Mechanism matters: preliminary evidence that activation of glucokinase by TTP399 does not increase plasma or urine ketones in type 1 diabetes

Jennifer LR Freeman, Imogene Dunn, Carmen Valcarce

vTv Therapeutics, High Point, NC, USA

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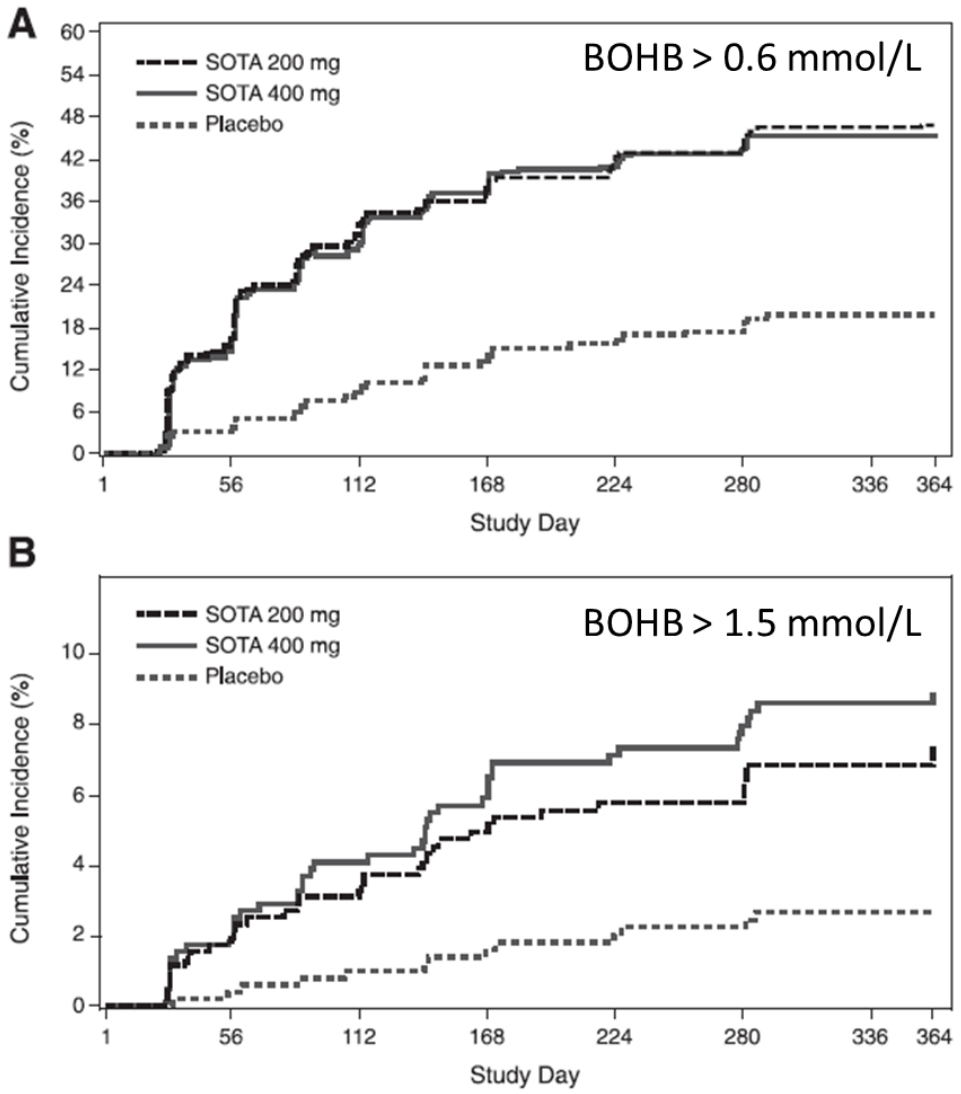
Disclosures – Jennifer LR Freeman

