The Simplici-T1 trial: Activation of glucokinase by TTP399 improves glycemic control in patients with T1DM

C. Valcarce[1], J.L.R. Freeman[1], I. Dunn[1], C. Dvergsten[1], K.R. Klein[2], J. Buse[2];

[1]vTv Therapeutics, High Point, NC
[2]University of North Carolina School of Medicine, Chapel Hill, NC

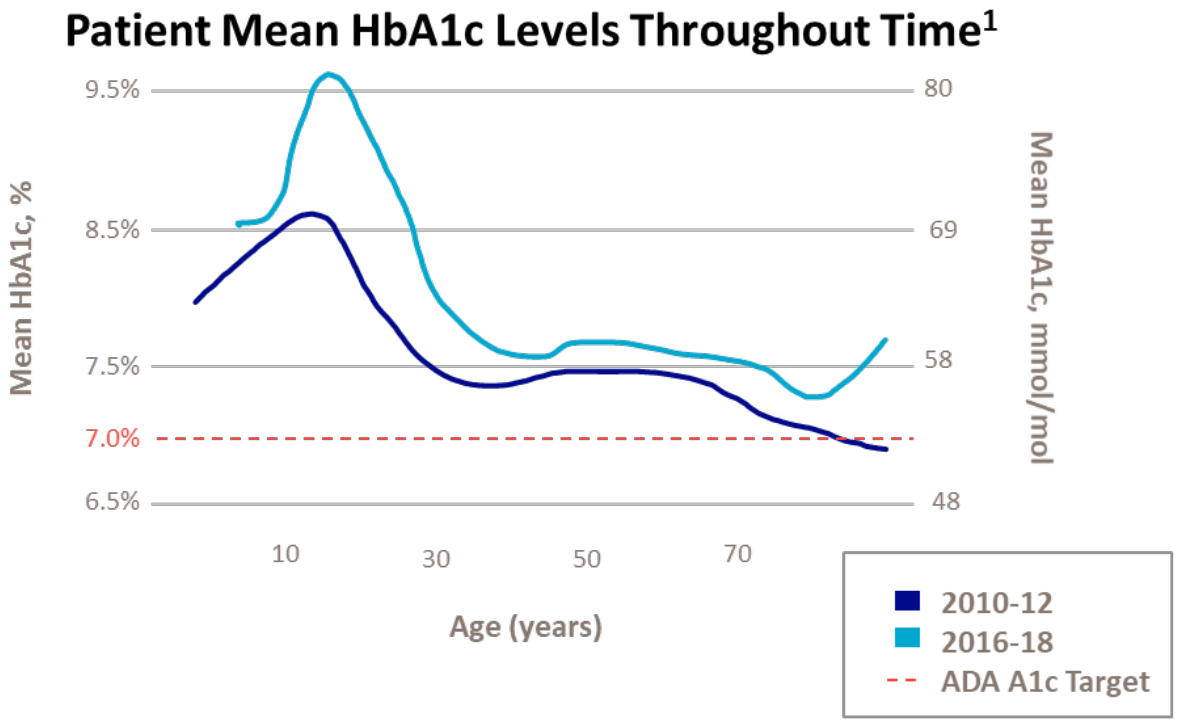
Disclosures – Carmen Valcarce

- vTv Therapeutics employee

Subcutaneous Insulin Alone is Not Enough

- **Nearly 80% of people with type 1 diabetes fail to achieve ADA target A1c levels[1]**

Despite improved and more widely adopted diabetes technology, clinical outcomes continue to decline[2]



Life-threatening, short-term complications of poor glycemic control

Severe Hypoglycemia:

- **6% of T1D patients** reported having a **seizure** or **loss of consciousness** (symptoms of severe hypoglycemia) over the previous 3-month period[3]
- **5% of T1D patients are hospitalized** or visit the ER at least once in the last year due to severe hypoglycemia[4]

Diabetic Ketoacidosis (DKA):

