The Simplici-T1 Trial: Relationship Between Glycemic Control And Insulin Dose

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Disclosures – Carmen Valcarce

- vTv Therapeutics employee

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

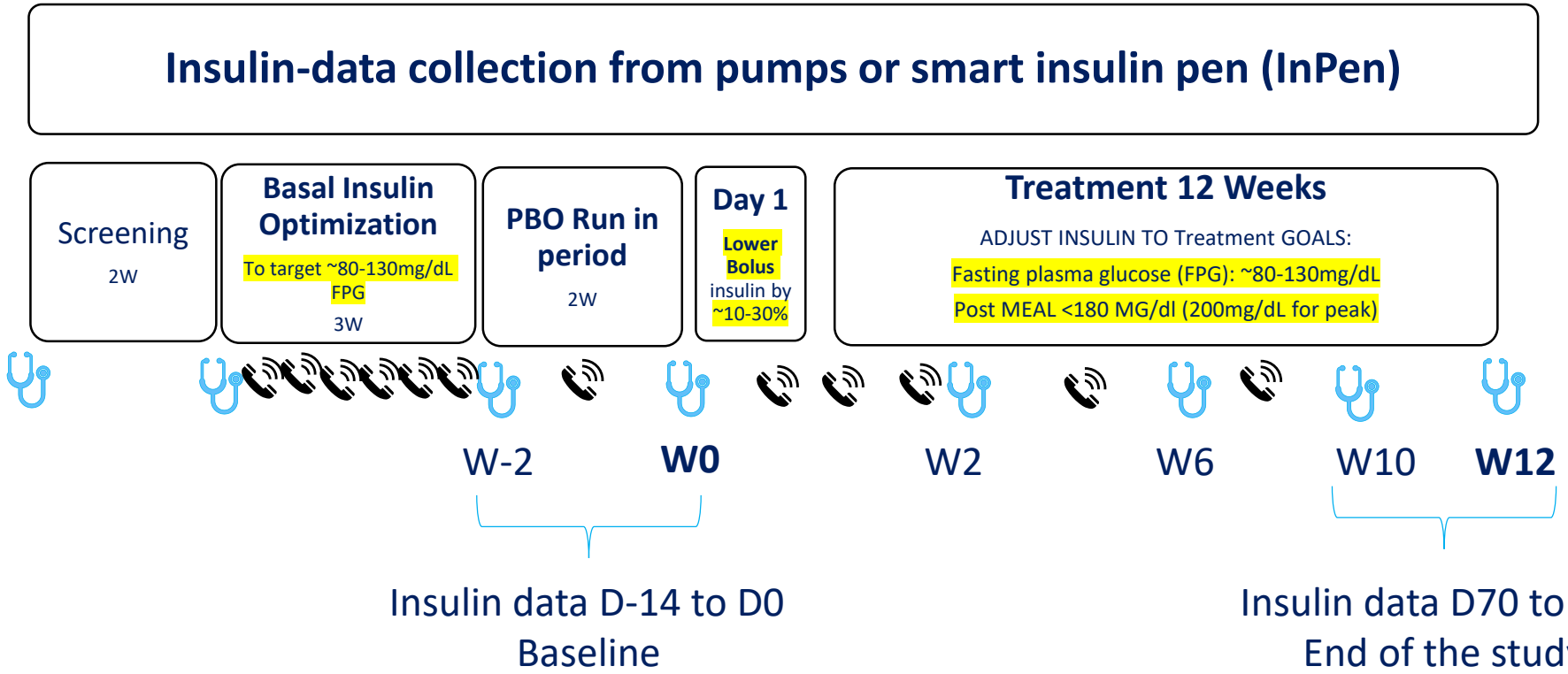
Note: ClinicalTrials.gov Identifier: NCT03335371.

(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

Part 2 Study Design:
Patient contact and insulin data collection



Methods

- The Simplici-T1 trial was designed to explore the safety and efficacy of a liver-selective GKA, TTP399, as an oral adjunctive therapy for T1D.