- vTv Therapeutics employee
- vTv Therapeutics stockholder

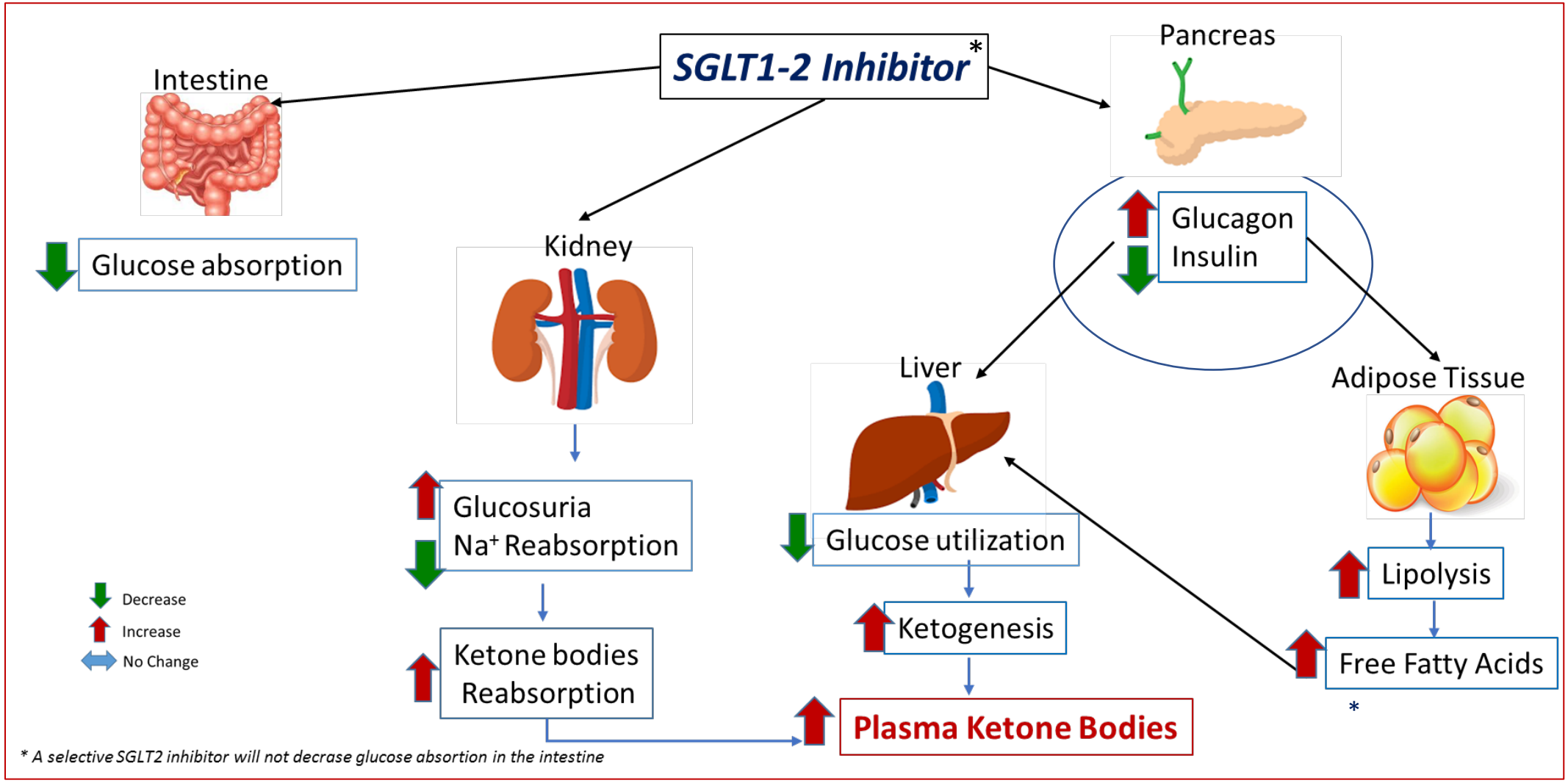
Improved treatments needed for type 1 diabetes

- Despite improvements in insulin delivery devices and glucose monitoring, nearly 80% of people with type 1 diabetes fail to achieve target A1c (Foster, et al. Diabetes Technol Ther. 2019 Feb;21(2):66-72)
- Oral adjunctive therapies inhibiting SGLT1-2s have shown:
  - Improvements in glycemic control, body weight, and blood pressure with less hypoglycemia
  - However, also an increased rate of diabetic ketoacidosis, an inherent risk for people with type 1 diabetes
  - Approved in Japan and the EU (BMI ≥27); no US approvals



