Results from the sentinel and learning phase of the Simplici-T1 study, the first clinical trial to test activation of glucokinase as an adjunctive treatment for type 1 diabetes

Carmen Valcarce[2], Jennifer L. Freeman[2], Imogene Dunn[2], Chris Dvergsten[2], Tom Soeder[3] and John B. Buse[1]. [1]UNC, Chapel Hill, NC, USA, [2]vTv Therapeutics, High Point, NC, USA, [3] Cato Research, Durham, NC, USA

Abstract

People living with type 1 diabetes (T1DM) have an unmet medical need for treatment options in addition to insulin that help achieve tighter blood glucose levels without increasing the risk of hypoglycemia or ketoacidosis. Glucokinase (GK) plays an essential role in blood glucose homeostasis. TTP399 is a small molecule, **liver-selective GK activator** in development as a new potential oral antidiabetic drug (OAD).[1]

Simplici-T1 is a multi-center, randomized, double-blind, adaptive study assessing the pharmacokinetics, pharmacodynamics, safety and tolerability of TTP399 as an adjunct to insulin therapy in adult subjects with T1DM.[2]

Treatment with TTP399 improved time in range (TIR) and reduced time in hyperglycemia, while showing the potential to decrease hypoglycemic events and bolus insulin dose. TTP399 was well tolerated. In Phase 2 - Part 1, subjects with T1DM treated with TTP399 (n=8) showed a statistically significant mean reduction in HbA1c of 0.6% at 12 weeks, while the group treated with placebo (n=11) showed a mean increase in HbA1c of 0.1%, resulting in a mean reduction of 0.7% in the TTP399 group relative to the placebo group (p=0.03). At the same time, trends toward decreased insulin usage were observed in the group treated with TTP399. These promising findings from Phase 2 - Part 1 and earlier Phase 1 (Sentinels) supported advancing into Phase 2 - Part 2 to confirm the results in a larger and more diverse T1DM population.

This study is co-sponsored by vTv Therapeutics and JDRF, the leading global organization funding research in T1DM.

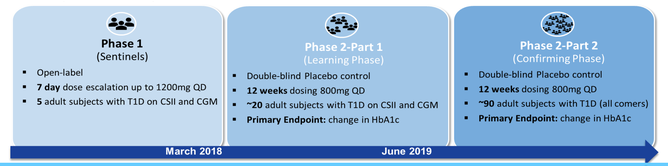
References:

[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; Vol. 11, Issue 475

[2] Buse J, Valcarce C, Freeman J, Dunn I, Dvergsten C, Kirkman S, Alexander K, Jamie D and Bergamo K. Simplici-T1: First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes; Presented at the American Diabetes Association 78th Scientific Sessions, June 25, 2018, Orlando, Florida

Simplici-T1 Study Aim and Design

To examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 as a potential adjunctive treatment in subjects with T1DM. **(NCT03335371)**.



Phase 1 (Sentinels)

Design: Open-label, weekly dose escalation study with up to 3 dose escalations in 5 adult subjects with T1DM. Subjects were using Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitors (CGM) and were dosed with TTP399 400mg, 800mg or 1200mg once daily for 7 days at each dose level.

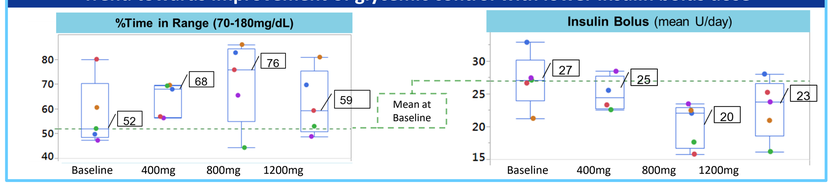
Demographics and baseline characteristics

Sex	Age (years)	Race	HbA1c (%)	Weight (kg)
Male (n=2); Female (n=3)	22-42	White (n=5)	Mean 6.9 (6.3-8.4)	Mean 75 (75.0-79.5)

Safety / Tolerability

No severe hypoglycemia, diabetic ketoacidosis (DKA) or SAEs. AEs were mild to moderate (mostly mild) with no detrimental effects on plasma lipids or LFTs noted. Additional information can be found on the Publications page at www.vtvtherapeutics.com

Trend towards improvement of glycemic control with lower insulin bolus dose



Phase 2 - Part 1 (Learning Phase)

Design: Double-blind, placebo-control study evaluating the effect of TTP399 (800mg QD) for 12 weeks in 19 adult subjects with T1DM on CSII and unblinded CGM.