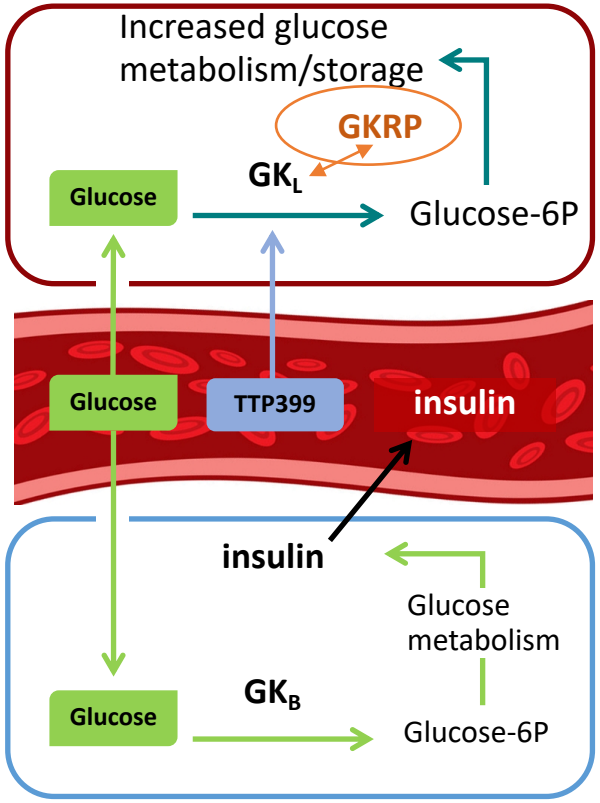
- DKA accounts **for 14% of all hospital admissions** of patients with diabetes and **16% of all diabetes-related fatalities[5]**

1. Diabetes Technol Ther. 2019 Feb;21(2):66-72. doi: 10.1089/dia.2018.0384. Epub 2019 Jan 18.
2. Foster et al. Diabetes Technology and Therapeutics (2019) 21:66-72; DOI: 10.1089/dia.2018.0384
3. Miller KM, et al. Diabetes Care 2015;38:971–978 | DOI: 10.2337/dc15-0078
4. Pettus J, et al. Diabetes Care 2019;42:2220-2227 I https://doi.org/10.2337/dc19-0830
5. Osama Hamdy, et al. Medscape May 31, 2019, Diabetic Ketoacidosis (DKA)

Hepatic Glucokinase Activation, a New Strategy to Treat T1D

Glucokinase (GK) is the glucose sensor of the body

- Key role in glucose homeostasis supported by strong genetic evidence
- Glucose sensitive kinetics
- No inhibited by Glucose-6P



Liver Hepatocyte

Pancreatic β-cell

TTP399: A liver selective Glucokinase Activator[1]

TTP399 activates GK in the liver

TTP399 does not activate GK in β-cells

TTP399 does not disrupt the interaction between GK and GKRP (GK Regulatory Protein) keeping physiological control of GK

in patients with T2D TTP399 significantly reduced HbA1bc (-0.9% *vs* Placebo) after 6-months of treatment without signs of tachyphylaxis

1. Vella A, Freeman J, Dunn I, Keller K, Buse J, Valcarce C. Targeting hepatic glucokinase to treat diabetes with TTP399, a hepatoselective glucokinase activator. Science Translational Medicine 16 Jan 2019

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

Study design

Phase 1
(Sentinels)

1 site – 

- **Open-label**
- **7 days** dose escalation up to 1200mg QD
- **5 adult subjects** with T1D on CSII and CGM(1)

Phase 2-Part 1
(Learning Phase)

4 sites - 

- **Randomized, Double-blind, Placebo control**
- **Treat to target** design
- **12 weeks Oral** dosing 800mg/placebo once a day
- **19 adult subjects** with T1D on CSII and CGM(1)
- **Primary Endpoint**: Δ in HbA1c
- Insulin dose optimized prior to randomization

Phase 2-Part 2
(Confirming Phase)

13 sites - 

- **Randomized, Double-blind, Placebo control**
- **Treat to target** design
- **12 weeks Oral** dosing 800mg/placebo once a day
- **85 adult subjects** with T1D (all comers)
- **Primary Endpoint**: Δ in HbA1c
- Insulin dose optimized prior to randomization

March 2018 → **June 2019** → **February 2020**

Note: ClinicalTrials.gov Identifier: NCT03335371.
(1) Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM).