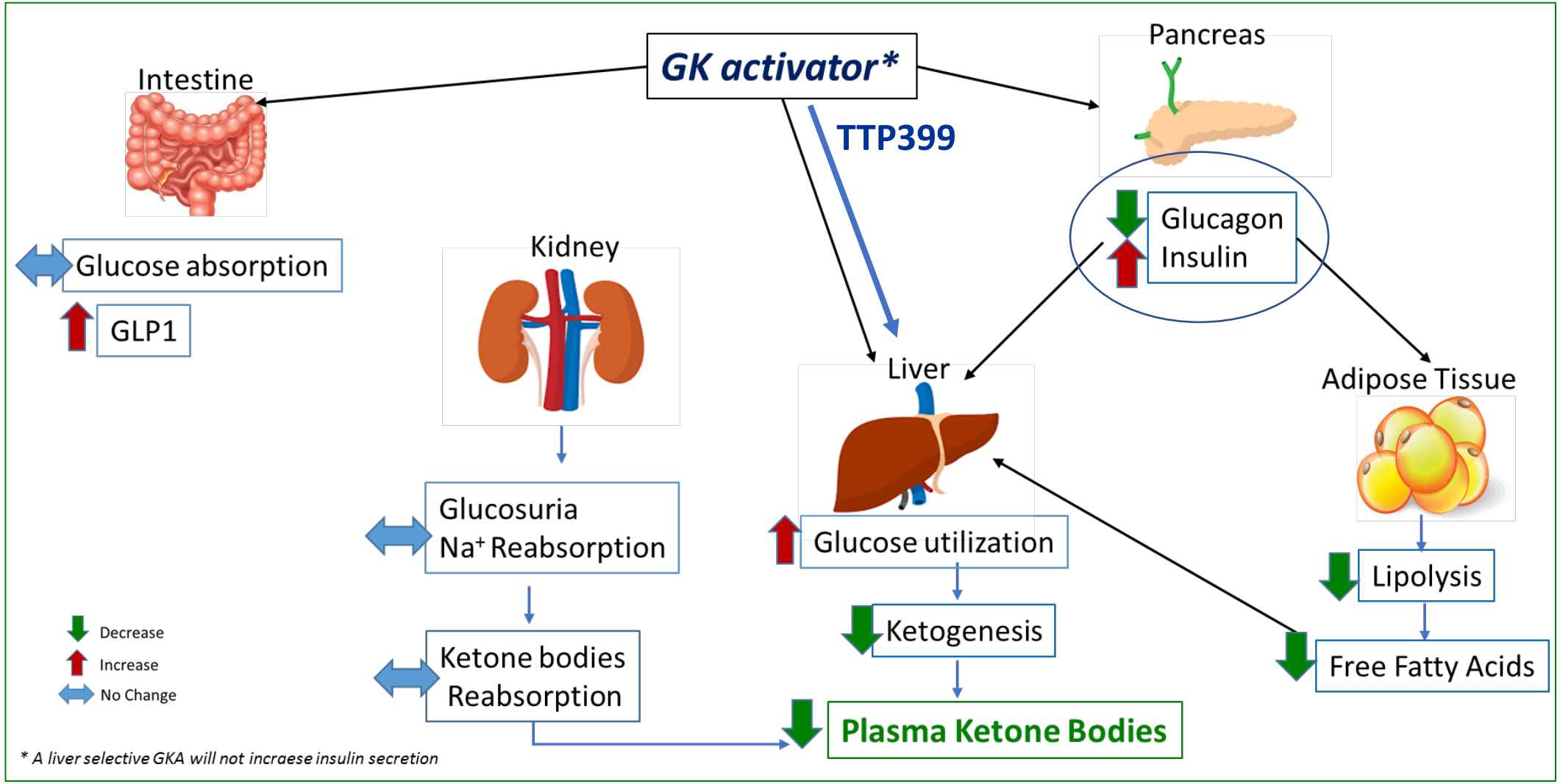
Pooled analysis of the inTandem 1 and 2 studies
Peters, et al, Diabetes Care (2020) https://doi.org/10.2337/dc20-0924

SGLT1-2 inhibitors decrease glucose absorption and increase ketogenesis



Modified from Taylor, et al. J Clin Endocrinol Metab, August 2015, 100(8):2849 –2852

Activation of Glucokinase increases glucose utilization in liver, decreases ketogenesis



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.