Demographics and baseline characteristics

Trait	Statistic	Placebo (n=11)	TTP399 (n=8)
Age (years)	Mean [Median] (min, max)	47 [43] (35,68)	38 [35] (23, 66)
Gender	Female (%)	8 (73%)	5 (63%)
Race	White (%)	11 (100%)	7 (88%)
Ethnicity	Non-Hispanic or Latino (%)	11 (100%)	8 (100%)
Weight (kg)	Mean (min, max)	82.8 (55, 115)	80.2 (61, 100)
BMI	Mean (min, max)	29.0 (20, 35)	28.4 (24, 32)
Baseline HbA1c (%)	Mean [Median] (min, max)	7.4 [7.3] (7.0, 8.2)	7.3 [7.4] (6.9, 7.9)
Use of Insulin Pump & unblinded CGM device	Number (%)	11 (100%)	8 (100%)

Safety / Tolerability

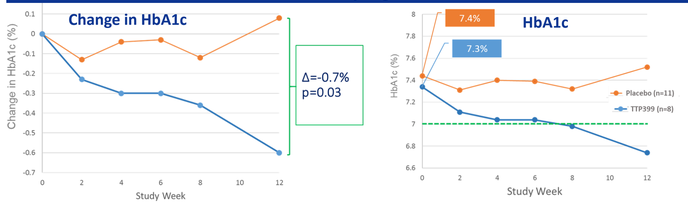
- No severe hypoglycemia, DKA or SAEs.
- No TEAE with incidence greater on TTP399 than on placebo.
- 5 Treatment related TEAEs: 3 of nausea (2 placebo; 1 TTP399), 1 of vertigo (placebo), 1 of vomiting (placebo).

Potential reduction in number of Level 1 and Level 2 hypoglycemic events observed after 12 weeks of dosing with TTP399

Mean number of hypoglycemic episodes/subject/week

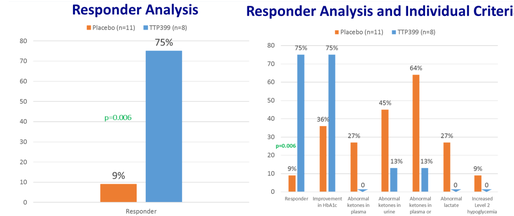
	Treatment Group	Baseline	End of Treatment	Change from baseline
Level 1 54-70 mg/dl, includes 54	TTP399 800 mg QD	3.70	1.95	-1.75 (47% improvement)
	Placebo	2.60	2.85	0.25 (10% worsening)
Level 2 < 54 mg/dl	TTP399 800 mg QD	1.20	0.83	-0.37 (31% improvement)
	Placebo	1.35	1.33	-0.02 (1% improvement)

Statistically Significant Reduction in HbA1c



Efficacy analysis was done on the full analysis set (FAS), consisting of all randomized subjects who received at least one dose of randomized study medication. The primary analysis used the intent-to-treat methodology and a main effects model for analysis of covariance (ANCOVA), with adjustment for baseline HbA1c levels.

Statistically Significant Increase in Responders

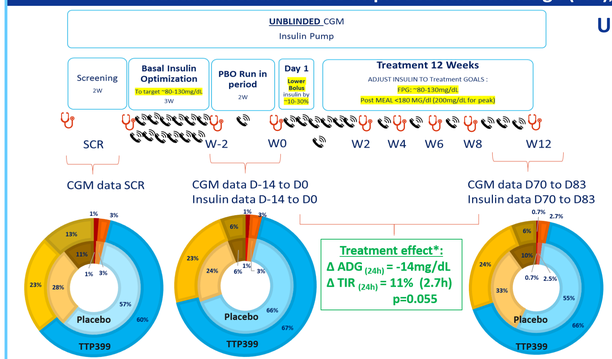


Responder definition:

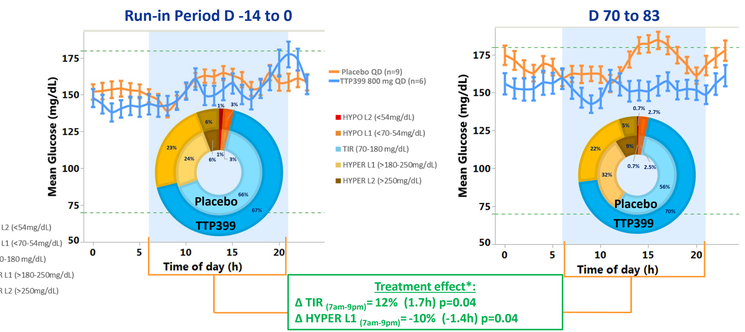
Proportions of subjects with improvement in HbA1c and without predefined risks of:

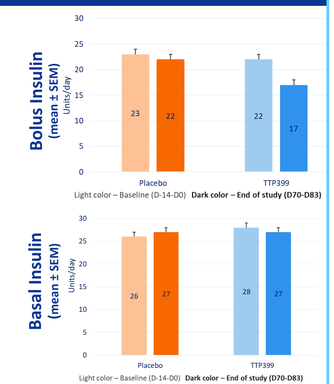
- Abnormal ketones in urine or plasma
- Abnormal lactate in plasma
- Increase in time in level 2 hypoglycemia (glucose <54 mg/dl)

Treatment with TTP399 improved Time in Range (TIR), reduced time in hyperglycemia, and showed potential to decrease hypoglycemic events and bolus insulin dose



Unblinded Continuous Glucose Monitoring





Full analysis set (FAS): all randomized subjects who received at least one dose of study drug and available data at baseline (days -14 to 0) and endpoint (days 70 to 83), observed cases ITT (no deletion; no imputation). Daytime 7am-9pm. Data are Lsmeans.