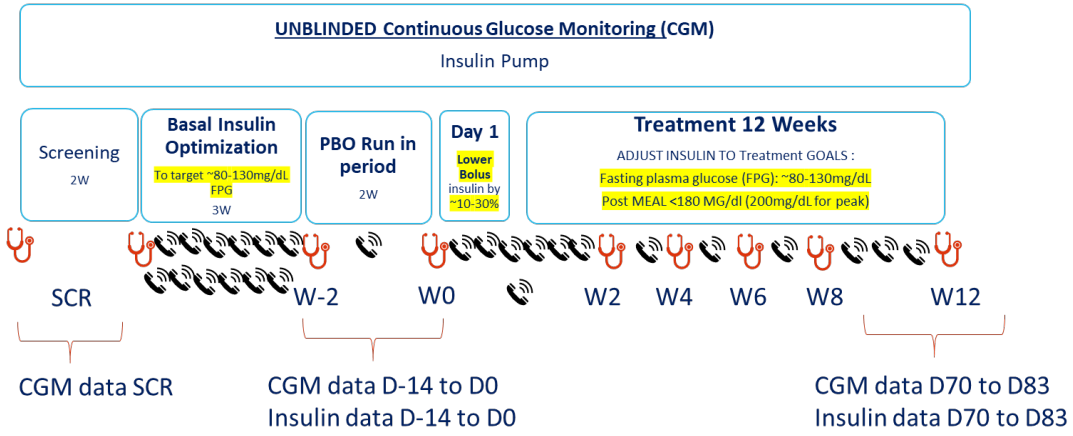
JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.

simplici-T1

Simplici-T1 Study Design: Key Differences Between Part 1 and 2

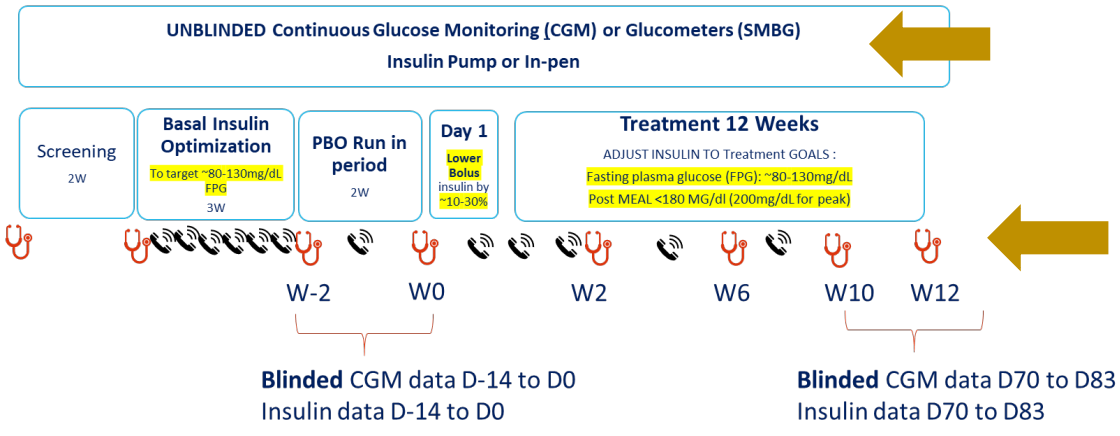
Part 1 (Learning Phase)

20 Subjects randomized
3 sites in NC, **1** site in CA (2 sites randomized >70%)



Part 2 (Confirming Phase)