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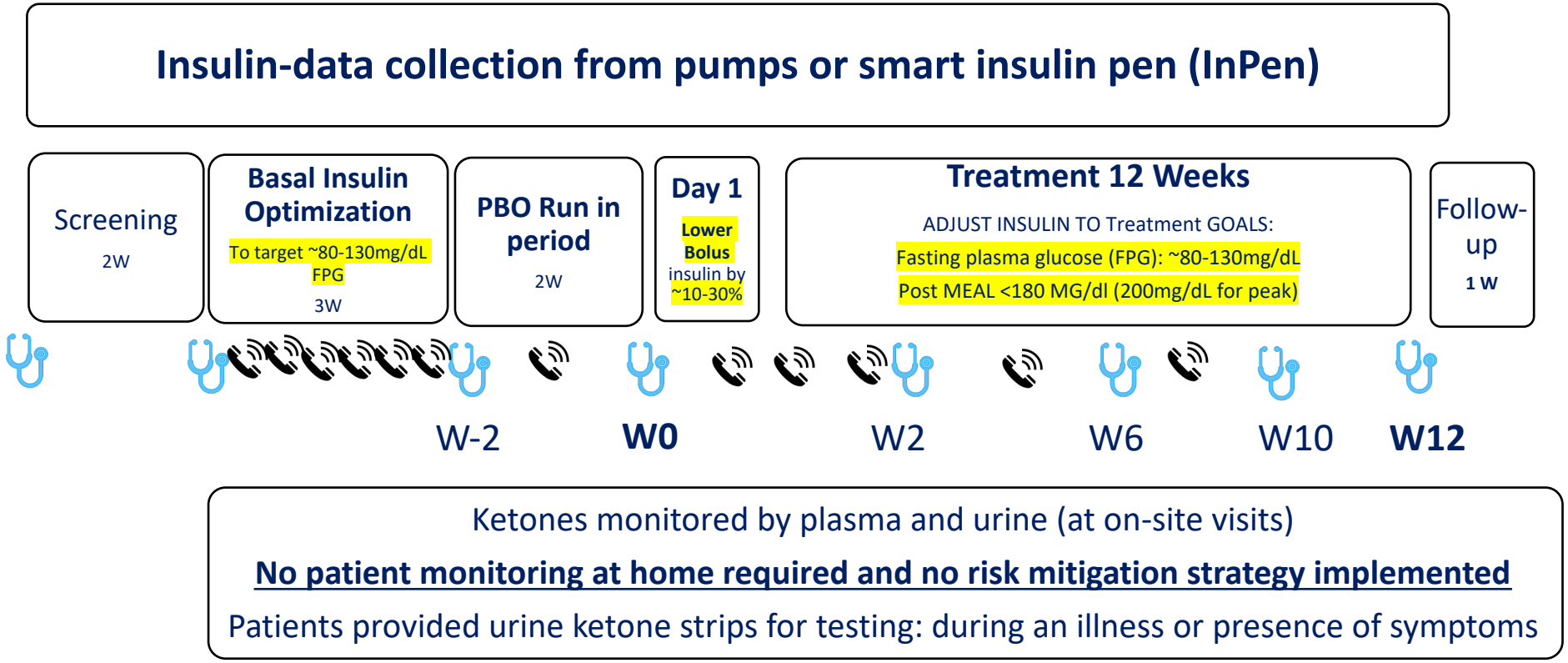
simplici-T1

Study Design: Treat-to-target
Patient contact, central lab and insulin data collection



Part 1: Patients required to use insulin pump and unblinded CGM (additional visit @ W4)
Part 2: All comers: Insulin pump/MDI users and personal CGM was not required