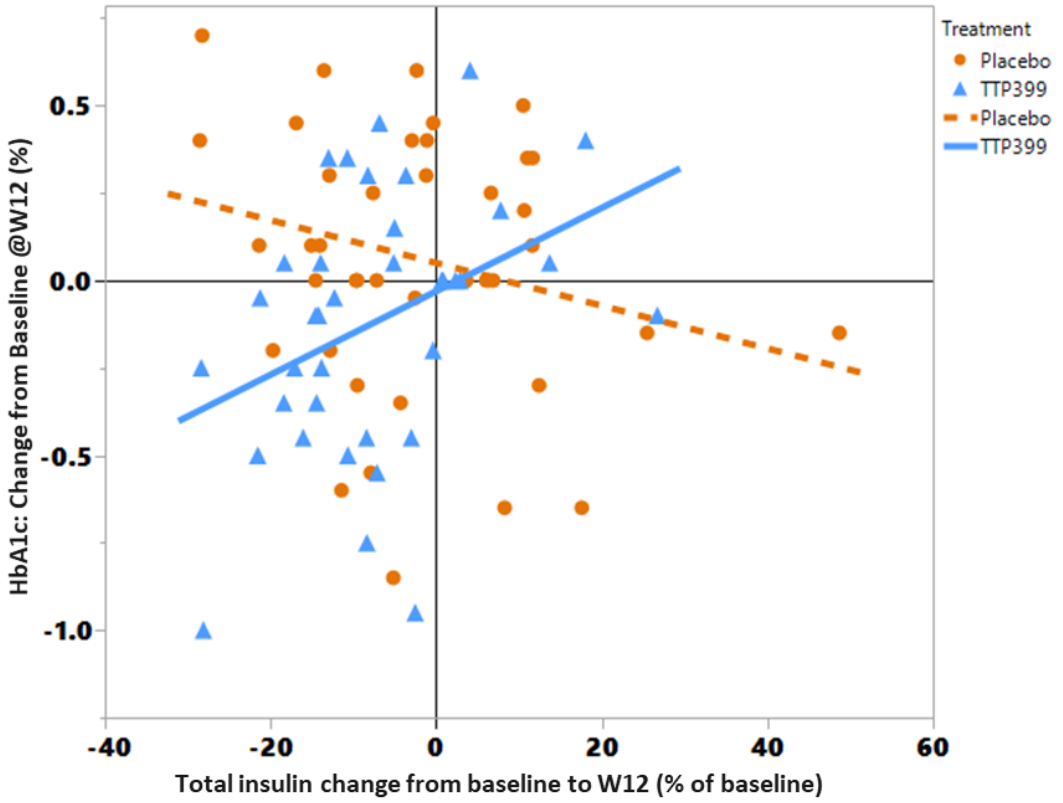
- Addition of TTP399 to an optimized insulin regimen improved glycemic control in subjects with T1D (see ePoster 122-LB).

- The treat-to-target (FPG: ~80-130mg/dL; post meal glucose: <180-200 mg/dL) design of the study allowed changes in insulin dose after the insulin-optimization period. To evaluate the effect that these changes had on HbA1c, several pre-planned analyses were performed:
  - Correlation between reduction in HbA1c and changes in insulin
  - Subgroup analysis by changes in total insulin. The criteria used to define the subgroups were based on change from baseline in Total Insulin (U/kg/day):
    - **Decreased insulin**: $\Delta \leq -0.06$ U/Kg/day
    - **Stable insulin**: $\Delta = -0.06 - 0.03$ U/Kg/day
    - **Increased insulin**: $\Delta \geq 0.03$ U/Kg/day

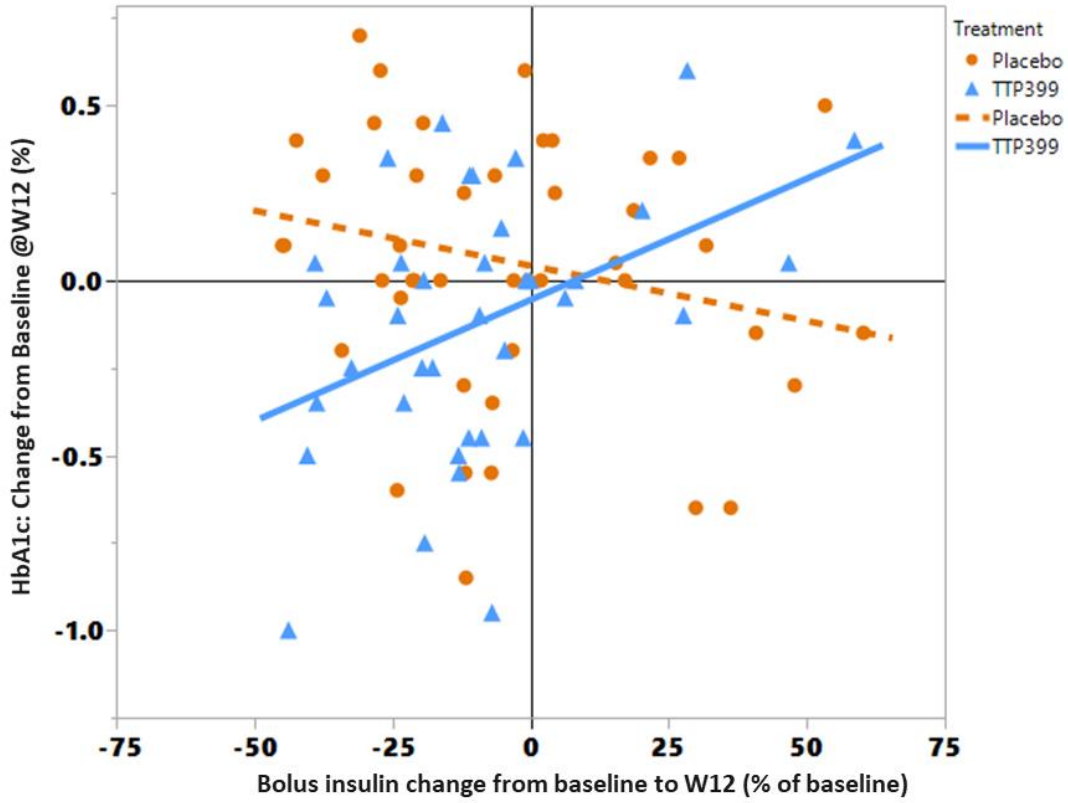
Change in HbA1c at W12 vs Change in Insulin