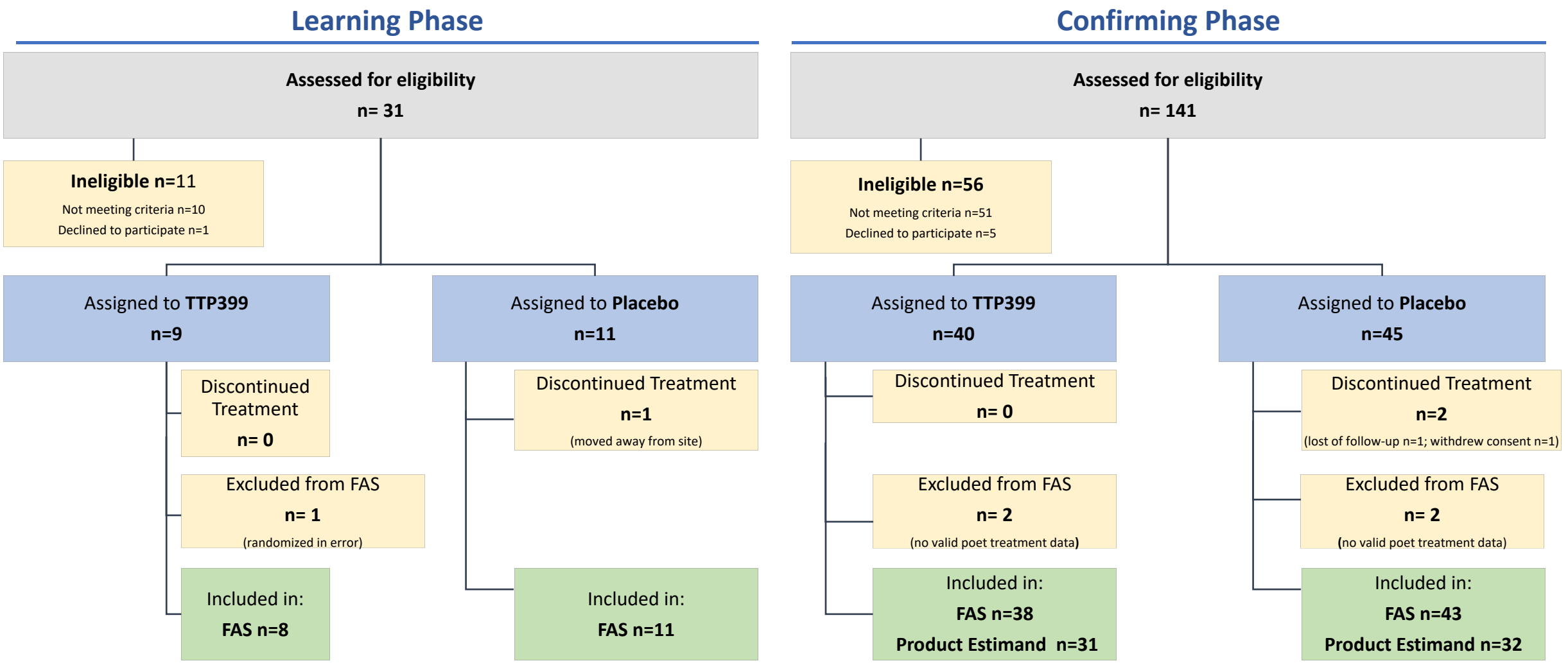
85 Subjects randomized
13 sites in US (2 sites randomized =28%)



- Eligible participants were adults diagnosed with type 1 diabetes before age 40 years and at least one year prior to screening with a hemoglobin A1c (HbA1C) 7·5-9·0% (53-80 mmol/mol).
- Treat-to-target design: pre-meal glucose target 4·4 to 7·2 mmol/L (80-130 mg/dL) post meal target <10mmol/L (180mg/dL). Insulin adjustments allowed throughout the study (except during the run-in period)
- Individual Insulin optimization prior randomization to reach pre-meal targets.

Subject Disposition:

No discontinuations in the TTP399 group



Baseline characteristics for the Full Analysis Set (FAS)

	Learning Phase		Confirming Phase	
	Placebo (n= 11)	TTP399 (n=8)	Placebo (n= 43)	TTP399 (n=38)
Sex, female	8 (73%)	5 (63%)	24 (56%)	14 (37%)
Age (years)	47 (10)	38 (15)	42 (13)	43 (15)
Race				
White	11 (100%)	7 (87%)	41 (95%)	36 (95%)
Black or African American	0	1 (13%)	1 (2%)	0
Asian	0	0	1 (2%)	2 (5%)
Ethnicity -not Hispanic or Latino	11(100%)	8 (100%)	41 (95%)	37 (97%)
Weight (kg)	82·8 (15·1)	80·2 (14·3)	83·6 (15·0)	83·1 (18·4)
BMI (kg/m^2)	29·0 (4·1)	28·4 (3·3)	28·3 (3·8)	27·6 (4·0)
Age at type 1 diabetes diagnosis	18 (11)	9 (7)	16 (10)	16 (9)
Duration of diabetes (years)	29 (17)	29 (16)	26 (14)	26 (13)
Insulin pump users	11 (100%)	8 (100%)	27 (63%)	20 (53%)
CGM User	11 (100%)	8 (100%)	25 (58%)	24 (63%)
HbA_{1c} Baseline				
%	7·4 (0·4)	7·2 (0·4)	7·5 (0·60)	7·6 (0·6)
mmol/mol	58 (4·5)	57 (4·7)	61 (6·5)	62 (5·8)
β-hydroxybutyrate (mmol/L)	0·19 (0·32)	0·12 (0·21)	0·14 (0·25)	0·11 (0·12)
C-peptide				
Undetectable (<0·004 ng/mL)	5 (45%)	5 (63%)	22 (51%)	20 (53%)
Daily Insulin dose (IU/kg)				
Total (IU/kg)	0·59 (0·14)	0·65 (0·11)	0·65 (0·20)	0·68 (0·27)
Basal (IU/kg)	0·31 (0·07)	0·38 (0·06)	0·30 (0·12)	0·32 (0·17)
Bolus (IU/kg)	0·28 (0·10)	0·27 (0·13)	0·35 (0·13)	0·37 (0·15)