Demographics: No imbalance between groups

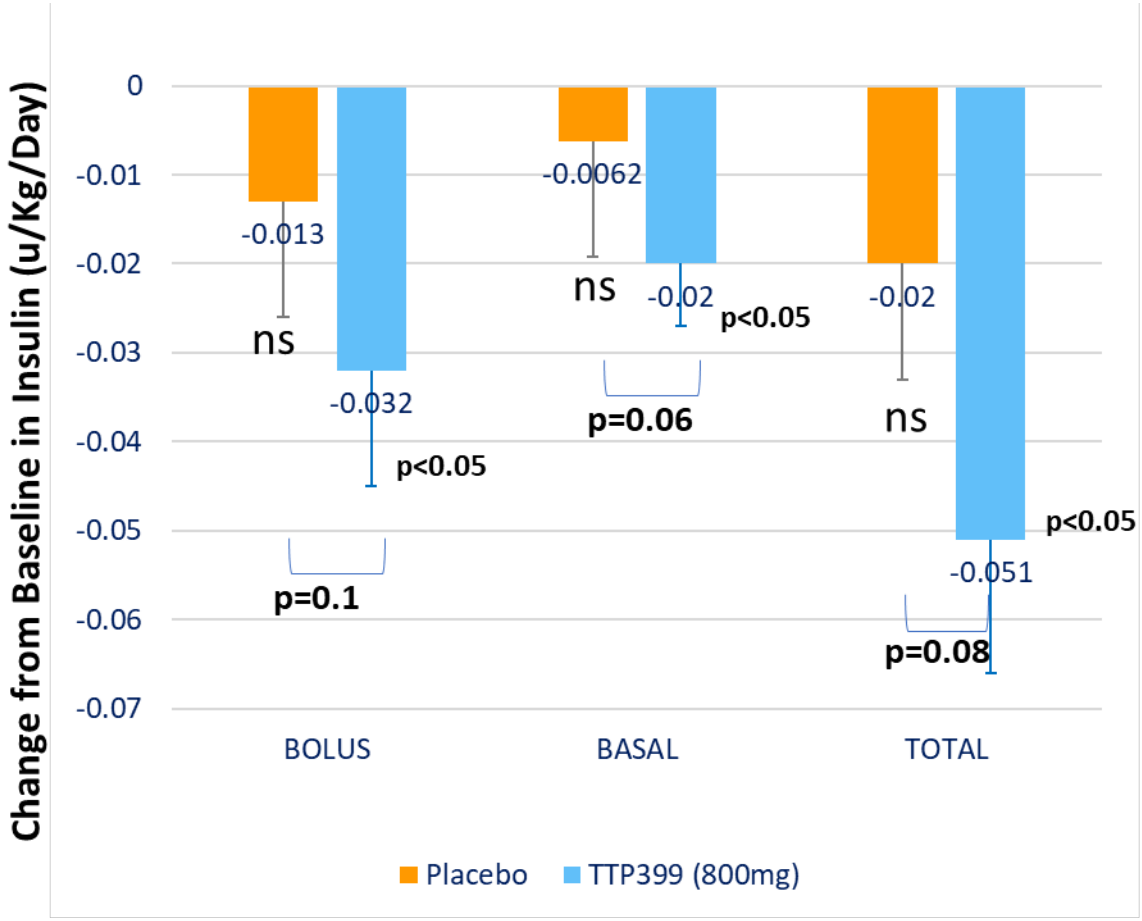
		Part 1		Part 2	
Trait	**Statistic**	**Placebo (N=11)**	**TTP399 800 mg (N=8)**	**Placebo (N=45)**	**TTP399 800 mg (N=40)**
Age (Years)	Mean [Median] (min, max)	47 [43.0] (35, 68)	38 [34.5] (23, 66)	42.4 [38.0] (24, 70)	43.4 [43.5] (20, 69)
Gender	Female (%)	8 (72.5%)	5 (62.5%)	25 (55.6%)	15 (37.5%)
Ethnicity	Not Hispanic or Latino (%)	11 (100%)	8 (100%)	43 (95.6%)	39 (97.5%)
Race	White (%)	11 (100%)	7 (87.5%)	43 (95.6%)	38 (95.0%)
Weight (kg)	Mean [Median] (min, max)	82.8 [81.3] (55, 115)	80.2 [78.4] (61, 100)	83.5 [83.0] (54, 117)	83.4 [80.8] (47, 123)
BMI (kg/m^2)	Mean [Median] (min, max)	29 [28.4] (20,35)	28.4 [29.7] (24, 32)	28.2 [28.3] (21, 38)	27.9 [27.4] (20, 37)