TTP399 treatment results in better glycemic control with lower insulin dose

ΔHbA1c vs ΔTOTAL Insulin



ΔHbA1c vs ΔBOLUS Insulin

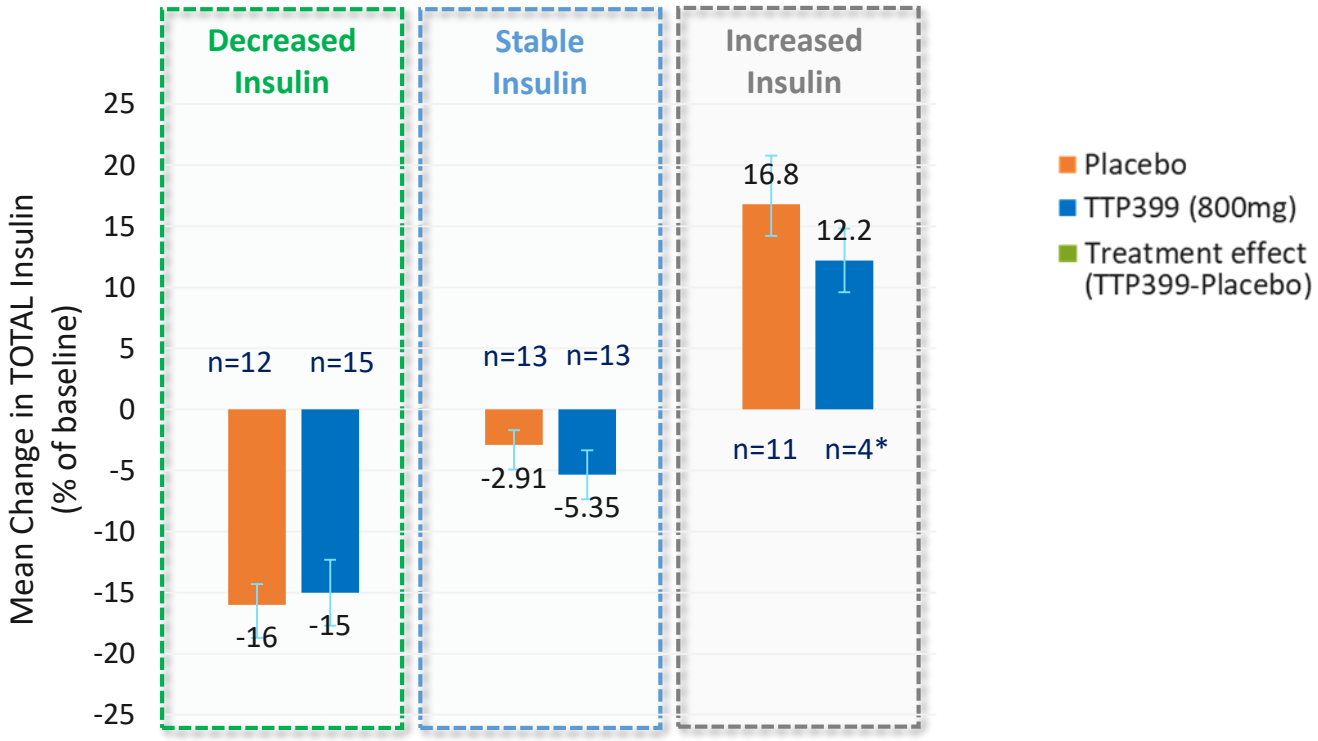


Presented data are complete cases (All patients with data at baseline and W12 are included)