Data are mean (SD), % (SD) or n (%).

Primary Endpoints:

Statistically significant improvement in glycemic control

	Learning Phase			Confirming phase		
	Placebo (n= 11)	TTP399 (n=8)		Placebo (n= 43)	TTP399 (n=38)	
HbA1c %						
Baseline (SD)	7·4 (0·4)	7·2 (0·4)		7·5 (0·60)	7·6 (0·6)	
Week 12 change from baseline (SE)	0·08 (0·20)	-0·60 (0·20)		0·07 (0·06)	-0.14 (0.06)	
Treatment effect (%) (CI, p)	**NA**	**-0.69** (-1.30, -0.07)	**p=0.032**	**NA**	**-0·21** (-0.39, -0.04)	**p=0.018**
Treatment effect (mmol/mol)		**-7.5**			**-2.3**	
Treatment effect (%) (CI, p) (Product estimand)*				**NA**	**-0·31** (-0.5, -0.12)	**p=0.0017**
Treatment effect (mmol/mol) (Product estimand)*					**-3.3**	
Responders**						
Proportion with composite response	0	5 (62%)		5 (12%)	16 (42%)	
Treatment effect (odds ratio)	**NA**		**p=0.005**	**NA**	**9.6** (2.5, 36.7)	**p=0.001**
Daytime % Time in Target Range						
Baseline	65% (13)	70% (9)		57% (11)	51% (14)	
Week 12 change from baseline	-9.2 (2.5)	2.6 (3.4)		-7.8 (2.3)	0.1 (2.6)	
Treatment effect (%)	**NA**	**11.8** (2.58, 20.95)	**p=0.016**	**NA**	**7.8** (0.93, 14.68)	**p=0.027**

**Product 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 product estimand analysis was pre-specified in the SAP and conducted consistent with current regulatory guidance.*

******Responder Definition****:*

Proportions of subjects with improvement in HbA1c without Treatment emergent:

- *abnormal ketones in plasma (>0.4mmol/L)*
- *abnormal lactate in blood, (>2.2mmol/L)*
- *increase in insulin bolus ≥3 units/day*
- *symptomatic or severe hypoglycemia*

For change from baseline and treatment effect Data are LSmean +/- SE. at least indicated in the table

Safety: High-level Summary

The incidence of treatment-emergent adverse events was similar between the groups

	Learning Phase		Confirming Phase	
	Placebo (n=11)	TTP399 (n=9)	Placebo (n=45)	TTP399 (n=40)
Number of AEs reported	16	13	83	58
Participants with at least one AE	8 (73%)	6 (67%)	29 (64%)	26 (65%)
Participants with at least 1 drug-related AE	2 (18%)	1 (11%)	3 (7%)	2 (5%)
Participants with AE leading to death	0	0	0	0
Participants with AE leading to discontinuation	0	0	0	0
Number of SAEs	0	0	1	1
Participants with at least 1 SAE related to drug	0	0	0	0
Participants with at least 1 SAE	0	0	1 (2%)	1 (2%)
Coronary Artery Disease	0	0	1 (2%)	0
Non-Cardiac Chest Pain	0	0	0	1 (2%)

Adverse Events of Special Interest

In contrast to other GK activators that have been in clinical development TTP399 did not alter liver function or increase plasma triglycerides

Liver Function:

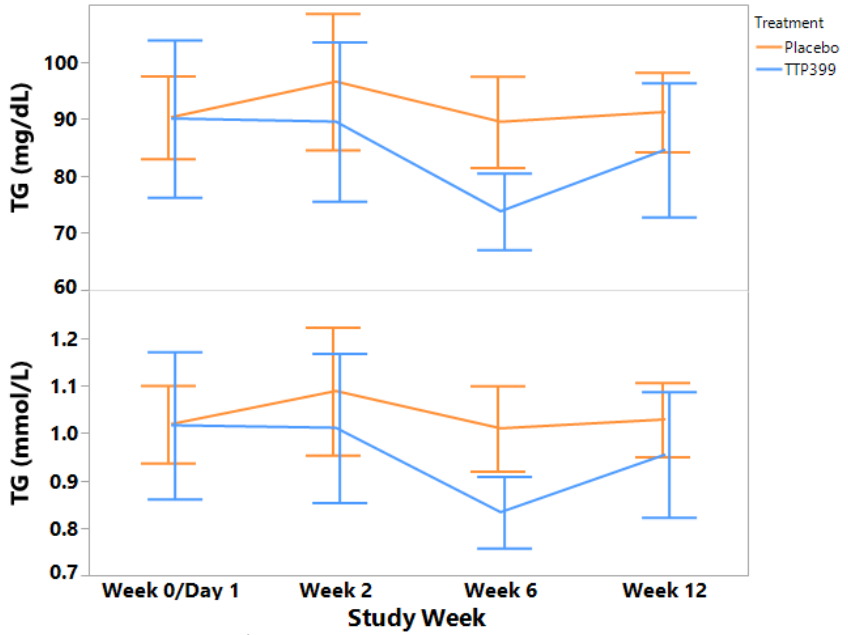
No significant changes in liver function

	Learning Phase		Confirming Phase	
	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 number of subjects with at least one episode. BILI=bilirubin. ALP=alkaline phosphatase. AST=Aspartate Aminotransferase. ALT= alanine aminotransferase

Triglycerides:

No significant changes in Triglycerides



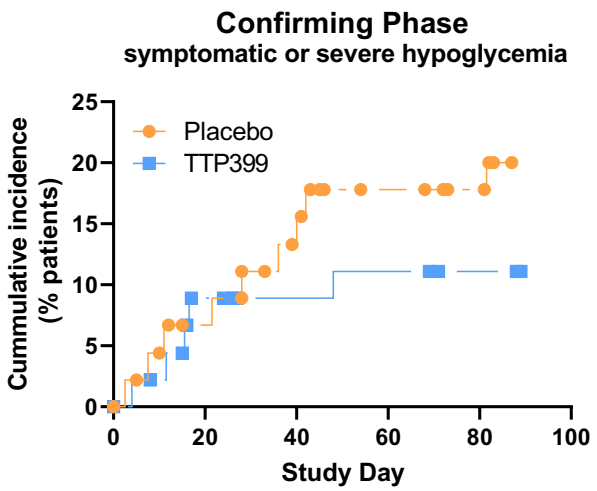
Data are mean +/- SE

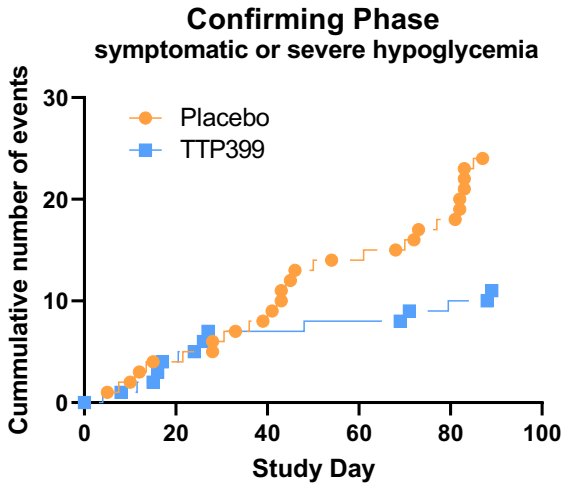
Adverse Events of Special Interest: Hypoglycemia

Trends towards reduction of risk of hypoglycemia in the TTP399-treated group while improving HbA1c

