The SimpliciT1 Study: Hepatoselective glucokinase activation via TTP399 for the treatment of type 1 diabetes mellitus

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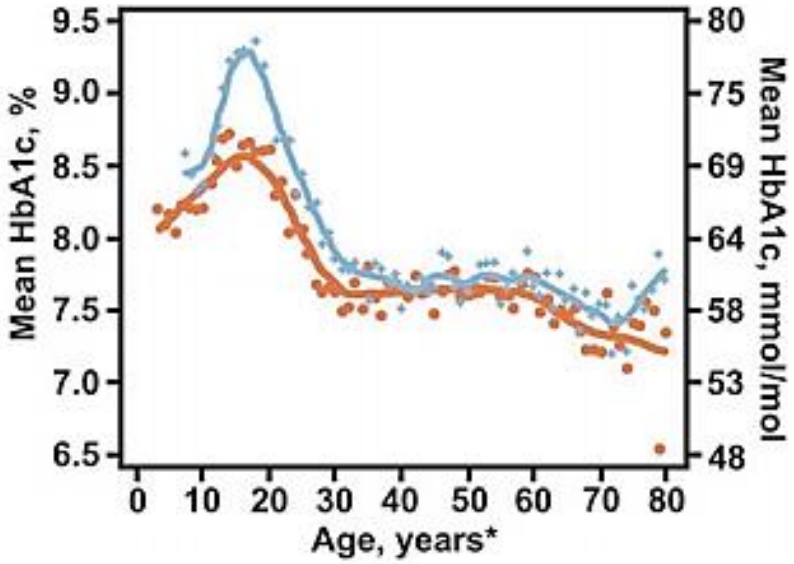
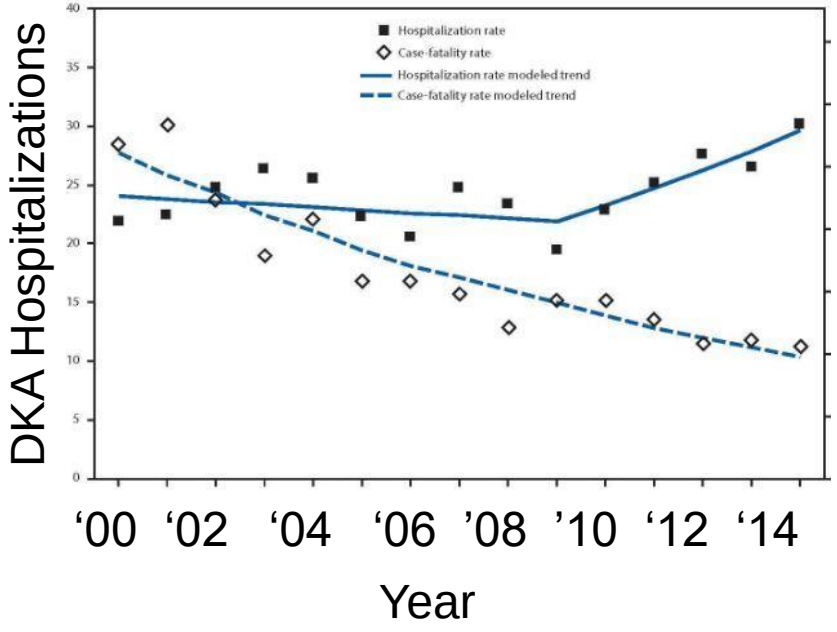
Despite improving diabetes technology, clinical outcomes in type 1 diabetes continue to decline