Conclusions

- ❑ TTP399 was well tolerated. No incidence of severe hypoglycemia, no diabetic ketoacidosis, no detrimental changes in plasma lipids or liver function were noted.
- ❑ Statistically significant and clinically meaningful reduction in HbA1c was observed after 12 weeks of dosing.
- ❑ TTP399 treated subjects had improved TIR, reduced time in hyperglycemia, and experienced a decrease in hypoglycemic events and bolus insulin dose.
- ❑ These promising findings from Phase 2 - Part 1 and the earlier Phase 1 (Sentinels) supported advancing into the on-going Phase 2 - Part 2 to confirm the results in a larger and more diverse T1DM population.

Abstract

People living with type 1 diabetes (T1DM) have an unmet medical need for treatment options in addition to insulin that help achieve tighter blood glucose levels without increasing the risk of hypoglycemia or ketoacidosis. Glucokinase (GK) plays an essential role in blood glucose homeostasis. TTP399 is a small molecule, liver-selective GK activator in development as a new potential oral antidiabetic drug (OAD).[1]

Simplici-T1 is a multi-center, randomized, double-blind, adaptive study assessing the pharmacokinetics, pharmacodynamics, safety and tolerability of TTP399 as an adjunct to insulin therapy in adult subjects with T1DM.[2]

Treatment with TTP399 improved time in range (TIR) and reduced time in hyperglycemia, while showing the potential to decrease hypoglycemic events and bolus insulin dose. TTP399 was well tolerated. In Phase 2 - Part 1, subjects with T1DM treated with TTP399 (n=8) showed a statistically significant mean reduction in HbA1c of 0.6% at 12 weeks, while the group treated with placebo (n=11) showed a mean increase in HbA1c of 0.1%, resulting in a mean reduction of 0.7% in the TTP399 group relative to the placebo group (p=0.03). At the same time, trends toward decreased insulin usage were observed in the group treated with TTP399. These promising findings from Phase 2 - Part 1 and earlier Phase 1 (Sentinels) supported advancing into Phase 2 - Part 2 to confirm the results in a larger and more diverse T1DM population.

This study is co-sponsored by vTv Therapeutics and JDRF, the leading global organization funding research in T1DM.

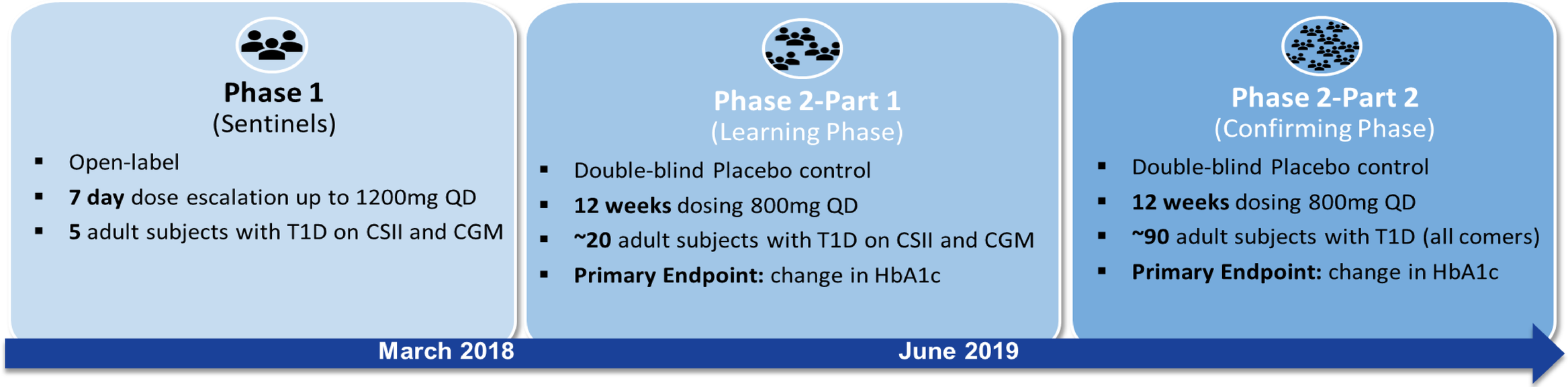
References:

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; Vol. 11, Issue 475

2 Buse J, Valcarce C, Freeman J, Dunn I, Dvergsten C, Kirkman S, Alexander k, Jamie D and Bergamo K. Simplici-T1: First Clinical Trial to Test Activation of Glucokinase as an Adjunctive Treatment for Type 1 Diabetes; Presented at the American Diabetes Association 78th Scientific Sessions, June 25, 2018, Orlando, Florida

Simplici-T1 Study Aim and Design

To examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 as a potential adjunctive treatment in subjects with T1DM. **(NCT03335371)**.



