**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 ketosis. Glucokinase (GK) plays an essential role in blood glucose homeostasis. TTP399 is a small molecule, selective GK activator in development as a new potential antidiabetic drug (SAD).

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.

**Design:**

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=12) showed a statistically significant mean reduction in HbA1c of 0.6% at 12 weeks, while the group treated with placebo (n=12) showed a mean increase in HbA1c of 0.1%, resulting in a mean reduction of 0.5% in the TTP399 group relative to the placebo group (p=0.003). In 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 JJF, 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 hepatic glucokinase activator. Simplicity-T1 Study Aim and Design.
2. Jan 2019; Vol. 11, Issue 475
3. Additional information can be found on the Publications page at www.vtvtherapeutics.com

**Phase 2 - Part 1 (Learning Phase)**

**Demographics and baselines characteristics**

<table>
<thead>
<tr>
<th>Trait</th>
<th>Male (n=5)</th>
<th>Female (n=3)</th>
<th>Placebo (n=6)</th>
<th>TTP399 (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 (37-51)</td>
<td>40 (38-42)</td>
<td>41 (36-51)</td>
<td>39 (34-51)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84 (75-98)</td>
<td>84.4 (77-85)</td>
<td>80.2 (72-91)</td>
<td>82.8 (75-93)</td>
</tr>
<tr>
<td>BMI</td>
<td>29.0 (25.5-32.2)</td>
<td>31.2 (28.3-33.8)</td>
<td>31.8 (28.3-35.3)</td>
<td>33.0 (29.0-36.2)</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>7.4 (7.3-7.9)</td>
<td>7.1 (6.9-8.0)</td>
<td>7.5 (7.3-8.2)</td>
<td>7.3 (7.3-7.8)</td>
</tr>
<tr>
<td>Use of Metformin</td>
<td>100% (5/5)</td>
<td>100% (3/3)</td>
<td>100% (6/6)</td>
<td>100% (6/6)</td>
</tr>
<tr>
<td>Use of Basal Insulin</td>
<td>100% (5/5)</td>
<td>100% (3/3)</td>
<td>100% (6/6)</td>
<td>100% (6/6)</td>
</tr>
<tr>
<td>Use of Bolus Insulin</td>
<td>90% (4/5)</td>
<td>100% (3/3)</td>
<td>100% (6/6)</td>
<td>100% (6/6)</td>
</tr>
</tbody>
</table>

**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

**Safety / Tolerance**

- No severe hypoglycemia, DKA or SAI.
- No TEAE with incidence greater on TTP399 than on placebo.
- No TEAE with incidence greater on TTP399 than on placebo.
- No TEAE with incidence greater on TTP399 than on placebo.
- No severe hypoglycemia, DKA or SAI.
- No TEAE with incidence greater on TTP399 than on placebo.
- No TEAE with incidence greater on TTP399 than on placebo.

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

**Conclusions**

- TTP399 was well tolerated. No incidence of severe hypoglycemia, no diabetic ketoacidosis, no detrimental changes in plasma lipids or LFTs noted.
- 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.
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:
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
To examine the safety, tolerability, pharmacokinetics and pharmacodynamics of TTP399 as a potential adjunctive treatment in subjects with T1DM. (NCT03335371).

**Simplici-T1 Study Aim and Design**

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

**Phase 2-Part 1** (Learning Phase)
- Double-blind Placebo control
- 12 weeks dosing 800mg QD
- ~20 adult subjects with T1D on CSII and CGM
- **Primary Endpoint**: change in HbA1c

**Phase 2-Part 2** (Confirming Phase)
- Double-blind Placebo control
- 12 weeks dosing 800mg QD
- ~90 adult subjects with T1D (all comers)
- **Primary Endpoint**: change in HbA1c

March 2018 - June 2019
**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

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (years)</th>
<th>Race</th>
<th>HbA1c (%)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (n=2); Female (n=3)</td>
<td>22-42</td>
<td>White (n=5)</td>
<td>Mean 6.9 (6.3-8.4)</td>
<td>Mean 75 (75.0-79.5)</td>
</tr>
</tbody>
</table>

### 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](http://www.vtvtherapeutics.com)
Trend towards improvement of glycemic control

### Mean at Baseline

**%Time in Range (70-180mg/dL)**

- Baseline: 52%
- 400mg: 68%
- 800mg: 76%
- 1200mg: 59%

**Insulin Bolus (mean U/day)**

- Baseline: 27 U/day
- 400mg: 25 U/day
- 800mg: 20 U/day
- 1200mg: 23 U/day
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.

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

<table>
<thead>
<tr>
<th>Mean number of hypoglycemic episodes/subject/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
</tr>
<tr>
<td>Level 1 54-70 mg/dl, includes 54</td>
</tr>
<tr>
<td>TTP399 800 mg QD</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Level 2 &lt; 54 mg/dl</td>
</tr>
<tr>
<td>TTP399 800 mg QD</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>
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.
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). 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)

Run-in Period D -14 to 0

D 70 to 83

**Treatment effect**:  
\[ \Delta \text{TIR (7am-9pm)} = 12\% (1.7h) \ p=0.04 \]  
\[ \Delta \text{HYPER L1 (7am-9pm)} = -10\% (-1.4h) \ p=0.04 \]

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

Phase 2 - Part 1 (Learning Phase)

Insulin dose

**Bolus Insulin (mean +/- SEM)**

- **Placebo**: 23, 22
- **TTP399**: 22, 17

**Basal Insulin (mean +/- SEM)**

- **Placebo**: 26, 27
- **TTP399**: 28, 27

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