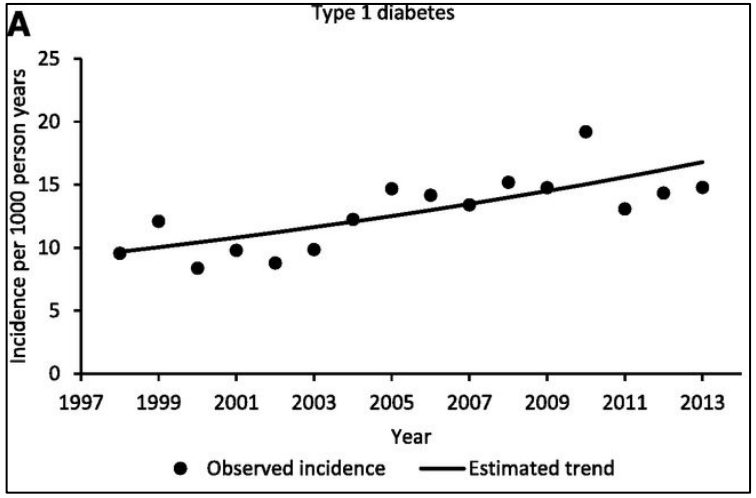
Few people with T1DM attain ADA recommended HbA1c targets[1]



The incidence of DKA hospitalizations is increasing[2]



The incidence of hypoglycemia hospitalizations is increasing[3]



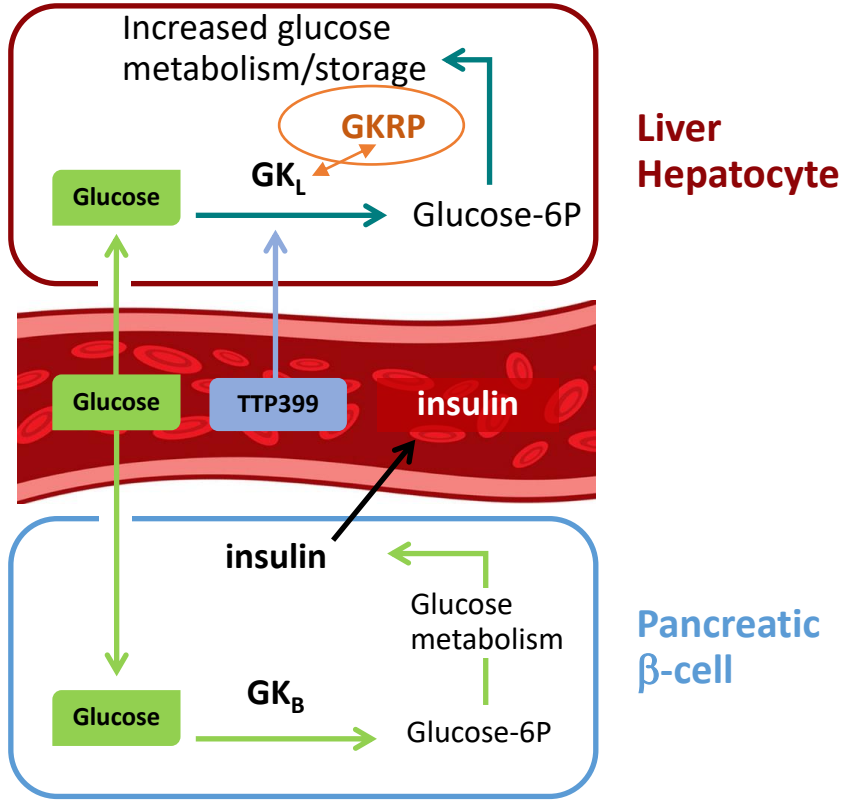
[1] *Foster et al. Diabetes Technology and Therapeutics (2019) 21:66-72; DOI: 10.1089/dia.2018.0384*

[2] Gosmanov et al. Hyperglycemic Crises: Diabetic Ketoacidosis (DKA), And Hyperglycemic Hyperosmolar State (HHS) South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279052/

Zhong et al, Diabetes Care 2017 Dec; 40(12): 1651-1660.

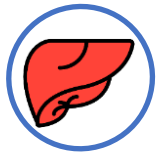
Glucokinase (GK) is a molecular glucose sensor

- GK has long been a target for the treatment of diabetes
- GK plays a key role in glucose homeostasis supported by strong genetic evidence
- Glucose sensitive kinetics, not inhibited by Glucose-6P
- In hepatocyte, the GK-GKRP interaction ensures that GK is only activated during periods of hyperglycemia



Hepatic glucokinase (GK) activation shows promise for diabetes

TTP399: A liver selective Glucokinase Activator[1]



TTP399 activates GK in the liver

TTP399 does not activate GK in ß-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 (SimpliciT1): 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). Part 1 required CGM and CSII. Participants on multiple daily injections and self monitored blood glucose with capillary glucose meter were not excluded in Part 2.

