulin



Treatment Emergent Adverse Events

Trends towards reduction in hypoglycemic and ketone events in the TTP399-treated group

		Placebo (n=45)	TTP399 (n=40)
TEAEs	Subjects with at least 1 TEAE	29	26
	Number of TEAEs reported	83	58
Hypoglycemia	**Total** number of **hypoglycemic AEs**	**27**	**12**
	Number of **severe hypoglycemic** events	**1**	**0**
	Number of **symptomatic hypoglycemia AE**	**26**	**12**
	Number of **subjects** with hypoglycemia event AE s **in the study** (from screening to FU)	**9 (20%)**	**5(12%)**
	Severe Hypoglycemia	**1**	**0**
	Symptomatic hypoglycemic events	**8**	**5**
	Number of events per person-exposure months	**0.2**	**0.1**
	Number of **subjects** with hypoglycemic AEs **in the last 10-weeks of dosing (stable insulin and TTP399 dose)**	**8 (18%)**	**2(5%)**
	Number of symptomatic hypoglycemia AEs	**21 (one severe)**	**5**
	Number of events per person-exposure months	**0.19**	**0.05**
DKA	**DKA events**	**0**	**0**
	Ketosis	**1**	**1***
	Abnormal Serum BOHB at any visit **>4 and ≤ 30 mg/dL**; (0.4-3nmol/L at any visit)	**11 (24.4%)**	**5(12.5%)**
	>10 and < 30 mg/dL (1-3 mmol/L)	**3 (6.6%)**	**1 (2.5%)**
	>4 and ≤10 mg/dL (0.4-1mmol/L)	**8(17.7%)**	**4(10%)**
	Change from baseline @ W12 (≥ 1mmol/L)	**2(4.5%)**	**0**
	Urine ketones >trace level at any visit	**5(11.1%)**	**3(7.5%)**

- 1 event of severe hypoglycemia reported (placebo)
- 5 TEAEs judged as “related to study drug” (3 on placebo; 2 on TTP399)
- No TEAEs leading to discontinuation
- 2 SAEs (1 on placebo; 1 on TTP399); not related
  - Coronary artery disease (placebo)
  - Non-cardiac chest pain (TTP399)

** Occurred concomitant to SAE of worsening of COPD*

BOHB: Beta-hydroxybutyrate

Conclusions

- The collective clinical data from the Simplici-T1 study support the hypothesis that activation of GK by TTP399 improves glycemic control without increasing the risk of hypoglycemia or DKA and without deleterious effects in lipids or liver function.

- Significant improvement in HbA1c was achieved with reduction in insulin dose under a treat-to-target design (i.e. compared to intensive insulin treatment) confirming the potential of TTP399 as a novel adjunctive therapy for T1DM.

- See ePoster 123-LB for additional details on the relationship of change in insulin dose to change in HbA1c and regarding ketosis.

- These results support pursuing larger and longer clinical trials to confirm the efficacy of TTP399 in type 1 diabetes and to explore its potential to reduce the risk of hypoglycemia and ketosis.