Phase 1 (Sentinels)

Design: Open-label, weekly dose escalation study with up to 3 dose escalations in 5 adult subjects with T1DM. Subjects were using Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitors (CGM) and were dosed with TTP399 400mg, 800mg or 1200mg once daily for 7 days at each dose level.

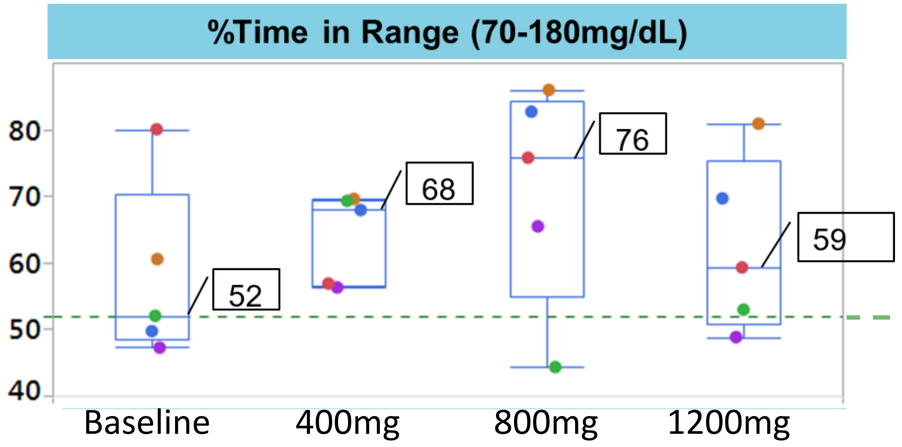
Demographics and baseline characteristics

Sex	Age (years)	Race	HbA1c (%)	Weight (kg)
Male (n=2); Female (n=3)	22-42	White (n=5)	Mean 6.9 (6.3-8.4)	Mean 75 (75.0-79.5)

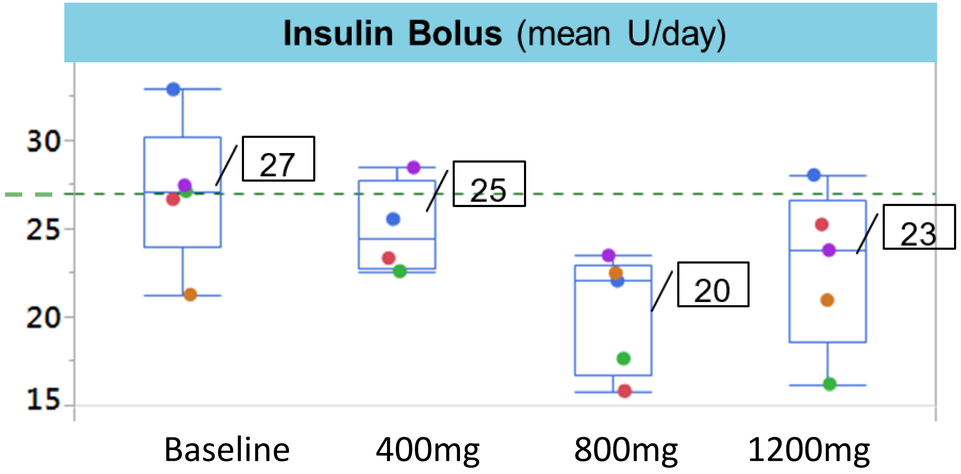
Safety / Tolerability

No severe hypoglycemia, diabetic ketoacidosis (DKA) or SAEs. AEs were mild to moderate (mostly mild) with no detrimental effects on plasma lipids or LFTs noted. Additional information can be found on the Publications page at www.vtvtherapeutics.com

Trend towards improvement of glycemic control



Mean at Baseline



Phase 2 - Part 1 (Learning Phase)

Design: Double-blind, placebo-control study evaluating the effect of TTP399 (800mg QD) for 12 weeks in 19 adult subjects with T1DM on CSII and unblinded CGM.

Demographics and baseline characteristics			
Trait	**Statistic**	**Placebo (n=11)**	**TTP399 (n=8)**
Age (years)	Mean [Median] (min, max)	47 [43] (35,68)	38 [35] (23, 66)
Gender	Female (%)	8 (73%)	5 (63%)
Race	White (%)	11 (100%)	7 (88%)
Ethnicity	Non-Hispanic or Latino (%)	11 (100%)	8 (100%)
Weight (kg)	Mean (min, max)	82.8 (55, 115)	80.2 (61, 100)
BMI	Mean (min, max)	29.0 (20, 35)	28.4 (24, 32)
Baseline HbA1c (%)	Mean [Median] (min, max)	7.4 [7.3] (7.0, 8.2)	7.3 [7.4] (6.9, 7.9)
Use of Insulin Pump & unblinded CGM device	Number (%)	11 (100%)	8 (100%)

Phase 2 - Part 1 (Learning Phase)

Safety / Tolerability

- No severe hypoglycemia, DKA or SAEs.
- No TEAE with incidence greater on TTP399 than on placebo.
- 5 Treatment related TEAEs: 3 of nausea (2 placebo; 1 TTP399), 1 of vertigo (placebo), 1 of vomiting (placebo).