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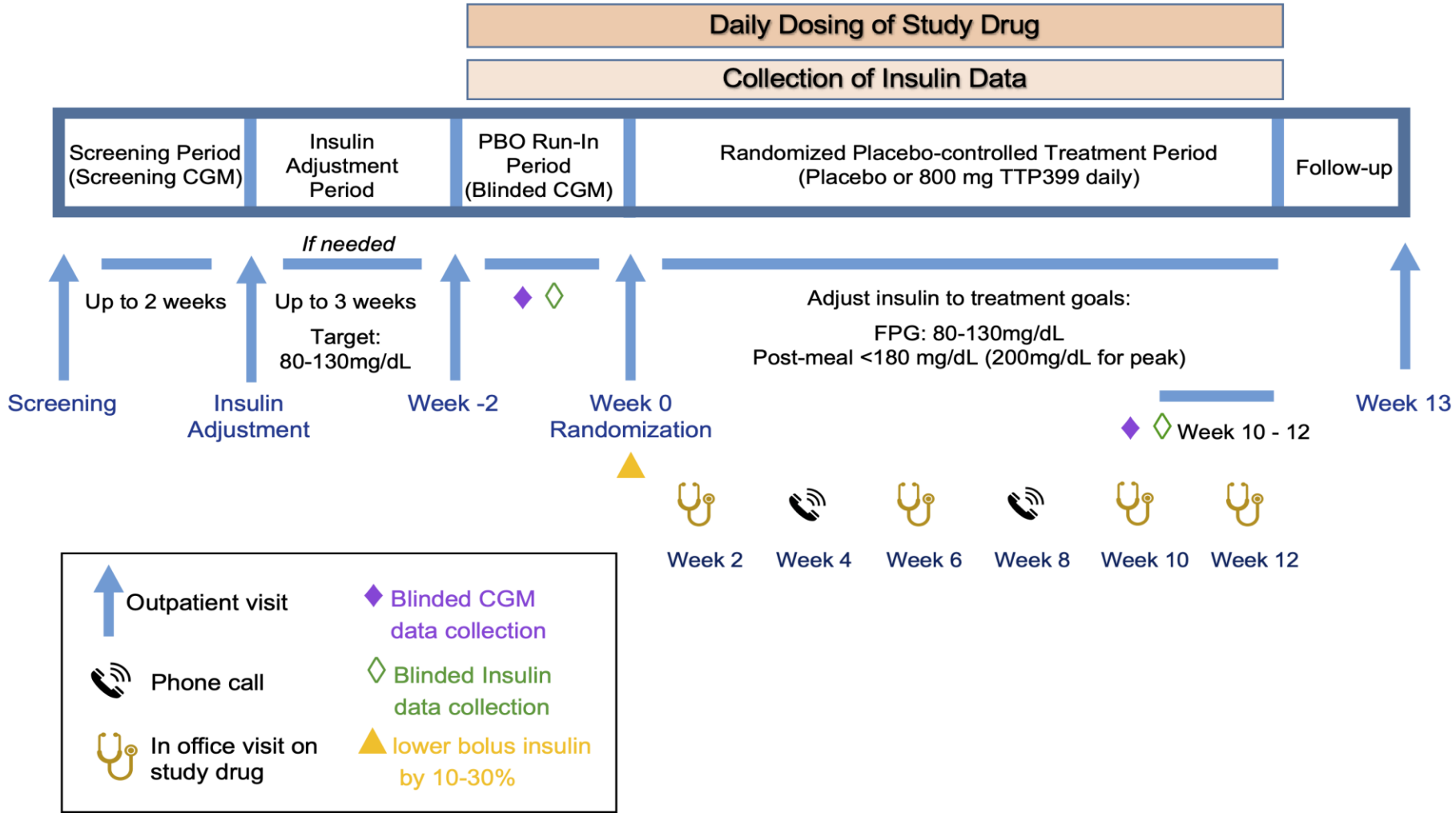