HbA1c	Mean [Median] (min, max)	7.4 [7.3] (7.0, 8.2)	7.3 [7.4] (6.9, 7.9)	7.52 [7.30] (6.5, 8.8)	7.66 [7.60] (6.7, 8.9)
β-hydroxybutyrate (mmol/L)	Mean [Median] (min, max)	0.19 [0.1] (0.0, 1.05)	0.12 [0.0] (0, 0.63)	0.14 [0.00] (0.0, 2.6)	0.05 [0.00] (0.0, 0.4)
Undetectable C-peptide (<0.004ng/mL)	%	45%	63%	53%	57%
CGM Use	CGM User (%)	100%	100%	56%	60%
Insulin Device	Pump (%)	100%	100%	62%	55%
Total Insulin (u/kg/day)	Mean [Median] (min, max)	0.59 [0.58] (0.4, 0.9)	0.66 [0.66] (0.5, 0.8)	0.64 [0.60] (0.3, 1.1)	0.68 [0.62] (0.3, 1.4)
Bolus Insulin (u/kg/day)	Mean [Median] (min, max)	0.28 [0.28] (0.1, 0.5)	0.27 [0.31] (0.1, 0.4)	0.30 [0.28] (0.1, 0.6)	0.31 [0.27] (0.1, 0.9)
Basal Insulin (u/kg/day)	Mean [Median] (min, max)	0.31 [0.30] (0.2, 0.4)	0.38 [0.39] (0.3, 0.5)	0.34 [0.33] (0.1, 0.6)	0.37 [0.32] (0.2, 0.8)