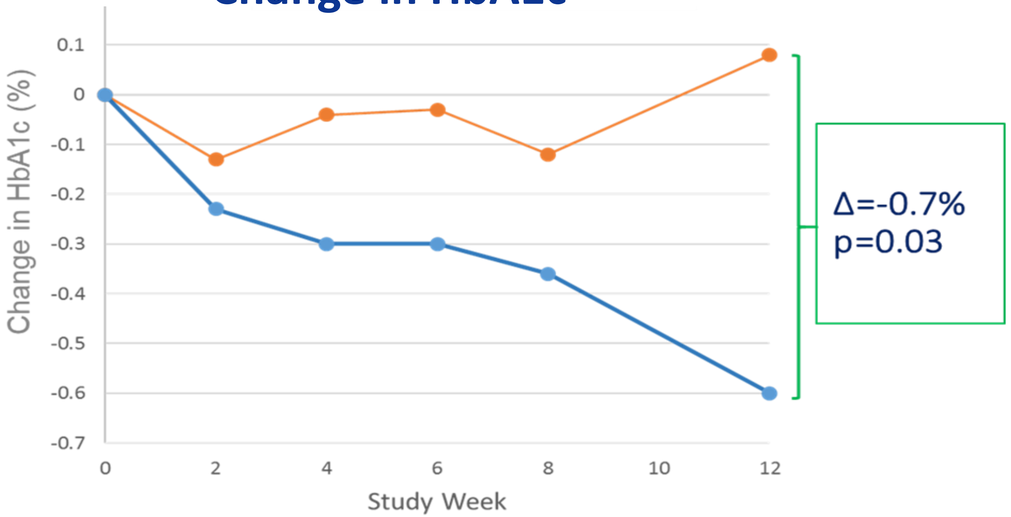
Potential reduction in number of Level 1 and Level 2 hypoglycemic events observed after 12 weeks of dosing with TTP399

Mean number of hypoglycemic episodes/subject/week

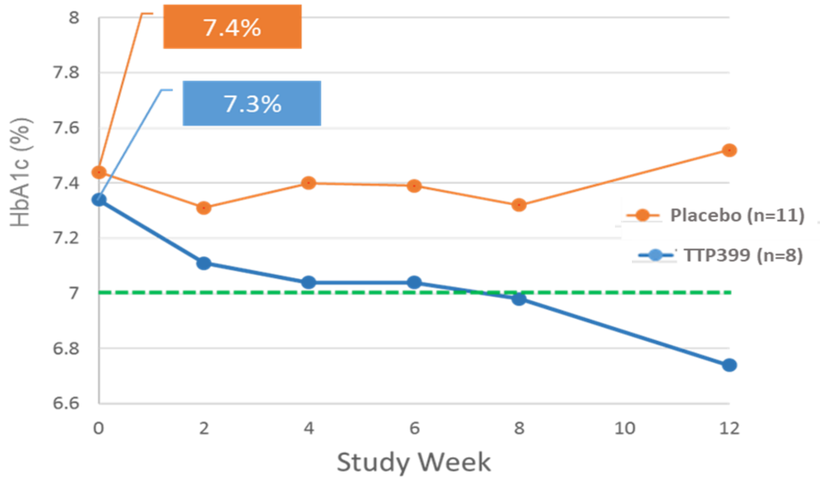
	Treatment Group	Baseline	End of Treatment	Change from baseline
Level 1 54-70 mg/dl, includes 54	TTP399 800 mg QD	3.70	1.95	-1.75 (47% improvement)
	Placebo	2.60	2.85	0.25 (10% worsening)
Level 2 < 54 mg/dl	TTP399 800 mg QD	1.20	0.83	-0.37 (31% improvement)
	Placebo	1.35	1.33	-0.02 (1% improvement)