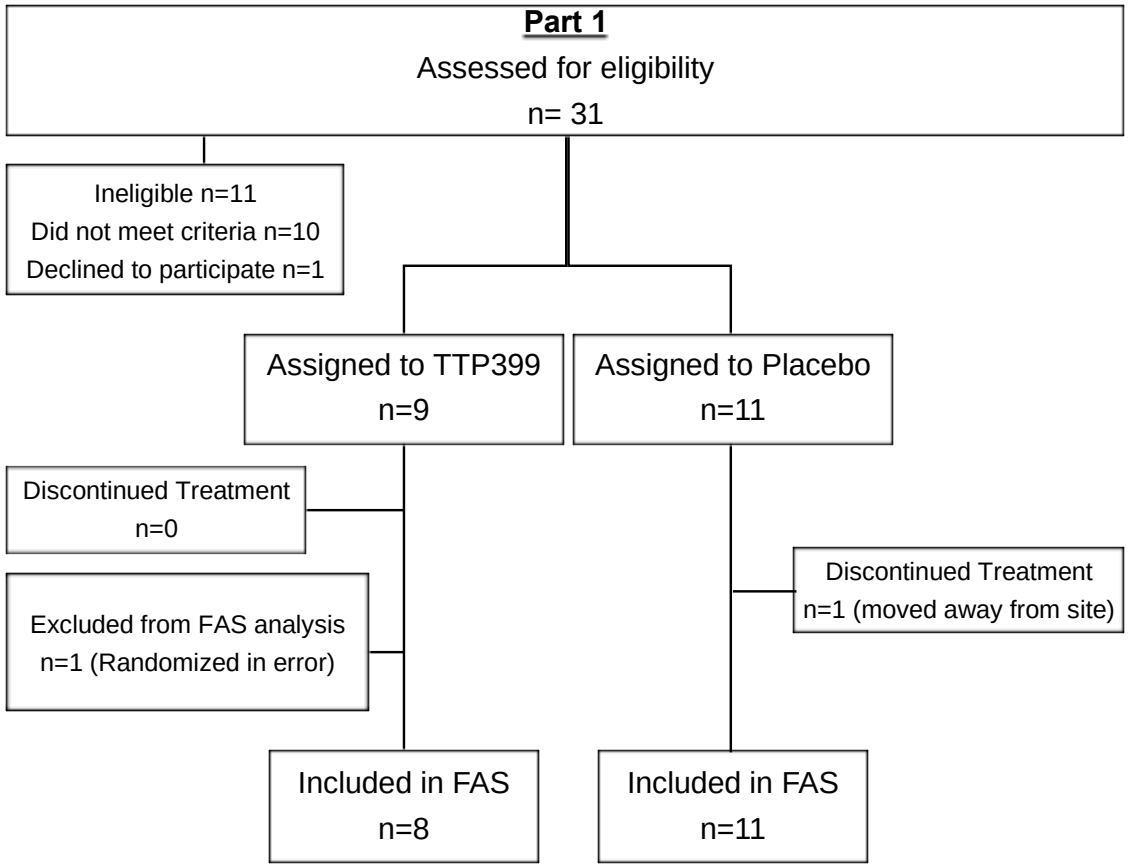