- **Learning phase**:
  - No AEs of symptomatic or severe hypoglycemia were reported in either group
- **Confirming Phase:**

	Placebo (n=45)	TTP399 (n=40)
Number of participants with hypoglycemic AEs	**9 (20%)**	**5 (12%)**
Total number of hypoglycemic AEs	27	12
Severe hypoglycemia	1	0
Symptomatic hypoglycemia	26	12
Events per person-exposure month	**0.2**	**0.1**
Week 2 visit to end of the study		
Number of participants with hypoglycemic AEs	**8 (18%)**	**2 (5%)**
Events per person-exposure month	**0.15**	**0.04**





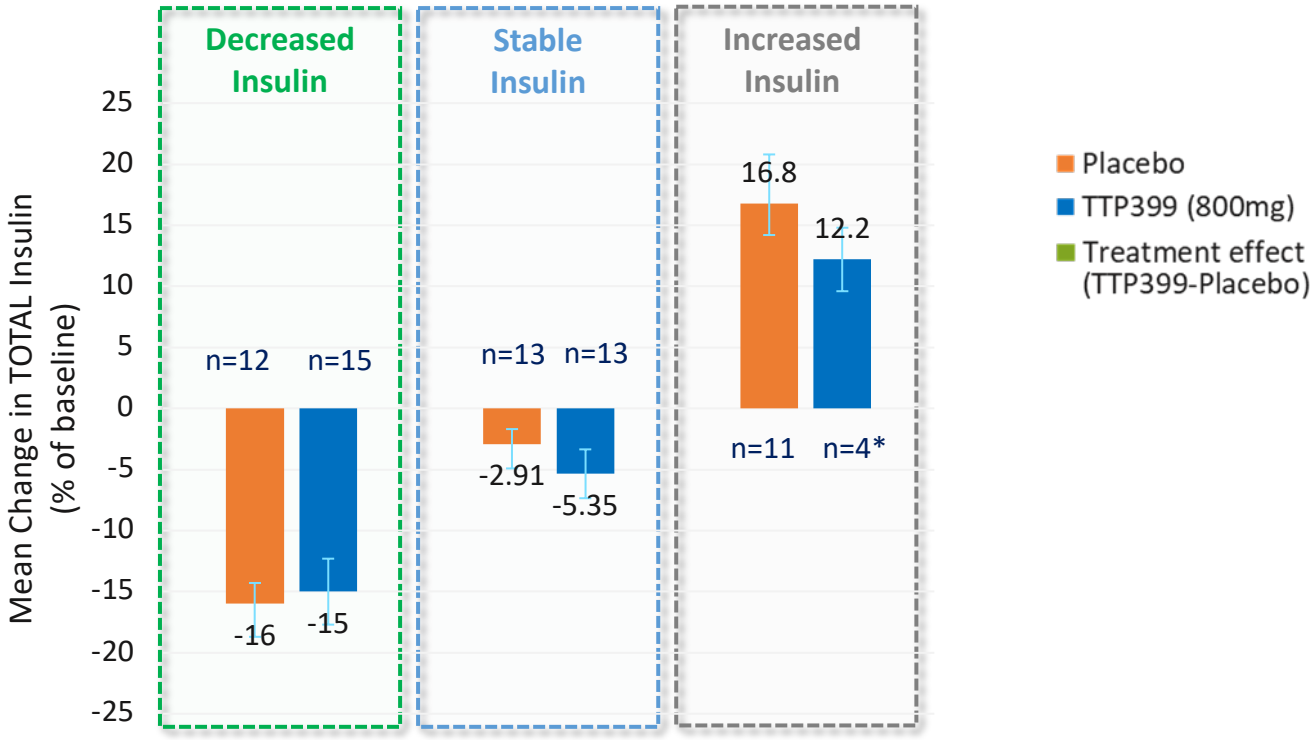
77% of the events in the placebo group were associated to blood glucose <54mg/dL (3mM)
66% of the events in the placebo group were associated to blood glucose <54mg/dL (3mM)

CGM data show no significant differences in number of asymptomatic hypoglycemic events between groups