Statistically Significant Reduction in HbA1c

Change in HbA1c



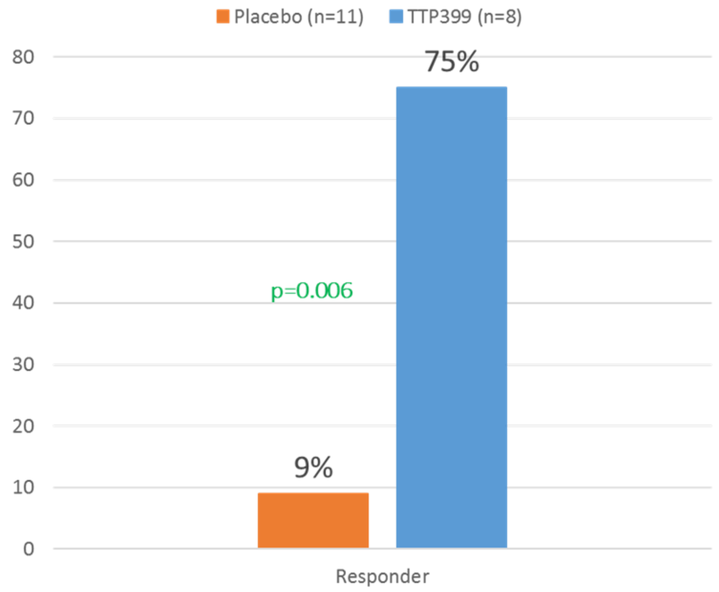
HbA1c



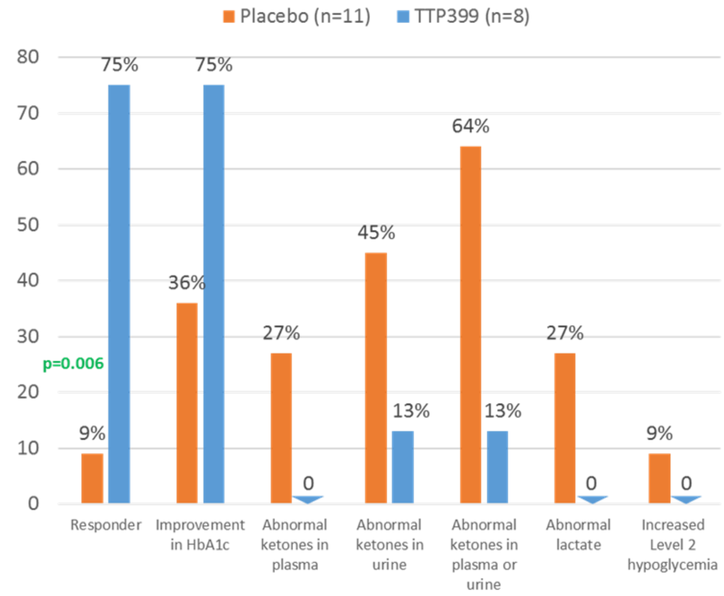
Efficacy analysis was done on the full analysis set (FAS), consisting of all randomized subjects who received at least one dose of randomized study medication. The primary analysis used the intent-to-treat methodology and a main effects model for analysis of covariance (ANCOVA), with adjustment for baseline HbA1c levels.

Statistically Significant Increase in Responders

Responder Analysis



Responder Analysis and Individual Criteria



Responder definition:

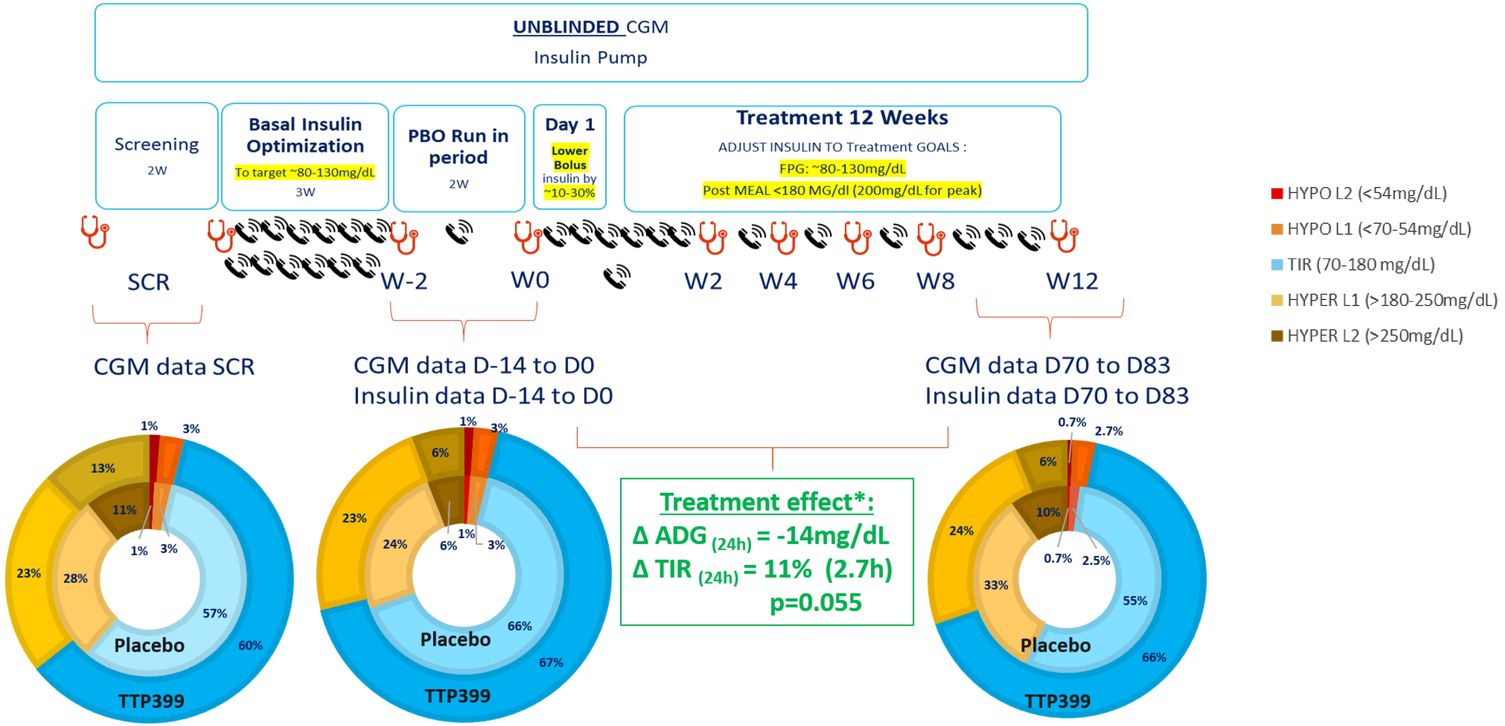
Proportions of subjects with improvement in HbA1c and without predefined risks of:

- Abnormal ketones in urine or plasma
- Abnormal lactate in plasma
- Increase in time in level 2 hypoglycemia (glucose <54 mg/dl)

Phase 2 - Part 1 (Learning Phase)

Treatment with TTP399 improved Time in Range (TIR), reduced time in hyperglycemia, and showed potential to decrease hypoglycemic events and bolus insulin dose

Unblinded Continuous Glucose Monitoring

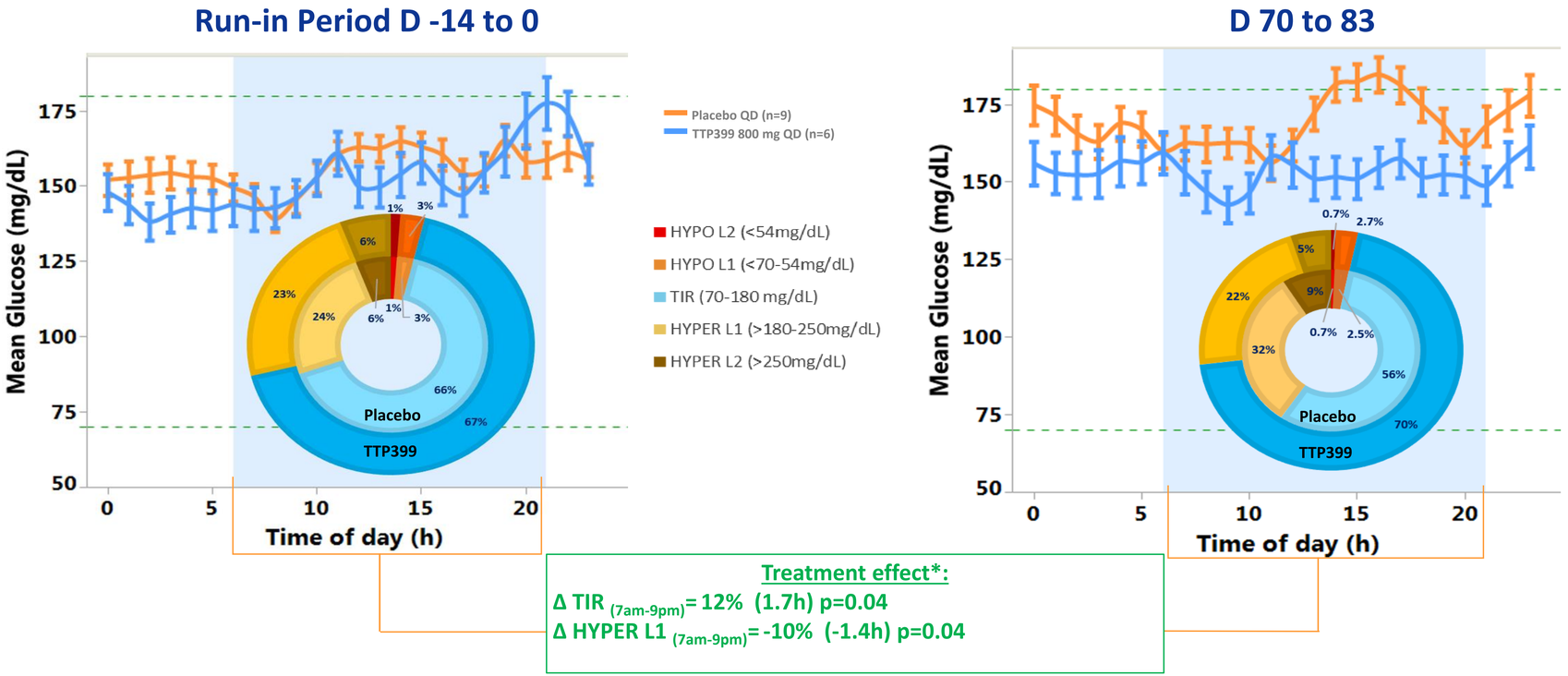


**Full analysis set (FAS): all randomized subjects who received at least one dose of study drug and available data at baseline (days -14 to 0) and endpoint (days 70 to 83), observed cases ITT (no deletion; no imputation). Data are Lsmeans.*