Simplici-T1 Study
Improved glycemic control while lowering insulin

Key Results

- **Statistically significant reduction in HbA1c** under a treat-to-target design (i.e. compared to intensive insulin treatment)
- **No report of diabetic ketoacidosis**, trends towards reduction in ketone events were observed in the TTP399 treated group compared to placebo
- **Fewer hypoglycemic episodes** in TTP399 vs. placebo treated group
- **Increase in time in range** relative to placebo
- **Reduced total daily insulin** relative to baseline

Insulin Change from Baseline



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

Ketone Monitoring

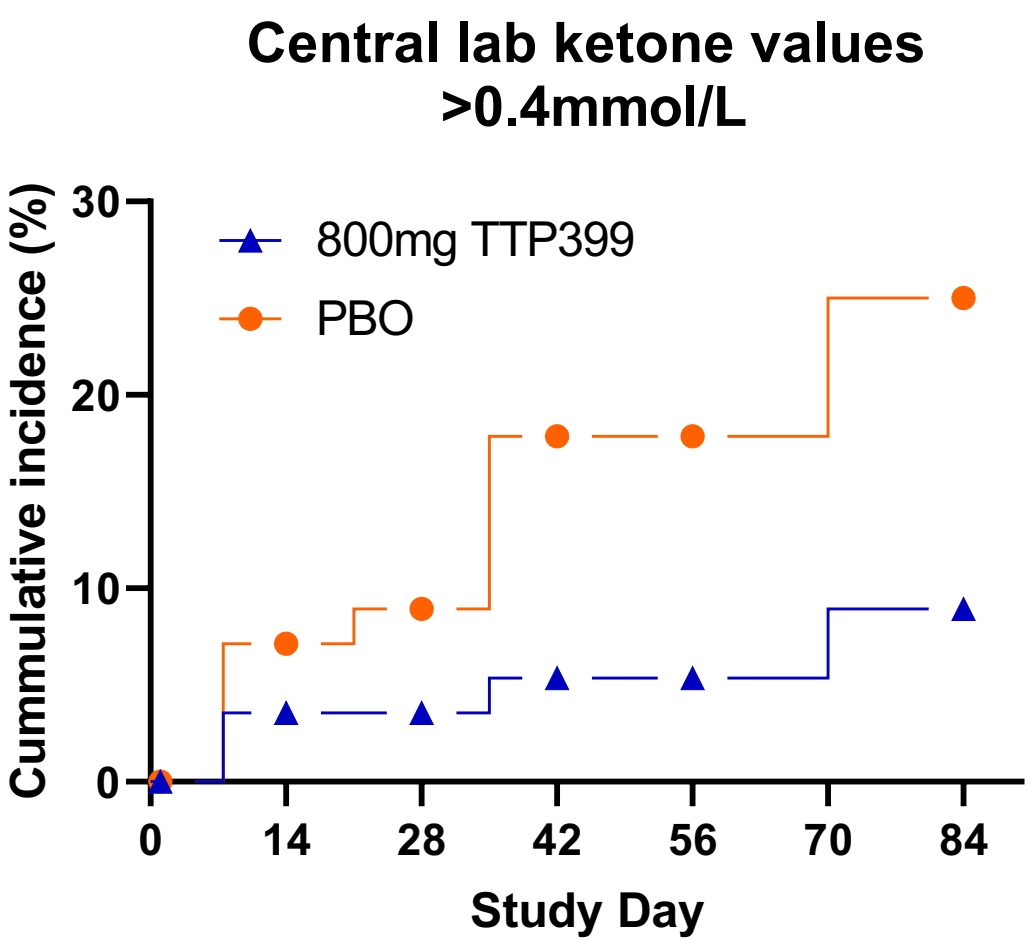
	Part 1		Part 2		Combined	
	Placebo (n=11)	TTP399 (n=9)	Placebo (n=45)	TTP399 (n=40)	Placebo (n=56)	TTP399 (n=49)
DKA events	**0**	**0**	**0**	**0**	**0**	**0**
Ketosis Treatment Emergent Adverse Events	**0**	**0**	**1**	**1***	**1**	**1***
Patients with at least one elevated serum BOHB level during dosing	**3 (27%)**	**0**	**11 (24%)**	**5 (13%)**	**14 (25%)**	**5 (10%)**
>1 mmol/L	**0**	**0**	**3 (7%)**	**1 (3%)**	**3 (5%)**	**1 (2%)**
>0.4 and ≤1 mmol/L	**3 (27%)**	**0**	**8 (18%)**	**4 (10%)**	**11 (20%)**	**4 (8%)**
Change from baseline @ W12 of ≥ 1 mmol/L	**0**	**0**	**2 (4%)**	**0**	**2**	**0**
Urine ketones >trace level at any visit	**3 (27%)**	**1 (11%)**	**5 (11%)**	**3 (8%)**	**8 (14%)**	**4 (8%)**