Subgroup Analysis by Changes in Total Insulin

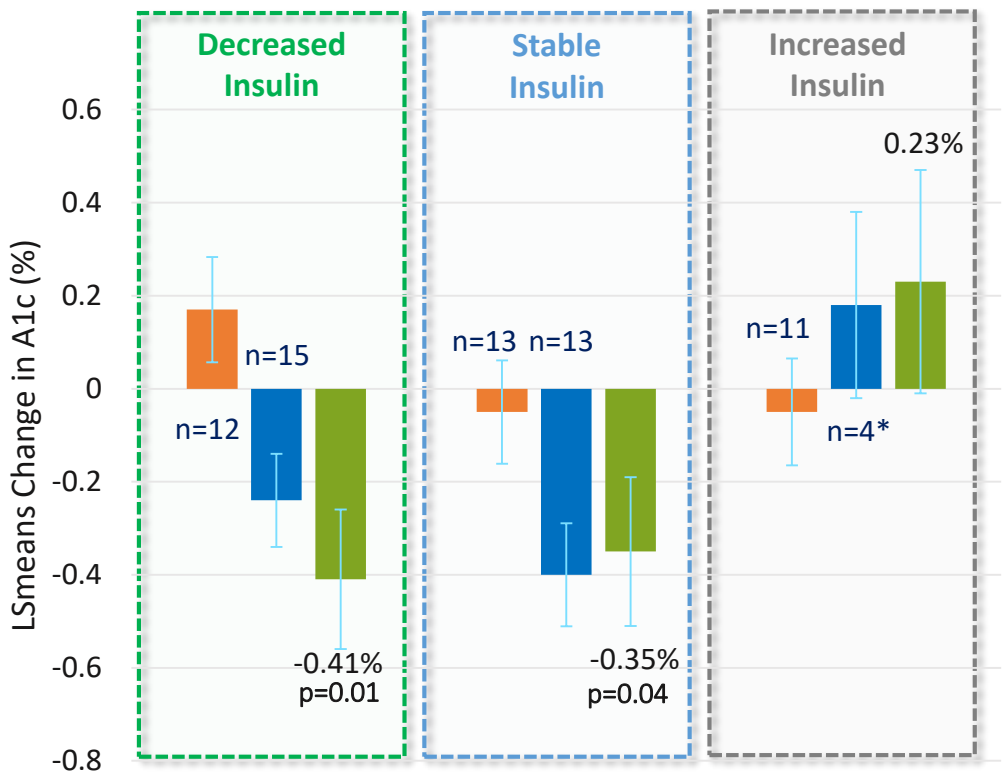
- TTP399 significantly reduced HbA1c compared to placebo in patients that decreased their insulin dose or maintained stable insulin dose throughout the study
- Significantly fewer patients in the TTP399 treated group needed to increase their insulin dose to maintain their glycemic targets

Change in Total Insulin @ W12 by Subgroup



The criteria used to define the subgroups were based on change from baseline in Total Insulin (U/kg/day):
Decreased insulin: Δ<= -0.06 U/Kg/day
Stable insulin: Δ =-0.06 - 0.03 U/Kg/day
Increased insulin: Δ >=0.03 U/Kg/day

Change in HbA1c @ W12 by Subgroup



***note:** TTP399 levels undetectable in two of the subjects that increased insulin dose during the study

Error bars are SE

Hypoglycemia and BOHB Per Insulin Group:

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

	Reduced Insulin		Stable insulin		Increased insulin	
Subjects with:	**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 (>4mg/dL; 0.4nmol/L at any visit)	4 (33%)	2 (13%)	4 (31%)	2 (15%)	4 (36%)	0
severe hypo event	1 (8%)	0	0	0	0	0
symptomatic hypo event	3 (25%)	0	4 (31%)	1 (8%)	1 (9%)	1 (25%)**

**undetectable TTP399 levels in 2 of the subjects; **occurred in one of the subject with undetectable TTP399 levels*

BOHB: Beta-hydroxybutyrate

Conclusions:

Liver Selective GKA shows potential as an adjunctive therapy for T1D

- Patients randomized to TTP399 achieved better glycemic control while reducing insulin dose. In the placebo-treated group, as expected, reduction in insulin dose was associated with increases in HbA1c.
- TTP399 significantly reduced HbA1c compared to placebo in patients that decreased their insulin dose or maintained stable insulin dose throughout the study.
- Significantly fewer patients in the TTP399 treated group required increases to their insulin dose to maintain their glycemic targets
- Trends towards reduction in hypoglycemic and ketone events were observed in the TTP399 treated group compared to placebo. This finding was not due to imbalance in baseline characteristics.
- Treatment effects should be evaluated in the context of insulin dose adjustment to observe the true efficacy of an adjunctive therapy in T1D as changes in HbA1c are a function of both the study drug and adjustments in insulin dose.