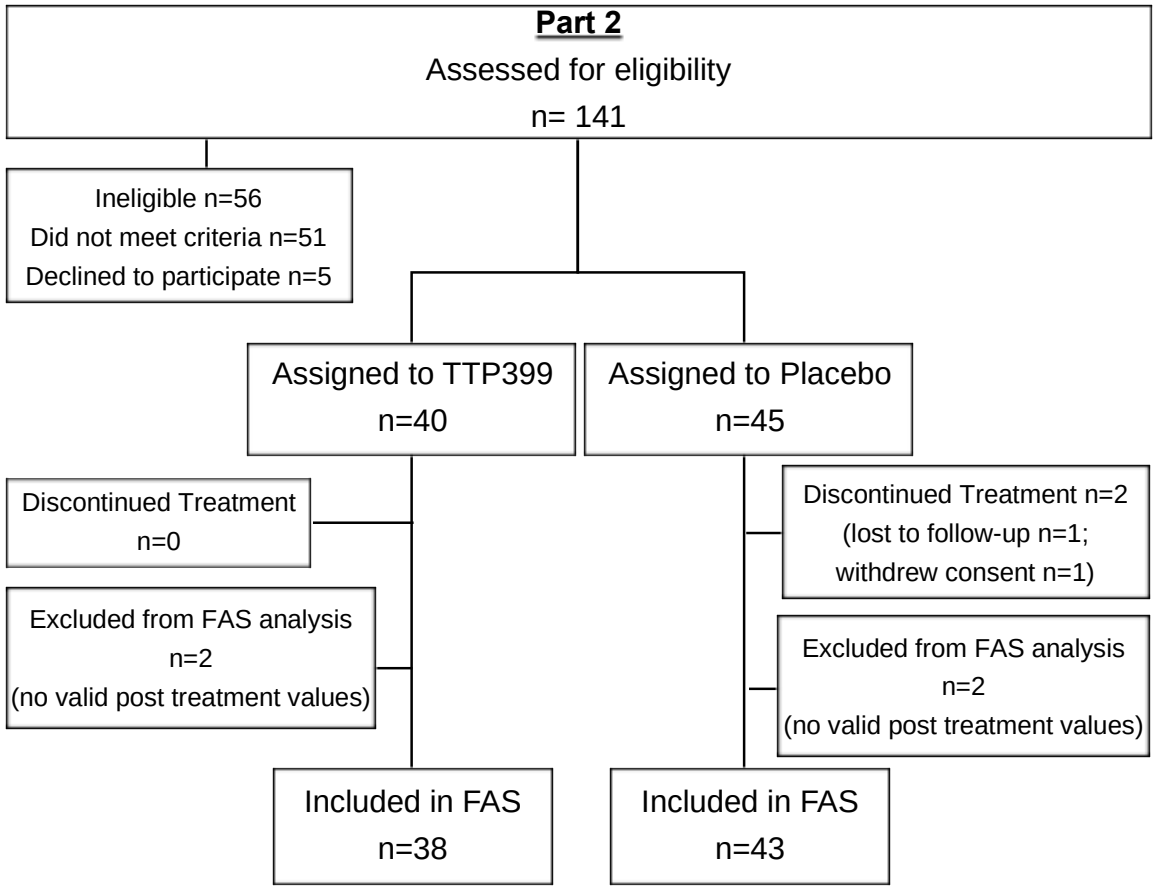
Study outline for Part 2 of the SimpliciT1 study