Phase 2 - Part 1 (Learning Phase)

Treatment with TTP399 improved Time in Range (TIR), reduced time in hyperglycemia, and showed potential to decrease hypoglycemic events and bolus insulin dose

Unblinded Continuous Glucose Monitoring (7AM-9PM)



Treatment effect*:

Δ TIR $_{(7am-9pm)}$ = 12% (1.7h) p=0.04

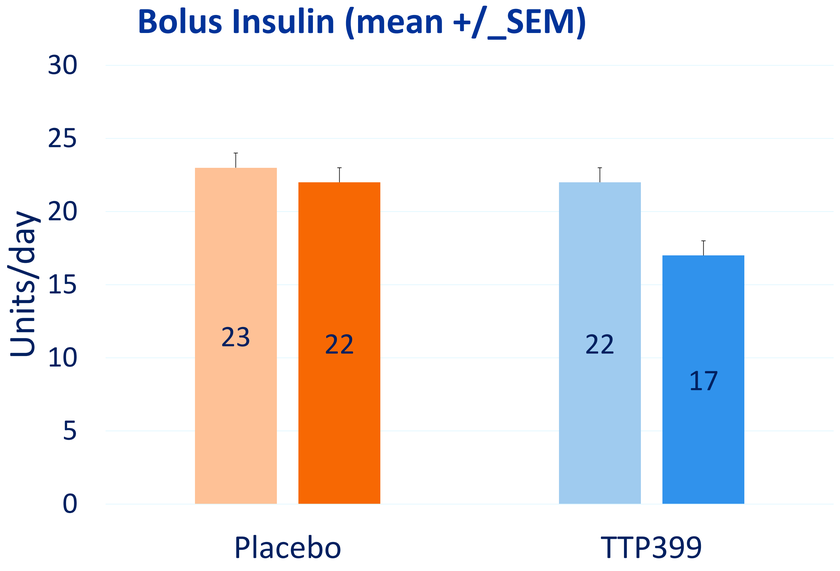
Δ HYPER L1 $_{(7am-9pm)}$ = -10% (-1.4h) p=0.04

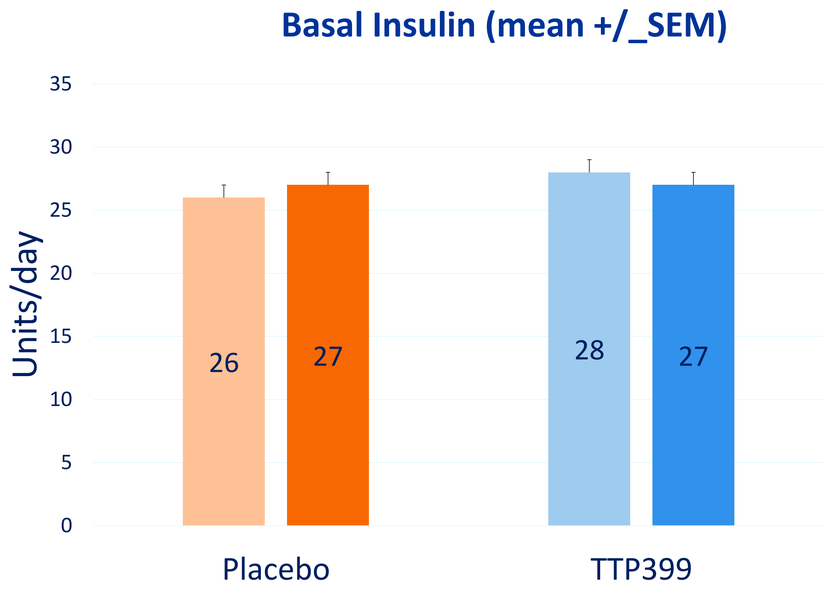
**Full analysis set (FAS): all randomized subjects who received at least one dose of study drug and available data at baseline (days -14 to 0) and endpoint (days 70 to 83), observed cases ITT (no deletion; no imputation). Daytime 7am-9pm. Data are Lsmeans.*

Phase 2 - Part 1 (Learning Phase)

Treatment with TTP399 improved Time in Range (TIR), reduced time in hyperglycemia, and showed potential to decrease hypoglycemic events and bolus insulin dose

Insulin dose





Light color – Baseline (D-14-D0) **Dark color – End of study (D70-D83)**

Conclusions

- TTP399 was well tolerated. No incidence of severe hypoglycemia, no diabetic ketoacidosis, no detrimental changes in plasma lipids or liver function were noted.
- Statistically significant and clinically meaningful reduction in HbA1c was observed after 12 weeks of dosing.
- TTP399 treated subjects had improved TIR, reduced time in hyperglycemia, and experienced a decrease in hypoglycemic events and bolus insulin dose.
- These promising findings from Phase 2 - Part 1 and the earlier Phase 1 (Sentinels) supported advancing into the on-going Phase 2 - Part 2 to confirm the results in a larger and more diverse T1DM population.