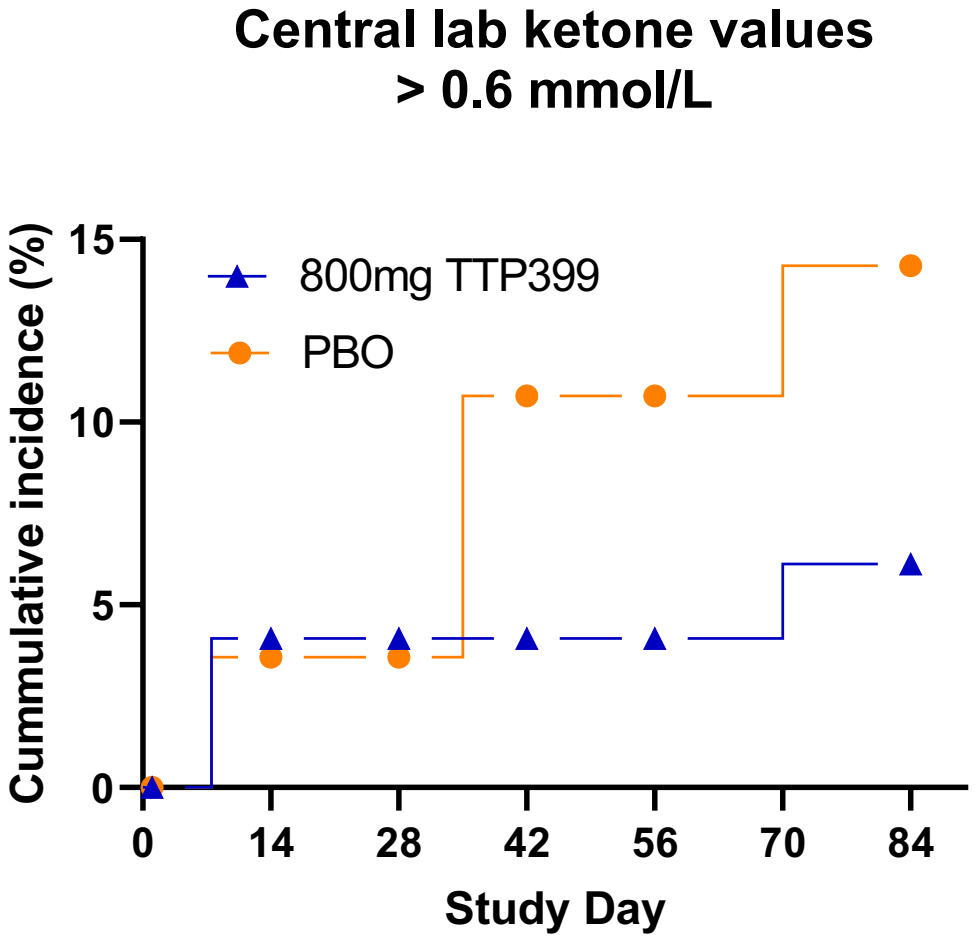
BOHB: Beta-hydroxybutyrate

**Occurred concomitant to SAE of worsening of COPD, considered not related to study drug*

Cumulative incidence of subjects with abnormal ketones

BOHB > 0.4 and 0.6 mmol/L as determined by Central Lab





Abnormal Ketones By Insulin Group

Trends towards reduction in abnormal ketones in the TTP399-treated group with improved glycemic control

Changes in Total Insulin	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)**
change in total insulin at W12 (% of baseline)	-16	-15	-2.9	-5.3	16.8	12.2
improved HbA1c	2 (16%)	10 (67%)	4 (31%)	8 (62%)	4 (36%)	0
abnormal BOHB (>0.4 mmol/L (4mg/dL) at any treatment visit)	4 (33%)	2 (13%)	4 (31%)	2 (15%)	4 (36%)	0

Criteria for insulin groups are as follows: Decreased total insulin: $\Delta \leq -0.06$ U/Kg/day, Stable total insulin: $\Delta = -0.06 - 0.03$ U/Kg/day, Increased total insulin: $\Delta \geq 0.03$ U/Kg/day.

Demographic characteristic at baseline were balanced with no difference between the groups

Abnormal ketones in undetectable C-peptide subgroup

Trend toward reduction of abnormal ketones in TTP399-treated group with improvement in glycemic control

	C-peptide	Placebo	TTP399	Treatment effect	P value
HbA1c	Undetectable	0.13 ± 0.07 (n=24)	-0.31 ± 0.07 (n=23)	-0.44±0.07	p<0.01
Abnormal BOHB (>0.4 mmol/L (4mg/dL)	Undetectable	8 (33%) n=24	2 (9%) n=23		

n = total number of patients in treatment arm subgroup. Undetectable c-peptide level is <0.004 ng/mL

HbA1c is reported as CFB mean and standard deviation per group with treatment effect relative to placebo.

Abnormal ketone reported at patient (%) = number of patients with abnormal ketones in serum and % of n.
Demographic characteristic at baseline were balanced with no difference between the groups

Conclusions: Mechanism DOES matter

Liver Selective GKA shows potential as an adjunctive therapy for T1D

- Trends towards reduction in ketone events were observed in the TTP399 treated group compared to placebo. This finding was not due to imbalance in baseline characteristics
- Trend toward reduction of abnormal ketones were not associated with a decreased insulin dose
- Trends towards lower abnormal ketone events with significant reduction of HbA1c in the TTP399 treated group for the subgroup of patients with undetectable c-peptide, suggesting potential benefit in subjects at higher risk for ketosis
- The collective clinical data from the Simplici-T1 study support the hypothesis that liver selective activation of GK by TTP399 improves glycemic control without increasing the risk of hypoglycemia or DKA.
- 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, the JDRF and the Simplici-T1 team for making this study possible