1. Klein KR, Freeman JLR, Dunn I, et al. 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. *Diabetes Care*. 2021:dc202684.

Study disposition for Part 1 and Part 2





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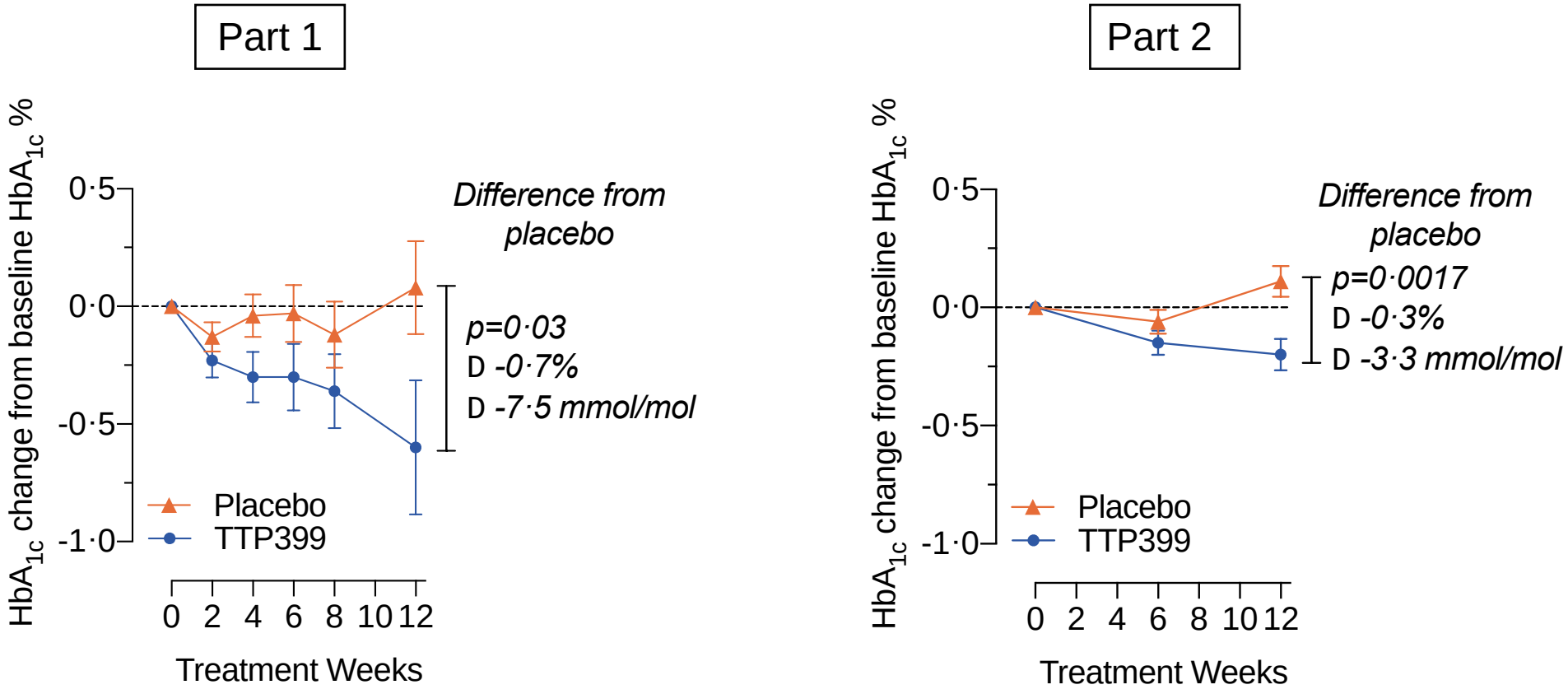
Baseline characteristics for Part 1 and Part 2

	Part 1		Part 2	
	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%)
Fasting plasma glucose (mg/dL)	ND	ND	153 (49)	141 (59)
HbA_{1c} (%)	7.4 (0.4)	7.2 (0.4)	7.5 (0.60)	7.6 (0.6)
β-hydroxybutyrate (mmol/L)	0.19 (0.32)	0.12 (0.21)	0.14 (0.25)	0.11 (0.12)
C-peptide (<0.004 ng/mL)	5 (45%)	5 (63%)	22 (51%)	20 (53%)
Daily insulin dose				
Total (IU)	48.9 (13.9)	52.6 (14.1)	55.8 (22.2)	57.5 (29.3)
Basal (IU)	26.0 (7.5)	30.0 (4.7)	29.8 (13.9)	30.4 (13.9)
Bolus (IU)	22.8 (8.8)	22.6 (12.3)	26.0 (12.5)	27.0 (18.7)

1. Klein KR, Freeman JLR, Dunn I, et al. 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. *Diabetes Care*. 2021:dc202684.