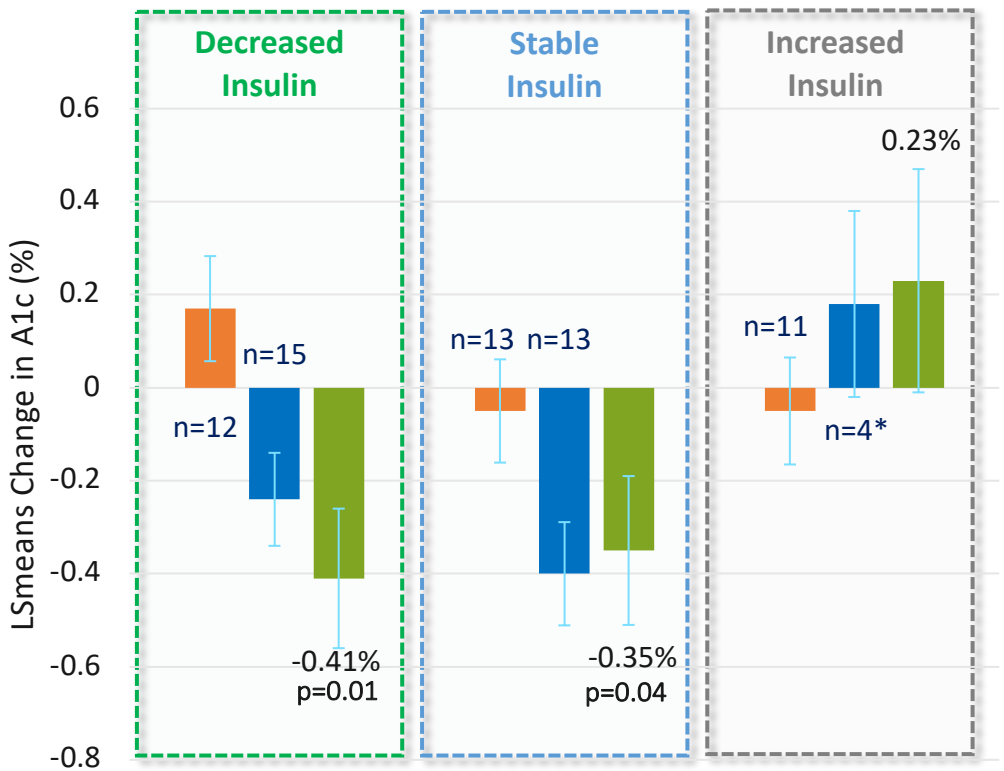
Subgroup Analysis by Changes in Total Insulin

- 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



Change in HbA1c @ 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

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

Observed case analysis. Data are mean +/- SE

Hypoglycemia Per Insulin Group:

Trends towards reduction in hypoglycemic events in the TTP399-treated group independent of the changes in insulin dose

	Reduced Insulin		Stable insulin		Increased insulin	
	Placebo (n=12)	**TTP399 (n=15)**	**Placebo (n=13)**	**TTP399 (n=13)**	**Placebo (n=11)**	**TTP399 (n=4)***
Number of participants with improved HbA1c (%)	**2 (16%)**	**10 (67%)**	**4 (31%)**	**8 (62%)**	**4 (36%)**	**0**
Number of participants with hypoglycemic AEs						
Day 1-to end of study						
severe hypo	**1 (8%)**	**0**	**0**	**0**	**0**	**0**
symptomatic hypo	**3 (25%)**	**2 (13%)**	**4 (31%)**	**2 (15%)**	**1 (9%)**	***1 (25%)****
Week 2 visit to end of the study						
severe hypo	**1 (8%)**	**0**	**0**	**0**	**0**	**0**
symptomatic hypo	**3 (25%)**	**0**	**4 (31%)**	**1(9%)**	**1 (9%)**	***1 (25%)****

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

Adverse Events of Special Interest:
DKA, Ketosis and Plasma beta-hydroxybutyrate

- No DKA was reported in the study.
- In contrast to other adjunctive therapies that have been in clinical development, TTP399, when compared to placebo, did not increase plasma beta-hydroxybutyrate.

More details on OP 09-#51 by Dr Jennifer L.R. Freeman

Conclusions

- The collective clinical data from the Simplici-T1 study support the hypothesis that activation of glucokinase 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).

- Trends towards a reduction in symptomatic and severe hypoglycemia were observed with TTP399 treatment

- 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.

Thank you to the patients, the investigators and their teams, the JDRF and the Simplici-T1 team to make this study possible