TTP399 improved glycemic control in both Part 1 and Part 2



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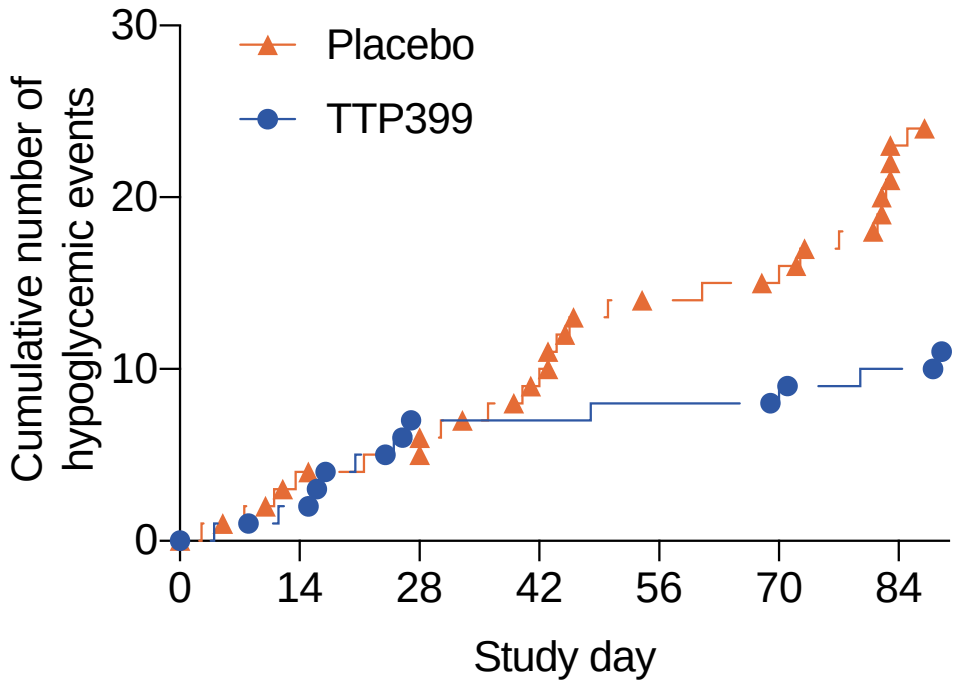
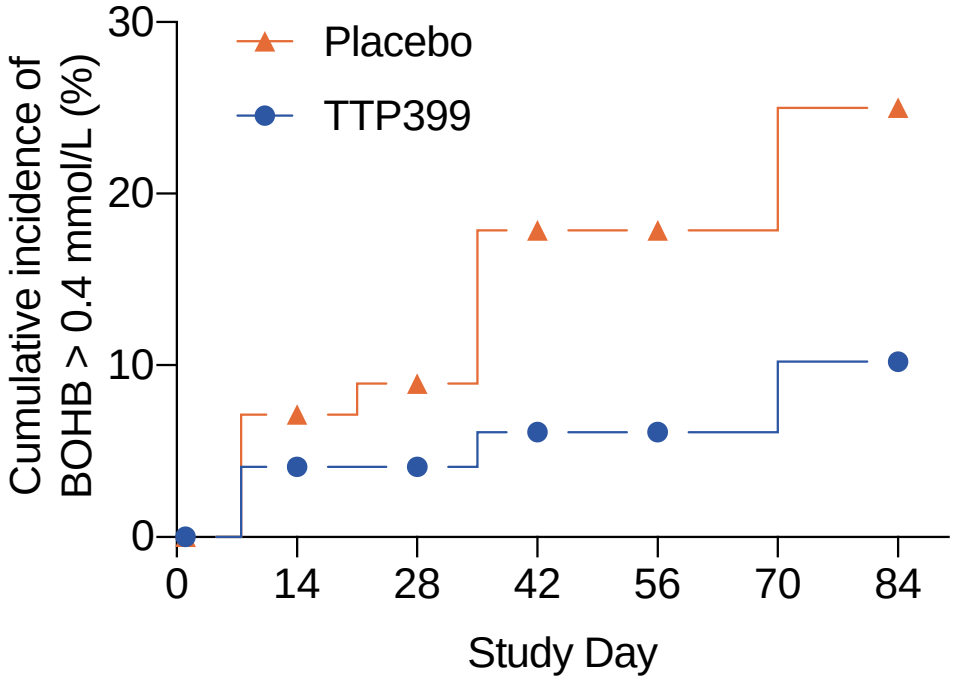
Treatment emergent AEs were similar between groups, but a reduction in hypoglycemia and ketosis events was noted in Part 2

Hypoglycemia events



Ketosis events



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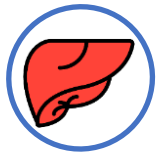
Conclusions and Future Directions



TTP399 significantly reduced HbA1c in Part 1 and Part 2 of the SimpliciT1 study

TTP399 had a favorable safety profile and showed trends in reduction of hypoglycemia and ketosis events

Longer and larger clinical trials required to confirm the findings in TTP399 in a larger and more diverse patient population

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